Basal Cell Carcinoma in The Netherlands

Sophie Christien Flohil

Financial support for the printing of this thesis was generously provided by Galderma, J.E. Jurriaanse Stichting, Abbott, Astellas, Pfizer BV, Leo Pharma BV, Bauerfeind Benelux BV, Louis Widmer, Janssen-Cilag, Fagron, Eucerin, Integraal Kankercentrum Zuid and ZonMw.

J.E. Jurriaanse Stichting

integraal kankercentrum Zuid

ISBN: 978-94-6169-317-4

Cover design: Fleur Flohil
Lay-out and printed by: Optima Grafische Communicatie, Rotterdam.

Basal Cell Carcinoma in The Netherlands

Het basaalcelcarcinoom in Nederland

Proefschrift

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
donderdag 20 december 2012
om 11.30 uur

door

Sophie Christien Flohil

geboren 10 april 1985 te Geldrop

PROMOTIECOMMISSIE

Promotoren:

Prof.dr. T.E.C. Nijsten

Prof.dr. H.A.M. Neumann

Overige leden:

Prof.dr. R.J. Baatenburg de Jong

Prof.dr. J.W.W. Coebergh

Dr. N.W.J. Kelleners – Smeets

Copromotor:

Dr. E. de Vries

LIST OF FREQUENTLY USED ABBREVIATIONS

AK	actinic keratosis
BCC	basal cell carcinoma
CI	confidence interval
EAPC	estimated annual percentage change
ESR	European standardized rate
FBSE	full body skin examination
KC	keratinocyte carcinoma
LB	lower bound
MM	malignant melanoma
Mel	melanoma
N	number
NMSC	non-melanoma skin cancer
Ref	reference
SCC	squamous cell carcinoma
UB	upper bound
USA	United States of America
UV	ultraviolet
WSR	world standardized rate

CONTENTS

CHAPTER 1

Introduction and aims of this thesis

INTRODUCTION

There are many different cutaneous malignancies, but malignant melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) represent approximately 98% of all skin cancers.[1-4] In literature, these three skin cancers are often divided into melanoma and non-melanoma skin cancers (NMSC; including BCC and SCC). However NMSC can be considered a misnomer, as there are many other rare cutaneous malignancies that are not a melanoma. A more appropriate term to classify BCC and SCC together could be keratinocyte carcinoma (KC) as they both arise from keratinocytes.[3]

Melanoma is the least common (about 11% of all skin cancers) but one of the most deadly types of skin cancer and develops from melanocytes.[4] BCC is the most common skin cancer (approximately 70% of all skin cancers) and also the least dangerous of the three.[5] However, substantial morbidity and cosmetic disfigurement can occur (figure 1), because around 80% of the BCCs are located within the chronically to the sun-exposed head and neck region. The studies presented in this thesis primarily focus on BCC.

Epidemiology

BCC is the most common cancer among Caucasians and incidence rates are increasing worldwide.[6-8] In general, a BCC is considered a disease of the elderly, although recent studies reported increases in the number of young patients.[9-10] The absolute BCC incidence is difficult to determine because it varies by age- and sex distribution within populations, study localisation, demographic shifts over time and differences in BCC registration across studies.[8] The number of population-based studies investigating trends in BCC incidence rates is limited, because only few (national) cancer registries collect BCC information. Countries that do register BCCs often report them together with SCC as NMSC or only report the first histologically confirmed BCC per patient because of practical problems such as the large number of

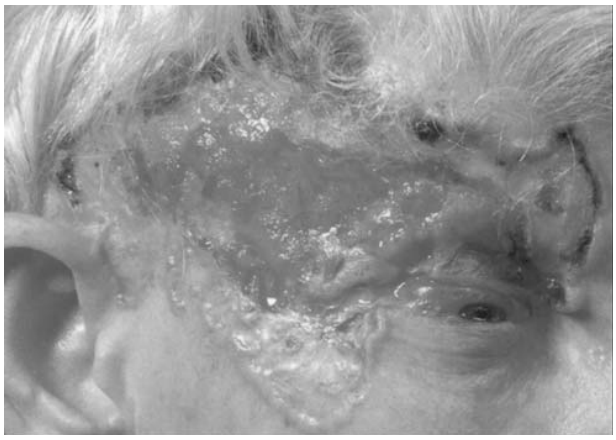


Figure 1. A patient with a basal cell carcinoma inducing significant cosmetic disfigurement and functional loss.

cases involved, difficulties accessing private clinics and the herewith associated time and costs.

The highest age-standardised incidence rates (to world standard population, WSR) are reported in Australia with 1,541 persons affected per 100,000 person-years, based on data from a followed population of the Nambour Skin Cancer Study (Queensland).[11] Although it is estimated that approximately two out of three Australians will develop skin cancer, Australian cancer registries do not collect BCC information and therefore true BCC estimates are unknown.[12] These high rates in Australia are followed by the United States (US) with rates (from relatively old cancer registry studies) ranging from 170 to 936 per 100,000 person-years (to US standard populations; 1970[13-14] and 1980[15]) and by Europe with 80 to 165 per 100,000 person-years (to European standard population, ESR).[6, 8, 12] This order in BCC incidence was to be expected as people in Australia have the highest amount of ultraviolet (UV) – exposure followed by US and Europe, and is primarily inhabited by people of primary Northern European descent with light pigmentation traits (i.e., light eye-, hair- and skin color).

Unfortunately strict comparisons of incidence rates are difficult because of the use of different standard populations (i.e., WSR and ESR). The increase of rates may be more easily compared. A recent systematic review estimated that BCC incidence is increasing by approximately 1 per 100,000 persons per year in Europe, but 6 per 100,000 persons in the United Kingdom.[8]

Limited population-based studies have investigated the number of patients developing multiple BCCs, mainly because cancer registries often only collect patient-based and not tumor-based BCC data for reasons explained above. Epidemiological studies with selected and small populations from the US and Australia reported that about 40 to 50% of patients with a prior BCC will develop a subsequent BCC within 5 years after first diagnosis.[11, 16] However these data cannot be generalized to The Netherlands as the other countries have different climates and latitudes with many more sun hours (with higher UV index) per year. In absence of these data, the exact size of BCC occurrence in The Netherlands is difficult to estimate, as the exact proportion of patients developing multiple BCCs remains unknown. Insight into the size of BCC occurrence in The Netherlands is important, as this cancer is becoming a worldwide public health concern and the life time risk for developing a BCC is currently increasing.

Carcinogenesis

Carcinogenesis of BCC is complex and includes multiple genetic alterations, which ultimately lead to growth of a malignant tumor. For BCC carcinogenesis, (UV-induced) mutations in p53 and *PTCH* tumor suppressor genes are important factors.

The p53 gene is the most frequently mutated gene in human cancer and controls signalling pathways involved in cell division and apoptosis.[1, 17-19] Around 50% of the sporadic BCC cases have mutated p53 proteins.[20] The *PTCH* gene controls proliferation and differentiation and encodes a large transmembrane protein which functions as receptor for the *hedgehog* protein in the *hedgehog* signalling pathway.[21] Loss-of-function mutations in *PTCH* or inap-

propriate activation of the *hedgehog* signalling pathway promotes proliferation rather than differentiation and leads to activation of the transmembrane G-protein receptor named Smoothened (*SMO*). Continuously activated *SMO* leads to overexpression of transcription factor *Gli* and downstream target genes, which is considered necessary for BCC development. Somatic loss-of-function mutations in *PTCH* gene are identified in 20% to 40% of the sporadic BCC cases, whereas germ-line mutations or loss of heterozygosity in this gene are associated with the nevoid basal cell carcinoma (or Gorlin's) syndrome.[19] This syndrome is inherited as an autosomal dominant trait and features of this syndrome are early onset of multiple BCC, skeletal abnormalities, jaw cysts, macrocephaly and palmoplantar pits.[22-23]

Risk factors

UV-radiation by sunlight is the best-known risk factor for BCC development. However, its associated risk ratios observed in several epidemiological studies are often less than 1.5.[24-27] Therefore, UV-radiation is not a strong, but a very common risk factor. The most important risk factors associated with BCC are summed in table 1.[1, 24, 26-29] However, a distinction between risk factor profiles of patients who develop one or multiple BCC(s) is not well documented. Identification of BCC patients who are at high risk of developing subsequent lesions may assist physicians in the adequate selection of individuals who should be followed-up more closely over time. Although genome-wide association studies (GWAS) have already detected

Table 1. Risk factors associated with basal cell carcinoma development

Patient characteristics	Relative risks	Risk
Men	1.0 – 1.5 [24, 33]	
Older age	1.1 – 1.4 [24, 33]	
Blond or red hair	1.5 – 1.7 [26-27, 29]	
Blue or green eyes	1.2 – 1.4 [26-27, 29]	
Light skin color	2.3 – 2.7 [26-27, 29, 34]	
History of prior BCC	17.4[35]	22 – 70% (3-yr CR[†]) [16, 28]
Environmental exposures		
Sun exposure	1.5 – 1.8 [25-27, 36]	
Other exposures to ultraviolet light (e.g. sun beds, PUVA)	1.2 – 4.1 [37-39]	
Ionizing radiation	2.6 – 3.3 [40-41]	
Chemicals (e.g. arsenic)	1.4 – 2.0 [42-44]	
Genodermatoses		
Albinism		~ 25%[+ 45-46]
Xeroderma pigmentosum[*]	> 10,000[+ 47-48]	
Nevoid basal cell carcinoma syndrome (Gorlin's syndrome)		38 – 85%[+ 23, 49]
Immunosuppression		
Recipients of solid-organ transplants or other patients with long-term immunosuppressive drug usage	6.4 – 21.0 [50-52]	

[†] CR, cumulative risk

[+] Risks based on case-series only

[*] Characterized by photosensitivity, premature skin aging and multiple skin cancers

more than ten common variants associated with the development of a first BCC (pigmentation- dependent and independent polymorphisms), the clinical and genetic susceptibility to develop multiple BCC has not yet been studied.[30-32]

Clinical presentation and histological appearance

A BCC develops most often on skin that is chronically exposed to the sun and can only develop in skin that contains hair follicles. In contrast with the other keratinocyte skin cancer SCC, which can develop from skin pre-malignancies such as Morbus Bowen or actinic keratosis (AK), BCC has no clear clinical precursor.

BCC occurs as several histological subtypes such as a nodular, superficial, infiltrative or miconodular growing BCC. A nodular (also known as 'solid') BCC is most common (~ 60% of the BCCs) and often has a pearly appearance and telangiectasia that may appear as an (ulcerated) papule or nodule with a shiny border.[53] In histology, large lobules of basaloid cells with peripheral palisading nuclei are seen, projecting into the reticular dermis or deeper.[53] A superficial growing BCC, which is the second most common subtype, presents as a slow growing thin erythematous patch and may resemble eczema or psoriasis. This variant occurs most frequently on the trunk.[54] In histology, superficial growing lobules of basaloid cells are attached to the undersurface of the epidermis and confined to the papillary dermis.[53] Both superficial and nodular BCC can be pigmented. In these cases, brown colored spoke-wheel areas and / or large blue-grey ovoid nests may be seen with dermatoscopy.[55] A sclerosing BCC (also known in literature as 'infiltrative'), typically appear as a pale scar-like lesion with poorly-defined margins. Histologically, this subtype has elongated strands of tumor cells infiltrating into the dermis and subcutis. Also, perineural invasion is particularly associated with this subtype. Another BCC subtype is the micronodular variant. This type clinically resembles a nodular BCC, but is like the infiltrative subtype considered more 'aggressive' because its tumor extension is (clinically) difficult to determine. In contrast to nodular BCCs, small lobules of basaloid cells grow into the dermis and sometimes extend widely into the subcutis. Besides the four common subtypes described above, there are also more rare variants such as a fibroepithelial BCC, BCC with adnexal differentiation, basosquamous carcinoma, keratotic BCC, a cystic, adenoid and infundibulocystic BCC.[53]

In addition, a BCC may contain a mixed histological subtype. Prevalence of mixed cases has been estimated ranging from 9% to 43%, often based on small studies.[56-57] A recent large observational study from Italy among 3513 patients who underwent conventional surgical excision for BCC, observed that mixed histology was found in 17.8% (95% confidence interval 16.5 – 19.%) of the cases, most often including the combination of superficial and nodular growing BCC.[58]

Histologically confirmed BCCs are most often located in the head and neck region, followed by trunk, legs and arms.[28, 54] Population-based incidence data of histological subtypes is not available as cancer registries often only register the anatomical location of the first histo-

logically confirmed BCC and ignore the histological subtype, also because patients may have two BCCs diagnosed simultaneously and it is not clear which BCC subtype should then be registered.

Diagnosis

A skin lesion, clinically suspected for a BCC, is most often diagnosed with punch biopsy in order to exclude other diagnoses and to identify the histological subtype. The latter influences the choice of treatment modality and appropriate surgical excision margins (3 versus 5 millimeter).[59] However, a recent Dutch study with 243 BCCs found that the agreement between BCC subtype on punch biopsy and the subsequent surgical excision in a primary BCC is only 60.9%.[60]

Also, physicians may diagnose and treat BCCs without histological confirmation.[54, 61] This has been suggested as a factor of substantial underestimation of BCC incidence in The Netherlands. It has been assumed that omitting histological confirmation may have become more common over the last decade, because of the introduction of new noninvasive treatments such as photo-dynamic therapy and imiquimod cream, which often have better cosmetic outcome than standard surgery. However, cancer registry and pathology databases cannot include clinically diagnosed BCCs without histological confirmation and therefore limited data about their frequency, location or suspected subtype is available.[54, 61]

Treatment

In The Netherlands, most BCCs are treated with standard surgical excision.[59, 61] The Dutch guideline recommends clinical excision margins of 3 millimeter (mm) for BCC lesions smaller or equal to 10 mm and clinical margins of 5 mm for lesions larger than 10 mm, infiltrative BCCs or recurrences. The five-year recurrence rates after standard surgical excision are around 4 to 10% for primary and 17% for recurrent BCC.[62-64] High risk BCCs or those on delicate sites (e.g., nose and eyelids) are eligible for treatment with Mohs micrographic surgery, which is an elegant tissue sparing method that uses a frozen-tissue technique with microscopic margin control. With this technique, unnecessary excision of uninvolved tissue is avoided, enabling a better preservation of function and cosmesis.[65-66] Compared to other treatment modalities MMS has the highest five-year cure rates ranging from 94% to 99% for primary and from 90% to 96% for recurrent BCCs.[67-69] Nevertheless, Mohs micrographic surgery is time-consuming, labour intensive, and needs specialized assistants and treatment facilities, and is only performed in a limited number of Dutch dermatological centers.[67]

Non-surgical treatments options such as photodynamic therapy, and topical imiquimod and 5-fluorouracil are alternatives for superficial BCCs when surgery is contra-indicated or because of their favorable cosmetic outcome compared to surgical intervention. However, disadvantages of these treatments are the lack of histological control and higher recurrence rates.[1] Therefore, in general, these treatments are not considered optimal for recurrent BCCs,

'aggressive' BCCs or for those BCCs located within the H-zone (i.e., represents the embryonic fusion planes and includes surroundings of eyes, nose, upper lip, pre-auricular regions and ears).[59] In addition, radiotherapy, cryotherapy and curettage with electrodessication are not routinely recommended for BCC treatment in The Netherlands.

Prognosis

The prognosis for patients with BCC is excellent with relative survival rates of around 100%, as they are slow growing and tend to be locally invasive.[70] Nevertheless, significant morbidity and cosmetic disfigurement can occur because BCCs are locally destructive of the skin and may invade underlying tissues such as nerves, muscles and bone (figure 1).[28] Although a BCC is a malignant tumor, metastases are very uncommon with percentages ranging from 0.0028 to 0.55%.[1, 71] Most common sites of metastases are the lymph nodes, bones and lungs. The disease is fatal when it reaches this stage.

Follow-up

Follow-up of BCC patients serves several purposes: (1) (early) detection of a recurrence or (2) a subsequent primary BCC and (3) for psychosocial support for the patient.[72-73] There is no international consensus on a suitable follow-up regime for BCC patients and no evidence-based guideline exists.[74] The British guideline recommends follow-up for at least 3 years for patients treated for recurrent disease or with multiple BCCs only.[73] In contrast, the German guideline suggests annual follow-up visits for all patients with a BCC for at least 3 years.[75] The guidelines of the United States are far more conservative, suggesting at least annual follow-up visits for all patients with a BCC for life.[76] Also, in Australia, all patients with a previous skin cancer are advised to undergo annual skin examinations for life, but as part of routine health checks by their health care provider.[77] In The Netherlands, it is suggested by the most recent Dutch BCC guideline to follow those patients with a BCC in a high-risk zone (e.g. nose and surroundings of the eye) or those patients with two or more BCCs. Follow-up frequency is not determined, but in general once a year is considered sufficient.[59]

Aims of this thesis

In this thesis different aspects of the epidemiology of BCC in The Netherlands are described in order to provide insight to the size of BCC occurrence to all clinicians and policy makers involved in management of these patients. I also present some of the results of the Rotterdam Study, a Dutch large prospective population-based cohort study among participants of 45 years and older living in the Ommoord district of Rotterdam, The Netherlands. Within the framework of the Rotterdam Study, I investigated the prevalence of AK, its risk factors and association with history of skin cancer (including BCC, SCC and melanoma).

The main questions addressed in this thesis are:

1. What are the incidence, prevalence and (future) trends of primary BCC in The Netherlands?
2. What are the cumulative risks and rates of developing a subsequent BCC?
3. How often are clinically suspected BCCs diagnosed without histological confirmation?
4. What are the risk factors associated with the development of single or multiple BCC(s)?
5. What is the prevalence of and what are risk factors for actinic keratosis in The Netherlands

Chapters 2 and 3 of this thesis are based on routinely collected cancer registry data of the Eindhoven Cancer Registry (ECR). ECR is located in the southeast Netherlands and registers since 1973 the first histologically confirmed BCC per patient. In chapter 2 we estimated the incidence, prevalence and future trends of primary BCC in The Netherlands. In chapter 3 current trends in BCC incidence rates were assessed and possible reasons for the increases in BCC incidence rates were explored.

To bridge the gap between known incidence data and a full assessment of the public health burden of BCC in The Netherlands, we investigated how many people developed multiple BCCs. Since 1999, ECR collects more than one BCC per patient according to certain registration rules (see appendix 1), however these data are not assumed completely reliable because of several methodological and practical issues.[78] In **chapter 4** the proportion of patients developing multiple BCCs was therefore investigated with data from PALGA, the nationwide network and registry of histo- and cytopathology in The Netherlands.[79] In **chapter 5** the observed proportion of patients with multiple BCCs in The Netherlands (from chapter 4) was compared to observations from other studies and countries by performing a systematic review and meta-analysis. In addition, the likelihood between a prior BCC and the risk of developing a subsequent SCC or melanoma was assessed.

Cancer registries and pathology databases only contain histologically confirmed BCCs, excluding the occurrence of clinically diagnosed BCCs without histological confirmation. This could underestimate the true size of BCC occurrence in The Netherlands. In **chapter 6** patient records of more than 1000 patients with a prior histologically confirmed BCC from four dermatology departments in The Netherlands were investigated to identify the proportion of clinically diagnosed BCCs without histological confirmation. In **chapter 7** the proportion of clinically diagnosed BCCs (from chapter 6) was compared to observations from Scotland, Finland and Malta.

The final aim of this thesis was to describe risk factors associated with BCC and AK development to provide guidance for primary and secondary prevention to patients, clinicians and health care policy makers. AK is one of the most sensitive markers for skin aging and may be an indicator for the risk of skin cancer. The research described in chapters 8 and 9 was performed using the Rotterdam Study. In **chapter 8** risk factors associated with the development of single and multiple BCC(s) were studied. In **chapter 9** full body skin examinations were performed among 2061 participants to investigate the prevalence of AK, its risk factors

and association with history of skin cancer. To conclude, in **chapter 10**, a summary of the results is given, five research questions are answered, and limitations of the included studies are discussed.

Appendix 1. Rules Non-Melanoma Skin Cancer Registration of the Eindhoven Cancer Registry

Registration of all skin cancers (except melanoma***), with incidence dates starting from 1-1-1999. Registration of localisation takes place according to the ICD-10 code.

Per patient more than one primary skin tumor with the same morphology can be registered according to the following rules:

- In the case of multiple tumors at the same time* on the same sub-localisation**: registration of one primary tumor with the remark "multifocal".
- In the case of multiple tumors at the same time* on different sub-localisations**: registration of a new primary tumor per sub-localisation.
- In the case of a "new" skin tumor at the same sub-localisation** as former skin tumor: regard this tumor as a recurrent tumor, register only the last date of contact and hospital or practice where the tumor was diagnosed.
- In the case of a "new" skin tumor on another sub-localisation ** than the former skin tumor: registration as a new primary tumor.

* At the same time means: incidence dates are within 3 months of each other.

** Same sub-localisation means: Fourth digit of the ICD-10 code AND lateralization are identical.

*** Melanomas are registered according to the rules of the national Dutch Cancer Registration.

REFERENCES

1. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med 2005;353:2262-9.
2. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med 2001;344:975-83.
3. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet 2010;375:673-85.
4. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. N Engl J Med 2004;351:998-1012.
5. Holterhues C, Vries E, Louwman MW, Koljenovic S, Nijsten T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989-2005. J Invest Dermatol 2010;130:1807-12.
6. Flohil SC, de Vries E, Neumann HAM, Coebergh JW, Nijsten T. Incidence, Prevalence, and Future Trends of Primary Basal Cell Carcinoma in the Netherlands. Acta Derm-Venerol 2011;91:24 - 30.
7. Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer 2007;121:2105-8.
8. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012;166:1069-80.
9. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. Int J Cancer 2010;127:2190-8.
10. Christenson LJ, Borrowman TA, Vachon CM, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. Jama 2005;294:681-90.
11. Richmond-Sinclair NM, Pandeya N, Ware RS, et al. Incidence of basal cell carcinoma multiplicity and detailed anatomic distribution: longitudinal study of an Australian population. J Invest Dermatol 2009;129:323-8.
12. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust 2006;184:6-10.
13. Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer 1999;81:555-9.
14. Harris RB, Griffith K, Moon TE. Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona, 1985-1996. J Am Acad Dermatol 2001;45:528-36.
15. Chuang TY, Popescu A, Su WP, Chute CG. Basal cell carcinoma. A population-based incidence study in Rochester, Minnesota. J Am Acad Dermatol 1990;22:413-7.
16. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524-30.
17. Tilli CM, Van Steensel MA, Krekels GA, Neumann HA, Ramaekers FC. Molecular aetiology and pathogenesis of basal cell carcinoma. Br J Dermatol 2005;152:1108-24.
18. Lovatt TJ, Lear JT, Bastrilles J, et al. Associations between ultraviolet radiation, basal cell carcinoma site and histology, host characteristics, and rate of development of further tumors. J Am Acad Dermatol 2005;52:468-73.
19. Rigel DS, Cockerell CJ, Carucci J, Wharton J. Actinic keratosis, basal cell carcinoma and squamous cell carcinoma (chapter 107). Bolognia JL, Jorizzo JL, Rapini RP (eds) In: Dermatology 2nd Edition 2008.
20. Ziegler A, Leffell DJ, Kunala S, et al. Mutation hotspots due to sunlight in the p53 gene of nonmelanoma skin cancers. Proc Natl Acad Sci U S A 1993;90:4216-20.

21. Toftgard R. Hedgehog signalling in cancer. Cell Mol Life Sci 2000;57:1720-31.
22. Gorlin RJ. Nevoid basal cell carcinoma (Gorlin) syndrome. Genet Med 2004;6:530-9.
23. Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet 1997;69:299-308.
24. Kiiski V, de Vries E, Flohil SC, et al. Risk factors for single and multiple Basal cell carcinomas. Arch Dermatol 2010;146:848-55.
25. Kricker A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. Int J Cancer 1995;60:489-94.
26. Rosso S, Zanetti R, Martinez C, et al. The multicentre south European study 'Helios'. II: Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. Br J Cancer 1996;73:1447-54.
27. van Dam RM, Huang Z, Rimm EB, et al. Risk factors for basal cell carcinoma of the skin in men: results from the health professionals follow-up study. Am J Epidemiol 1999;150:459-68.
28. Flohil SC, Koljenovic S, de Haas ER, Overbeek LI, de Vries E, Nijsten T. Cumulative risks and rates of subsequent basal cell carcinomas in the Netherlands. Br J Dermatol 2011;165:874-81.
29. Zanetti R, Rosso S, Martinez C, et al. The multicentre south European study 'Helios'. I: Skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. Br J Cancer 1996;73:1440-6.
30. Stacey SN, Gudbjartsson DF, Sulem P, et al. Common variants on 1p36 and 1q42 are associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits. Nat Genet 2008;40:1313-8.
31. Stacey SN, Sulem P, Masson G, et al. New common variants affecting susceptibility to basal cell carcinoma. Nat Genet 2009;41:909-14.
32. Gudbjartsson DF, Sulem P, Stacey SN, et al. ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat Genet 2008;40:886-91.
33. Karagas MR, Stukel TA, Greenberg ER, Baron JA, Mott LA, Stern RS. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin Cancer Prevention Study Group. Jama 1992;267:3305-10.
34. Gallagher RP, Hill GB, Bajdik CD, et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. Arch Dermatol 1995;131:157-63.
35. Flohil SC, van der Leest RJT, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. 2012 *(submitted)*.
36. Kricker A, Armstrong BK, English DR, Heenan PJ. A dose-response curve for sun exposure and basal cell carcinoma. Int J Cancer 1995;60:482-8.
37. Stern RS, Lange R. Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment. J Invest Dermatol 1988;91:120-4.
38. Zhang M, Qureshi AA, Geller AC, Frazier L, Hunter DJ, Han J. Use of tanning beds and incidence of skin cancer. J Clin Oncol 2012;30:1588-93.
39. Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. J Natl Cancer Inst 1998;90:1278-84.
40. Lichter MD, Karagas MR, Mott LA, Spencer SK, Stukel TA, Greenberg ER. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. Arch Dermatol 2000;136:1007-11.

41. Karagas MR, Nelson HH, Zens MS, et al. Squamous cell and basal cell carcinoma of the skin in relation to radiation therapy and potential modification of risk by sun exposure. Epidemiology 2007;18:776-84.
42. Kennedy C, Bajdik CD, Willemze R, Bouwes Bavinck JN. Chemical exposures other than arsenic are probably not important risk factors for squamous cell carcinoma, basal cell carcinoma and malignant melanoma of the skin. Br J Dermatol 2005;152:194-7.
43. Guo HR, Yu HS, Hu H, Monson RR. Arsenic in drinking water and skin cancers: cell-type specificity (Taiwan, ROC). Cancer Causes Control 2001;12:909-16.
44. Karagas MR, Stukel TA, Morris JS, et al. Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study. Am J Epidemiol 2001;153:559-65.
45. Kromberg JG, Castle D, Zwane EM, Jenkins T. Albinism and skin cancer in Southern Africa. Clin Genet 1989;36:43-52.
46. Opara KO, Jiburum BC. Skin cancers in albinos in a teaching Hospital in eastern Nigeria - presentation and challenges of care. World J Surg Oncol 2010;8:73.
47. Bradford PT, Goldstein AM, Tamura D, et al. Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. J Med Genet 2011;48:168-76.
48. Parren LJ, Frank J. Hereditary tumor syndromes featuring basal cell carcinomas. Br J Dermatol 2011;165:30-4.
49. Tom WL, Hurley MY, Oliver DS, Shah MR, Bree AF. Features of basal cell carcinomas in basal cell nevus syndrome. Am J Med Genet A 2011;155A:2098-104.
50. Jensen AO, Svaerke C, Farkas D, Pedersen L, Kragballe K, Sorensen HT. Skin cancer risk among solid organ recipients: a nationwide cohort study in Denmark. Acta Derm Venereol 2010;90:474-9.
51. Berg D, Otley CC. Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. J Am Acad Dermatol 2002;47:1-17; quiz 8-20.
52. Jemec GB, Holm EA. Nonmelanoma skin cancer in organ transplant patients. Transplantation 2003;75:253-7.
53. LeBoit PE, Burg G, Weedon D, Sarasin A. Pathology and Genetics of Skin Tumors. World Health Organization Classification of Tumors (WHO). Chapter 1. 2006:13-25.
54. Flohil SC, van Tiel S, Koljenovic S, et al. Frequency of non-histologically diagnosed basal cell carcinomas in daily Dutch practice. J Eur Acad Dermatol Venereol 2012 doi: 10.1111/j.1468-3083.2011.04407.x. [Epub ahead of print]
55. Altamura D, Menzies SW, Argenziano G, et al. Dermatoscopy of basal cell carcinoma: morphologic variability of global and local features and accuracy of diagnosis. J Am Acad Dermatol 2010;62:67-75.
56. Sloane JP. The value of typing basal cell carcinomas in predicting recurrence after surgical excision. Br J Dermatol 1977;96:127-32.
57. Cohen PR, Schulze KE, Nelson BR. Basal cell carcinoma with mixed histology: a possible pathogenesis for recurrent skin cancer. Dermatol Surg 2006;32:542-51.
58. Betti R, Radaelli G, Crosti C, Ghiozzi S, Moneghini L, Menni S. Margin involvement and clinical pattern of basal cell carcinoma with mixed histology. J Eur Acad Dermatol Venereol 2012;26:483-7.
59. Dutch Society for Dermatology and Venereology. Evidence-based guideline Treatment of the basal cell carcinoma. http://www.huidarts.info/documents/?v=2&id=69 accessed at August 2nd 2010.
60. Roozeboom MH, Mosterd K, Winnepenninckx VJL, Nelemans PJ, Kelleners-Smeets NWJ. Agreement between histological subtype on punch biopsy and surgical excision in primary basal cell

carcinoma. J Eur Acad Dermatol Venereol 2012 doi: 10.1111/j.1468-3083.2012.04608.x. [Epub ahead of print].
61. Flohil SC, Proby CM, Forreset AD, et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. Br J Dermatol 2012;167:22-9
62. Rowe DE, Carroll RJ, Day CL, Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. J Dermatol Surg Oncol 1989;15:315-28.
63. Rhodes LE, de Rie MA, Leifsdottir R, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol 2007;143:1131-6.
64. Avril MF, Auperin A, Margulis A, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. Br J Cancer 1997;76:100-6.
65. Shriner DL, McCoy DK, Goldberg DJ, Wagner RF, Jr. Mohs micrographic surgery. J Am Acad Dermatol 1998;39:79-97.
66. Muller FM, Dawe RS, Moseley H, Fleming CJ. Randomized comparison of Mohs micrographic surgery and surgical excision for small nodular basal cell carcinoma: tissue-sparing outcome. Dermatol Surg 2009;35:1349-54.
67. Mosterd K, Krekels GA, Nieman FH, et al. Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomised controlled trial with 5-years' follow-up. Lancet Oncol 2008;9:1149-56.
68. Wennberg AM, Larko O, Stenquist B. Five-year results of Mohs' micrographic surgery for aggressive facial basal cell carcinoma in Sweden. Acta Derm Venereol 1999;79:370-2.
69. Julian CG, Bowers PW. A prospective study of Mohs' micrographic surgery in two English centres. Br J Dermatol 1997;136:515-8.
70. de Vries E, Steliarova-Foucher E, Spatz A, Ardanaz E, Eggermont AM, Coebergh JW. Skin cancer incidence and survival in European children and adolescents (1978-1997). Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42:2170-82.
71. Berlin JM, Warner MR, Bailin PL. Metastatic basal cell carcinoma presenting as unilateral axillary lymphadenopathy: report of a case and review of the literature. Dermatol Surg 2002;28:1082-4.
72. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localised primary cutaneous melanoma. Lancet Oncol 2005;6:608-21.
73. Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. Br J Dermatol 2008;159:35-48.
74. European Dermatology Forum http://www.euroderm.org/images/stories/guidelines/guideline_Basal_Cell_Carcinoma.pdf accessed at August 22th 2012.
75. Hauschild A, Breuninger H, Kaufmann R, et al. Short German guidelines: basal cell carcinoma. J Dtsch Dermatol Ges 2008;6 Suppl 1:S2-4.
76. NCCN Clinical Practice Guidelines in Oncology. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp accessed at January 28th 2011.
77. Clinical practice guide: basal cell carcinoma, squamous cell carcinoma (and related lesions) - a guide to clinical management in Australia. http://www.cancer.org.au/File/BasalcellcarcinomaSquamouscellcarcinomaGuideNov2008Final.pdf accessed at April 21th 2011.
78. van der Geer S, Siemerink M, Reijers HA, et al. The burden of skin cancer in dermatology. 2012 *(submitted)*.
79. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29:19-24.

CHAPTER 2

Incidence, prevalence and future trends of primary basal cell carcinoma in The Netherlands

S.C. Flohil

E. de Vries

H.A.M Neumann

J.W.W. Coebergh

T. Nijsten

Acta Derm Venereol 2011;91:24-30

ABSTRACT

Basal cell carcinoma (BCC) incidence rates are increasing worldwide. This study's objective was to estimate occurrence of BCC in The Netherlands in terms of incidence and prevalence. Data on first primary BCC were retrieved from the Eindhoven Cancer Registry and extrapolated to the Dutch population. Extrapolated data showed a total of 444,131 first, histologically confirmed BCCs in The Netherlands between 1973 and 2008. In this period, age-adjusted incidence rates (European Standard population) increased approximately three folds from 40 to 148 per 100 000 in males and from 34 to 141 in females. Life time risk for BCC was 1 in 5-6 for Dutch citizens. BCC prevalence in The Netherlands was 1.4% and almost four times higher (5.4%) in the oldest age group (65 years or more). BCC trend predictions for the future showed no signs of flattening. These estimates should urge Dutch policymakers to provide solutions for this growing group of BCC patients.

INTRODUCTION

Non-melanoma skin cancer (NMSC) is by far the most common cancer in Caucasians and numerous studies have shown that incidence rates, especially of basal cell carcinomas (BCC) are increasing worldwide.[1-5] The burden of BCC is becoming an increasingly important public health issue, because of rapidly increasing incidence rates of patients with a BCC history, the total number of BCC patients and their treatment and follow up related costs.[4, 6-7]

A Dutch population-based survey observed increases in European Standardised BCC incidence rates between 1973 and 2000, from 40 to 92 per 100 000 in men and 34 to 79 per 100 000 in women.[6] Forecasts of BCC incidence in The Netherlands, which were based on data from the Eindhoven Cancer Registry (ECR) for the years 1989 – 2000, estimated an annual incidence rate of 122 per 100 000 for males and 119 for females in 2015.[7]

Main causes of this continuous rise in BCC incidence are the effects of altered UV exposure patterns in the past, population-aging and the increasing number of people with a prior skin cancer diagnosis, who are at high risk of developing subsequent skin cancers, and an increased awareness for skin cancer among patients and physicians (i.e., detection bias). An estimated 40% of patients with a first BCC will develop subsequent tumors in the next 5 years.[8-9]

Whilst BCC has very low mortality, it is associated with considerable functional and cosmetic morbidity as most lesions are located on the face and are most often treated surgically. There is currently a shortage of dermatologists in The Netherlands (about 475 full and part-time dermatologists for a population of 16.4 million) and the rising incidence rates of BCC is putting a heavy burden on the already limited healthcare system in terms of diagnosis, treatment and especially follow up, which represents a substantial proportion of dermatologists' workload.[10]

Earlier predictions for 2015 (made in 2004), warned Dutch policy makers about the need to provide solutions in order to continue to be able to provide sufficient management for the already large and continuously growing group of BCC patients. Direct treatment-related costs depend on the number of treated lesions and selected therapies. In order to make correct workload en cost estimates, we need recent accurate estimates of size of the BCC problem in The Netherlands, which are currently not up-to-date, including estimates on the prevalence of BCC that is lacking.

Therefore, the objective of this study was to reliably estimate occurrence of BCC in The Netherlands with up-to-date data from the ECR in terms of incidence and prevalence. With BCC data available from 1973 until 2008 we were the first to estimate the 19-years prevalence of first, histologically proven BCC in The Netherlands. Additionally, new predictions were made for incidence rates and numbers in The Netherlands for the years 2010, 2015 and 2020.

METHODS

Data

Data were obtained from the Eindhoven Cancer Registry (ECR) which is part of The Netherlands Cancer Registry, located at the Comprehensive Cancer Center South, which is the only population-based cancer registry in The Netherlands that routinely registers the first, histologically proven BCC per patient using the national pathology laboratories network (PALGA) as a signaling source.[6] All individuals with a histologically proven first primary BCC, diagnosed between 1973 and 2008, were included. ECR also registers data concerning BCC body location. During the study period (1st of January 1973 until 1st of January 2009) the population size of the ECR catchment region increased from 591,916 to 2,252 757, mainly due to an expansion of the registry area.[11] Age-adjustment was performed by direct standardization according to the European and World Standard Population (European standardized rates [ESR] and World standardized rates [WSR], respectively). Annual incidence rates were computed per 100 000 person-years for each sex and calculated as 5-year moving means, except for annual incidence by site (3-year moving means).[6]

Statistical analysis

The incidence of the first primary, histologically confirmed BCC was calculated. Number of BCC cases (by sex and eighteen 5-year age groups [0-4, 5-9, 10-14, etc.] were divided by the number of inhabitants in the catchment area of the ECR in those same categories. Sex- and age-specific incidence rates were multiplied by the population size of these specific categories in The Netherlands in the concerning year, resulting in an estimated number of first primary BCC patients in The Netherlands. The population sizes were gained from Statistics Netherlands and estimated on the first of January of the considered year.[12]

The cumulative incidence rates at age 84 were calculated as the sum of the age-specific incidence rates for ages 0-84, multiplied with the width of the age groups (5 year). Cumulative risks were derived from the cumulative incidence rates and calculated with the following formula; Cumulative risk = 100 x (1-exp (cumulative rate/100)).

To calculate the prevalence of BCC in the ECR catchment areas between 1990 and 2008, we retrieved data of the vital status on all patients diagnosed with a BCC since 1990 and still alive on the first of January 2009. Therefore, we used the method previously used for reports on cancer prevalence in The Netherlands.[13]

The predicted numbers of BCC cases in The Netherlands in 2010, 2015 and 2020 were estimated by first predicting the incidence rates on the basis of observed rates for 2000 – 2008, and then multiplying these rates by the population forecasts for these periods, derived from Statistics Netherlands. The statistical models used have been described before and the best fitted model, $Em_{it} = \alpha_i + \beta_i * t$ was chosen.[7, 14]

All statistical analyses were performed using SPSS 15.0 for windows (SPSS inc., Chicago, IL) and p-values were two-sided and considered significant if <0.05.

Table 1. Data of first, primary histologically confirmed BCC cases extrapolated to The Netherlands

First, primary histologically confirmed BCC in Netherlands				
	Men		Women	
	1973	2008	1973	2008
ESR	40	148	34	141
WSR	27	101	22	101
Cumulative risk*	5.0	19.3	5.2	16.3
Total number BCC	1,946	13,891	2,233	15,094

* Calculated at age 84

Abbreviations: BCC, basal cell carcinoma; ESR, European Standard Rate; WSR, World Standard Rate

RESULTS

Incidence data ECR

A total of 48,221 first primary BCC cases were diagnosed in the ECR catchment areas between the 1st of January 1973 and 31st December 2008; of whom 23,918 (49.6%) were men and 24,303 (50.4%) were women. The age-adjusted ESR for BCC increased from 40 to 148 per 100 000 for males and from 34 to 141 per 100 000 for females (Table 1 and Figure 1A). The age-adjusted incidence rates calculated with the WSR rose from 27 to 101 per 100 000 for males and from 22 to 101 per 100 000 for females (Table 1). In this 25-year period the cumulative incidence risk at age 84 for BCC development increased from 5.0% to 19.3% in males and from 5.2% to 16.3% in females (Table 1). This implies that 1 in 5 men and 1 in 6 women had developed a BCC before the age of 85 in 2008.

We plotted the age-adjusted BCC incidence rates stratified by age and sex for the most recent year (2008) in Figure 1B. This Figure showed that up to the age of 60 women had higher BCC incidence rates than men, which turned the other way around after the age of 60.

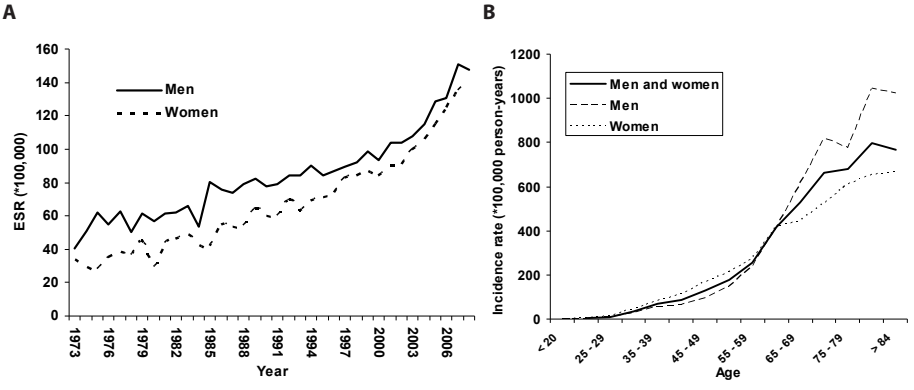


Figure 1.

A. Age-adjusted BCC incidence of first primary BCCs diagnosed between 1973 and 2008 in The Netherlands

B. Age-adjusted BCC incidence of first primary BCCs by age and sex for The Netherlands in 2008

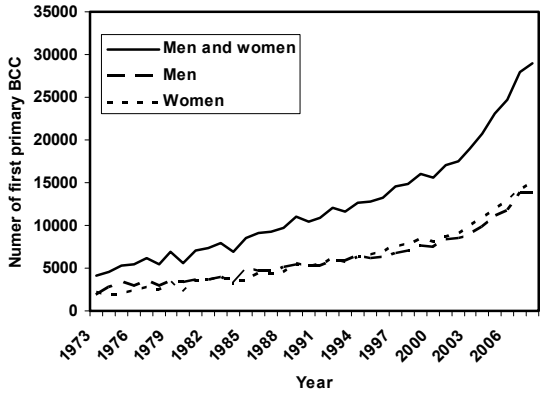


Figure 2. Estimated absolute number of first primary BCCs diagnosed between 1973 and 2008 in The Netherlands

Incidence data extrapolated to The Netherlands

We assumed age-specific ESR of the ECR region to be representative for The Netherlands as a whole. Extrapolating the age-specific incidence rates to the Dutch population sizes estimated a total of 444,131 primary BCC cases diagnosed between 1973 and 2008; of whom 220,758 were men and 223,373 were women. In this study period the total annual number of newly diagnosed BCC patients diagnosed rose from 4,179 to 28,985 (for men from 1,946 to 13,891 and for women from 2,233 to 15,095; Table 1 and Figure 2).

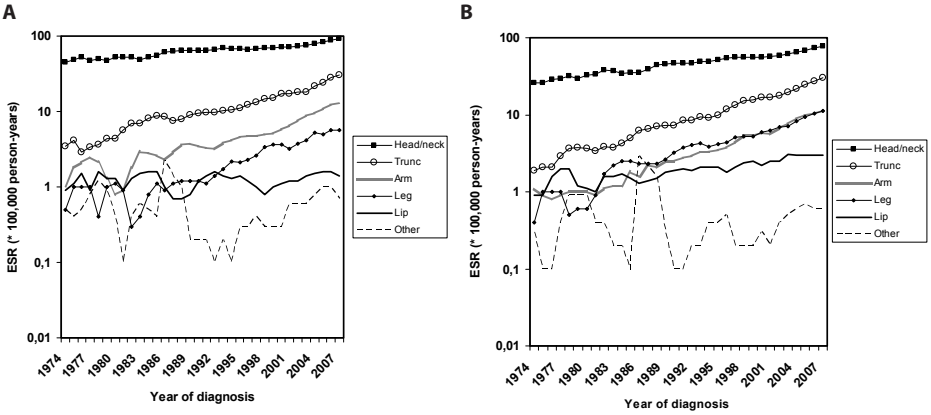


Figure 3.

A. Incidence of BCC by body site for men by 3-year moving average, European Standardized Rates (ESR) (* 100 000 person years)

B. Incidence of BCC by body site for women by 3-year moving average, European Standardized Rates (ESR) (* 100 000 person years)

Incidence data by site

For both sexes BCCs occurred approximately ten folds more likely in the head and neck region compared to the other regions such as trunk and limbs. Men had higher BCC rates in the head and neck region compared to women (Figure 3). There was an increase in rates observed for all sites, with the most prominent increases observed on the trunk and the smallest for the lips, which remained close to 1/100 000 person-years. Extrapolating these estimates to The Netherlands between 1999 and 2008 showed an increase of 280% in women with first BCC on legs, followed by the head and neck region (234%) and arms (216%). For men, the largest increase was seen on trunk (290%), followed by arms (267%) and legs (185%).

BCC prevalence

Of the 39,595 patients with a first, primary BCC diagnosed between 1990 and 31 December 2008, 31,414 (79.3%) patients were still alive on the 1st of January 2009, 7,916 (20.0%) had died and 265 (0.7%) were lost to follow-up. Of the 31,414 BCC patients alive on the 1st of January 2009, 14,904 (47.4%) were men and 16,510 (52.6%) were women. Based on these numbers, the overall prevalence in the ECR catchment areas was estimated to be 1.4% (1.3% and 1.5% for men and women, respectively). The overall 19-year prevalence for age group 65+ was

Table 2. 5- and 19-years prevalence of BCC in The Netherlands

Prevalence	Sex	Age groups	BCC cases	Population	Prevalence (%) (* 100)
5 years	**Total**		16356	2252757	0.7
	Men		7896	1125315	0.7
	Women		8460	1127442	0.8
	Total	15 - 34	224	535445	0.04
		35 - 64	6954	979963	0.7
		65 +	9178	342381	2.7
	Men	15 - 34	85	274553	0.03
		35 - 64	3112	497898	0.6
		65 +	4699	151004	3.1
	Women	15 - 34	139	260892	0.05
		35 - 64	3842	482065	0.8
		65 +	4479	191377	2.3
19 years	**Total**		31414	2252757	1.4
	Men		14904	1125315	1.3
	Women		16510	1127442	1.5
	Total	15 - 34	299	535445	0.06
		35 - 64	12474	979963	1.3
		65 +	18641	342381	5.4
	Men	15 - 34	114	274553	0.04
		35 - 64	5527	497898	1,1
		65 +	9263	151004	6.1
	Women	15 - 34	185	260892	0.07
		35 - 64	6947	482065	1.4
		65 +	9378	191377	4.9

5.4% (6.1% for men and 4.9% women). The overall 5-year prevalence of BCC for the elderly people (65+ years) was 2.7% (3.1% and 2.3% for men and women, respectively; Table 2).

BCC predictions

Trends in BCC incidence for 2010, 2015 and 2020 (estimations based on the data available for 2000 – 2008) increased continuously among all age groups and both sexes. The predicted rates and absolute numbers of BCC showed no signs of flattening or levelling off up to 2020 (Table 3). Compared to the observed rates and numbers in 2005, the steepest increases in 2020 were observed for both sexes in the oldest age group (65+ years), except for the expected rates for women, which had the highest increase in age group 35 - 64.

Trends in BCC incidence by subsite based on the years 2000 - 2008, calculated for the four most common BCC locations, increased constantly (Table 4). Predictions revealed the head and neck area to be the most common site for first, primary BCCs for all predicted years. In 2020 rates for first primary BCCs in men, located on the arm, are expected to have more than two and half times doubled compared with observed rates in 2005. Within women the steepest increase was seen for first, primary BCCs located at trunk (234%). The highest

Table 3. Predicted BCC incidence rates (European Standardised Rates) and numbers by age.

Rates					
BCC	**Age**	**2005**	**2010**	**2015**	**2020**
		Observed	**Expected (95% PI)**	**Expected (95% PI)**	**Expected (95% PI)**
Men	15-34	7.8	9.8 (6.5 - 12.9)	12.2(7.1 - 17.3)	14.6 (7.5 - 21.7)
	35 – 64	136.5	167.6 (155.8 - 179.3)	198.2 (178.9 - 217.5)	228.8 (201.5 - 256.1)
	65 +	658.1	859.9 (813.6 - 906.3)	1067.5 (992.4 - 1142.6)	1275.0 (1169.7 - 21688.8)
	All	139.5	162.7 (155.8 - 169.5)	198.1 (186.9 - 209.3)	233.5 (217.7 - 249.2)
Women					
	15-34	14.2	16.1 (11.9 - 20.3)	18.71 (12.0 - 25.4)	21.3 (12.0 - 30.6)
	35 – 64	160.7	216.0 (202.9 - 229.6)	267.4 (246.0 - 288.8)	318.7 (288.7 - 348.8)
	65 +	458.8	587.3 (556.0 - 618.7)	727.6 (677.5 - 777.8)	867.9 (797.9 - 938.0)
	All	143.7	153.4 (147.2 - 159.6)	189.5 (179.4 - 199.6)	225.6 (211.5 - 239.8)
Numbers					
BCC	**Age**	**2005**	**2010**	**2015**	**2020**
		Observed	**Expected (95% PI)**	**Expected (95% PI)**	**Expected (95% PI)**
Men	15-34	163	195 (131 - 259)	251 (146 - 357)	306 (157 - 456)
	35 – 64	4741	6235 (5798 - 6672)	7335 (6616 - 8054)	8604 (7565 - 9642)
	65 +	6347	9584 (9067 – 10101)	14308 (13300 -15316)	200019 (18350 - 21689)
	All	11250	16011 (15335 - 16687)	21884 (20646 - 23123)	28913 (26943 - 30883)
Women					
	15-34	304	320 (237 - 403)	377 (242 - 512)	418 (238 - 598)
	35 – 64	5463	7846 (7369 - 8323)	9670 (8892 - 10448)	11627 (10514 - 12741)
	65 +	6074	8750 (8301 - 9199)	12252 (11433 - 13072)	16282 (15010 - 17555)
	All	11841	16913 (16248 - 17579)	22288 (21130 - 23447)	28338 (26596 - 30080)

Abbreviations: BCC, basal cell carcinoma; PI, prediction interval.

Table 4. Predicted BCC incidence rates (European Standardised Rates) and numbers by body site

Rates					
BCC	**Site**	**2005**	**2010**	**2015**	**2020**
		Observed	**Expected (95% PI)**	**Expected (95% PI)**	**Expected (95% PI)**
Men	Head/Neck	83.1	100.6 (95.7 - 105.5)	117.2 (109.3 - 125.1)	133.8 (122.7 - 145.0)
	Trunk	26.2	36.0 (33.0 - 39.0)	46.8 (42.0 - 51.5)	57.5 (50.9 - 64.2)
	Arm	10.3	16.2 (14.6 - 17.9)	21.7 (19.2 - 24.3)	27.2 (23.7 - 30.7)
	Leg	5.8	7.3 (6.0 - 8.5)	9.4 (7.4 – 11.4)	11.5 (8.7 - 14.3)
Women	Head/Neck	67.2	85.1 (80.9 - 89.4)	101.0 (94.1 – 107.8)	116.8 (107.2 - 126.3)
	Trunk	24.6	36.0 (33.3 - 38.7)	46.8 (42.6 - 51.0)	57.6 (51.7 - 63.4)
	Arm	9.7	13.9 (12.1 - 15.7)	24.7 (15.3 - 21.1)	22.6 (18.6 - 26.6)
	Leg	9.7	13.5 (12.0 - 15.0)	17.5 (15.1 - 20.0)	21.5 (18.2 - 24.9)
Numbers					
BCC		**2005**	**2010**	**2015**	**2020**
		Observed	**Expected (95% PI)**	**Expected (95% PI)**	**Expected (95% PI)**
Men	Head/Neck	7188	9972 (9487 - 10456)	13221 (12331 - 14111)	17190 (15764 - 18616)
	Trunk	2350	3477 (3189 - 3765)	4945 (4438 - 5451)	6651 (5876 - 7427)
	Arm	907	1579 (1419 - 1738)	2339 (2064 - 2614)	3200 (2780 - 3620)
	Leg	500	721 (597 - 845)	1048 (824 – 1272)	1454 (1099 - 1809)
Women	Head/Neck	7131	9856 (9388 - 10324)	12576 (11762 - 13390)	15785 (14552 - 17018)
	Trunk	2273	3537 (3279 - 3796)	4797 (4371 - 5222)	6083 (5472 - 6694)
	Arm	974	1466 (1280 - 1652)	2083 (1762 - 2403)	2750 (2275 - 3225)
	Leg	989	1491 (1327 - 1655)	2113 (1832 - 2394)	2827 (2405 - 3249)

Abbreviations: BCC, basal cell carcinoma; PI, prediction interval.

increase for predicted BCC numbers in 2020 compared to the observed numbers in 2005 was seen in arms for men (352%) and in legs for women (285%).

DISCUSSION

BCC is the most common skin malignancy in people of European ancestry. The very high incidence rates of BCC observed in the past decades has continued to rise in the last years and is likely to further increase in the next decade. In the last 25 years, the absolute numbers of patients with first, histologically confirmed BCC increased with about 700% in both men and women in The Netherlands. Furthermore, 1:5 and 1:6 of men and women, respectively, will have developed a BCC before the age of 85 years. The 19-year BCC prevalence in the ECR region was 1.4% of the population and was assumed to be representative for The Netherlands in a whole. Although the epidemiology of BCC varies geographically, it is difficult to compare these observations to international studies because very few cancer registries document BCC and its prevalence has not been studied extensively. Nevertheless, other studies confirm the increasing trend of BCC in time.[5, 15] A recent study in the United States based on a mathematical model found a 31-year prevalence of nearly 5% of people with (multiple) skin cancer(s).[16] Although their prevalence was about 3 times higher than ours, we calculated the prevalence

for first primary, histologically confirmed BCC cases alone and our prevalence was not based on a statistical model but on data from a population-based cancer registry.

The ECR does not have reliable data on multiple BCCs. A recent Dutch prospective population-based cohort study among people aged 55+ showed that approximately one third of BCC patients developed multiple BCCs during an average of almost 10 years of follow-up, of whom 18.1% developed two and 12.9% three or more BCCs.[9] Taking these proportions into considerations, the absolute number of BCC tumors in The Netherlands since 1990 might be up to more than 300,000. Moreover, high risk for developing subsequent BCC tumors puts a heavy burden on the dermatologists' restricted time since besides diagnosis and treatment, follow up is extremely time consuming. Although recent revisions of the BCC guideline recommend that only patients with high-risk and/or multiple BCCs should be followed, this means in practice that almost all BCC patients are followed once a year up to 5 years after diagnosis.[17]

Incidence predictions for the future, showed no signs of flattening or levelling off; therefore policymakers and the dermatologic communities should work together on finding a solution to the ever growing burden of BCC. Raised awareness of the population may have contributed to the increase in BCC detection, but the main causes of the 'BCC epidemic' are probably due to aging and life style changes, such as altered UV-exposition patterns in the past. Although earlier skin cancer and sun tanning campaigns have increased awareness among people, they have failed to influence our UV-exposition behavior (so called, 'knowledge-behavior gap').[18-20] The use of commercial sunbeds has been regulated recently in The Netherlands (>18 years of age and joules per exposure are depending on skin type), but it could be banned completely or at least the ability to purchase a sunbed for home use because indoor tanning represents an avoidable risk factor for NMSC.[21] Other strategies than prevention that have to be addressed to deal with the upcoming and already beginning 'BCC epidemic' is to increase workforce of dermatologists and re-evaluate its organizational structure. Therefore investments in supportive professionals such as specialized nurses and nurse practitioners could release pressure of the dermatologist's nowadays already restricted time. Furthermore, technical advances in the management of BCC patients may alleviate the pressure on specialized care. BCC treatments other than surgery, could contribute to a more efficient way to deal with the large group of BCC patients. Although new therapies such as photodynamic therapy and imiquimod have been developed over the last decade, these therapies may not be very effective in reducing the BCC burden. Currently, no new technological perspectives are known that could make BCC care in the future more efficient, although promising research has been done for early stage diagnosis of NMSC with fluorescence detection.[19, 22]

Strengths and limitations

Extrapolating data from ECR gave us an impression of the annual number of newly diagnosed BCC patients in The Netherlands. Nevertheless, demographic factors such as high socio-economic status, (work related) UV-exposition and ethnicity differ across the country; which can influence BCC development.[23-25] Indeed, nationwide age-specific incidence rates of melanoma standardized to the European Standard population do slightly differ from melanoma incidence rates calculated by ECR, however this difference is relatively small (20.0 versus 18.8 ESR, respectively) and indicates an underestimation of our extrapolated BCC estimates.[26]
ECR is the only cancer registry of The Netherlands that registers first, histologically proven BCCs, and is therefore the only database available to calculate estimates of size for BCCs in The Netherlands. In practise BCCs may be treated without histological verification (especially when treated with non-surgical therapies or when a patient has had a previous BCC diagnosis). BCCs based on a clinical diagnosis will therefore not appear in the cancer registry. Although, this likely underestimates the absolute numbers of first histologically proven BCCs in the ECR data and thus in the calculated numbers for The Netherlands, it implies that the BCC incidence numbers are actually even higher than thought. Furthermore, it is almost impossible for ECR to register multiple BCCs per patients, since it would consume lots of limited resources because of its volume and it is difficult to distinguish between primary tumors and recurrences and to decide which of the BCCs that occur on the same day would be the 'first'.
Our observed first, primary BCC numbers by subsite extrapolated to The Netherlands are in concordance with the results of a large Dutch population-based study including more than 11,000 people of 55 years or more, with the head and neck area being the predominant site for BCCs in both studies followed by trunk.[9] Therefore, location by subsite seems to be adequately registered by ECR with PALGA as a signalling source. To validate the prediction methods used, we compared predicted with observed BCC incidence rates and numbers in The Netherlands for the year 2005 (Table 3).[7] The rates and numbers for predicted BCC of 2005 have been re-calculated compared to the previous publication of de Vries et *al.* because of corrections in the registry database, but using the same methodology and based on the corrected data of 1989 – 2000.[7] Observed BCC incidence in 2005 was higher than predicted, suggesting that rates increased faster than assumed based on data from 1989 – 2000 (data not shown). The total number of patients diagnosed with a first BCC in 2005 was 23,091 versus 19,023 (95% PI 17,913 – 20,132) predicted, which is 21% higher. This 21% underestimation of the predicted numbers is likely due to an apparent acceleration of the estimated absolute numbers of first, primary BCCs starting around the year 2000 as is seen in figure 1B. The most probable explanation for this relatively steep acceleration in first, primary BCC incidence rates and numbers is changes in medical practice, i.e. increased (early) detection and more BCCs being diagnosed with histological verification. Other causes could be real accelerations in the increasing trends in BCCs or methodological problems in the prediction models.[27] The time period on which the predictions were based was probably correct, as the increases in incidence were steady over time since 1989. However, our recent predictions made for the future

should be interpreted with caution and be used as guidelines by health care organizations, since BCC rates and numbers will probably be much higher than suggested.

In addition, the advantage of using prevalence data is that the 'multiple' BCCs are of less importance. Patients who have been diagnosed with one or multiple tumors are still 'only' one person; hence the number of prevalent cases is informative. Moreover, since we know from previous studies that within 5 years after diagnosis about 40% of BCC patients have developed multiple tumors, we can apply these numbers to the prevalence data to get a grasp of the multiple BCC problem.[8-9]

CONCLUSION

This observational study shows that BCC is a significant health care issue and that its burden is likely to further increase over time. The incidence and prevalence estimates of BCC should urge policymakers to provide solutions, since this growing group of BCC patients are already and will remain a serious healthcare problem in terms of numbers of patients treated and monitored and related health care costs.

REFERENCES

1. Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. Arch Dermatol 1999;135:781-6.
2. Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer 1999;81:555-9.
3. Buettner PG, Raasch BA. Incidence rates of skin cancer in Townsville, Australia. Int J Cancer 1998;78:587-93.
4. Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer 2007;121:2105-8.
5. Holterhues C, de Vries E, Louwman M, Koljenovic S, Nijsten T. Incidence and Trends of Cutaneous Malignancies in the Netherlands, 1989-2005. J Invest Dermatol 2010;130:1807-12.
6. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. J Invest Dermatol 2004;123:634-8.
7. de Vries E, van de Poll-Franse LV, Louwman WJ, de Gruijl FR, Coebergh JW. Predictions of skin cancer incidence in the Netherlands up to 2015. Br J Dermatol 2005;152:481-8.
8. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524-30.
9. Kiiski V, de Vries E, Flohil SC, et al. Risk factors for single and multiple basal cell carcinomas. Arch Dermatol 2010;146:848-55.
10. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med 2005;353:2262-9.
11. Coebergh JW, Neumann HA, Vrints LW, van der Heijden L, Meijer WJ, Verhagen-Teulings MT. Trends in the incidence of non-melanoma skin cancer in the SE Netherlands 1975-1988: a registry-based study. Br J Dermatol 1991;125:353-9.
12. Statistics Netherlands. http://statlinecbsnl/StatWeb/publication/?DM=SLNL&PA=7461BEV&D1=0&D2=1-2&D3=101-120&D4=23-58&VW=T accessed at January 25th 2010.
13. Signaleringscommissie Kanker: Werkgroep Prevalentie van kanker. Kanker in Nederland. Trends, prognoses en implicatie van zorgvraag. Oisterwijk: Signaleringscommissie kanker van KWF kankerbestrijding 2004.
14. Dyba T, Hakulinen T, Paivarinta L. A simple non-linear model in incidence prediction. Stat Med 1997;16:2297-309.
15. Hoey SE, Devereux CE, Murray L, et al. Skin cancer trends in Northern Ireland and consequences for provision of dermatology services. Br J Dermatol 2007;156:1301-7.
16. Stern RS. Prevalence of a history of skin cancer in 2007: results of an incidence-based model. Arch Dermatol 2010;146:279-82.
17. Nederlandse vereniging voor Dermatologie en Venereologie N. Evidence-based richtlijn. Behandeling van het basaalcelcarcinoom. In: Nederlandse vereniging voor Dermatologie en Venereologie (NVDV) 2007.
18. Guile K, Nicholson S. Does knowledge influence melanoma-prone behavior? Awareness, exposure, and sun protection among five social groups. Oncol Nurs Forum 2004;31:641-6.
19. Holterhues C, de Vries E, Nijsten T. De epidemiologie van huidkanker: zorg om de zorg. Nederland Tijdschr Dermatol Venereol 2009;19:451-5.

20. Schneider S, Zimmermann S, Diehl K, Breitbart EW, Greinert R. Sunbed use in German adults: risk awareness does not correlate with behaviour. Acta Derm Venereol 2009;89:470-5.
21. Woo DK, Eide MJ. Tanning beds, skin cancer, and vitamin D: An examination of the scientific evidence and public health implications. Dermatol Ther 2010;23:61-71.
22. de Leeuw J, van der Beek N, Neugebauer WD, Bjerring P, Neumann HA. Fluorescence detection and diagnosis of non-melanoma skin cancer at an early stage. Laser Surg Med 2009;41:96-103.
23. van Hattem S, Aarts MJ, Louwman WJ, et al. Increase in basal cell carcinoma incidence steepest in individuals with high socioeconomic status: results of a cancer registry study in The Netherlands. Br J Dermatol 2009;161:840-5.
24. Gloster HM, Jr., Neal K. Skin cancer in skin of color. J Am Acad Dermatol 2006;55:741-60; quiz 61-4.
25. Radespiel-Troger M, Meyer M, Pfahlberg A, Lausen B, Uter W, Gefeller O. Outdoor work and skin cancer incidence: a registry-based study in Bavaria. Int Arch Occup Environ Health 2009;82:357-63.
26. Comprehensive Cancer Centre Netherlands. www.ikcnet.nl accessed January 25th 2010.
27. Dyba T, Hakulinen T. Do cancer predictions work? Eur J Cancer 2008;44:448-53.

CHAPTER 3

Trends in basal cell carcinoma incidence rates: a 37-year Dutch observational study

S.C. Flohil

I. Seubring

M.M. van Rossum

J.W.W. Coebergh

E. de Vries

T. Nijsten

J Invest Dermatol 2012 (accepted for publication)

ABSTRACT

Basal cell carcinoma (BCC) incidence rates are increasing. From 1973-2009, data on all first histologically confirmed BCCs were gained from the Eindhoven Cancer Registry to estimate trends in patient-based BCC incidence rates by sex, age group and site in the southeast of The Netherlands. Trends in European age-standardised (ESR) and age- and site- specific incidence rates were assessed by calculating the estimated annual percentage change (EAPC). Between 1973 and 2009, the ESR quadrupled from 40 to 165 per 100 000 person-years for men and from 34 to 157 for women, significantly increasing since 1973 in both sexes, but accelerating from 2002 until 2009 with an EAPC of 6.8% (95% confidence interval [CI] 5.3 to 8.3) for men and 7.9% (95% CI 6.2 to 9.7) for women. Women below forty exhibited a constant linear increase of 6.3% since 1973. Head and neck was most often affected in both sexes, but the steepest increase was seen for the trunk (EAPC men 13%, women 15%).

In the absence of reliable tumour-based rates, these alarming patient-based rates are probably an interesting indicator for the impact of more intensive ultraviolet-exposure in a prosperous European population.

INTRODUCTION

The incidence rates of ultraviolet (UV)-induced skin cancers, including basal cell carcinoma (BCC), are increasing worldwide and are becoming a major public health concern.[1-4] Mortality rates associated with BCC are low (< 0.1%), but localized tissue invasion may induce considerable functional and cosmetic morbidity, especially since the majority of the lesions are located on the face.[5-7] Only few cancer registries record BCC and in most cases only the first histologically confirmed BCC per patient is included.[1, 3-4] This is mainly due to the large number of tumors involved and its associated costs.

In general, BCCs are considered a disease of the elderly.[1, 4, 8] However, a recent large Danish population-based study between 1978 and 2007 showed that the average percentage change in BCC incidence was significantly higher among those younger than forty years than in older persons, especially in women.[1, 3] This was in accordance with most other studies reporting a trend toward higher increase in BCC incidence in younger persons.[9-11] For squamous cell carcinoma (SCC) and melanoma similar increases in rates have been observed for younger persons.[12] An increase in the number of BCC patients, especially in younger age groups, may lead to an exponential rise in the overall occurrence of BCC over time, particularly since the population ages and most likely around 30% will develop subsequent BCCs within 5 years.[13]

A previous study of the BCCs registered in the Dutch Eindhoven Cancer Registry (ECR) from 1973 until 2000, observed significant and consistent increases in BCC rates for both sexes.[14] [9] The objective of this study was to investigate potential changes in trends in the increasing BCC incidence rates by age and site in the southeast Netherlands (latitude 51° north), using up-to-date ECR data until 2009.

RESULTS

Age-standardised incidence rates

Between 1973 and 2009, 52 831 first histologically confirmed BCCs were registered in 52 831 patients recorded in the ECR, corresponding to 26 155 (49.5%) men and 26 676 (50.5%) women. During this 37-year-period, the age-standardised incidence rates increased with approximately a fourfold for both men and women, respectively from 40 to 165 and 34 to 157 per 100 000 person-years (figure 1 and table 1).

The highest relative increase in rates (12-fold) was found in women below forty years, with an increase from 1.82 to 22.2 per 100 000 persons-years, followed by women aged between 40 – 64 years (table 1). For men, this was observed within the oldest age group (4.4-fold), while women in this age group had the lowest increase (3-fold) over time.

For all body sites, the age-standardised BCC incidence rates increased significantly between 1973 and 2009. In 2009, the head and neck region was most often affected in both men and women (99.2 and 85.5 per 100 000 persons-years, respectively). More than 58% of the total number of newly diagnosed BCCs (n = 4 511) in 2009 was located within the head and neck

region. However, during the 37-years of observation, the highest relative increase in rates was found on trunk in men (77-fold), followed by legs (32-fold) and trunk (25-fold) in women (table 1).

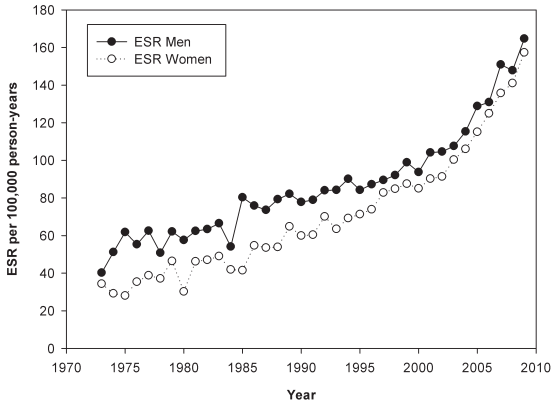


Figure 1. Age-standardised incidence rates (European standardised rates [ESR]) from 1973 to 2009 of first, histologically confirmed basal cell carcinoma in the southeast Netherlands by men and women

Trends by age

Since 1973, a significant increase in patient-based incidence rates was observed with joinpoint analyses for men and women, 2.3% and 3.9% respectively (table 2). Around the years 2002 – 2003 until 2009, this trend accelerated, which resulted in a more than doubled EAPC of 6.8% for men and 7.9% for women. Men within the youngest age group had no significant

Table 1. Age-standardised incidence rates (European standardised rates [ESR]) by age and site from 1973 to 2009 of first, histologically confirmed basal cell carcinoma in the southeast Netherlands

	ESR Men		ESR Women	
	1973	**2009**	**1973**	**2009**
Age (yrs)				
All	40.2	164.7	34.4	157.3
< 40	2.4	9.9	1.8	22.2
40 - 64	53.9	203.1	35.4	242.8
≥ 65	196.6	854.6	199.6	608.8
Site				
Head/neck	37.7	99.2	28.5	85.5
Trunk	0.5	38.7	1.7	41.7
Arms	1.4	15.0	1.8	12.5
Legs	0.5	8.5	0.4	12.8
Lip	0.0	2.4	1.4	4.2

Legend: European standardised rate (ESR) expressed per 100 000 persons-years

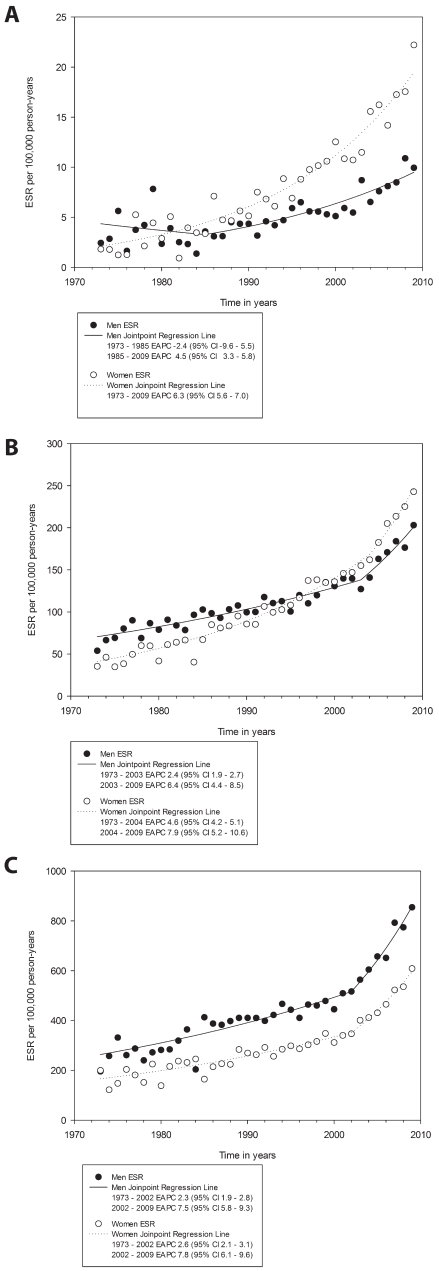


Figure 2. Joinpoint regression lines based on basal cell carcinoma age-standardised incidence rates (European standardised rates [ESR]) from 1973 to 2009 in the southeast Netherlands

A. Men and women < 40 years

B. Men and women 40 - 64 years

C. Men and women ≥ 65 years

Abbreviations: CI, confidence interval; EAPC, estimated annual percentage change (within joinpoint time segment); ESR, European Standardised Rate

Table 2. Time trends in age- and site-specific incidence rates of basal cell carcinoma among men and women in the southeast Netherlands from 1973 to 2009

	Men				Women			
	Trend 1		Trend 2		Trend 1		Trend 2	
	Years[1]	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)
Age (yrs)								
All	1973 - 2002	2.3 (2.0 - 2.7)	2002 - 2009	6.8 (5.3 - 8.3)	1973 - 2003	3.9 (3.5 - 4.2)	2003 - 2009	7.9 (6.2 - 9.7)
< 40	1973 - 1985	-2.4 (-9.6 - 5.5)	1985 - 2009	4.5 (3.3 - 5.8)	1973 - 2009	6.3 (5.6 - 7.0)		
40 - 64	1973 - 2003	2.4 (1.9 - 2.7)	2003 - 2009	6.4 (4.4 - 8.5)	1973 - 2004	4.6 (4.2 - 5.1)	2004 - 2009	7.9 (5.2 - 10.6)
≥ 65	1973 - 2002	2.3 (1.9 - 2.8)	2002 - 2009	7.5 (5.8 - 9.3)	1973 - 2002	2.6 (2.1 - 3.1)	2002 - 2009	7.8 (6.1 - 9.6)
Site								
Head/ neck	1973 - 2003	1.6 (1.2 - 1.9)	2003 - 2009	4.7 (2.3 - 7.1)	1973 - 2004	2.8 (2.4 - 3.1)	2004 - 2009	5.8 (2.8 - 8.8)
Trunk	1973 - 2003	5.6 (4.6 - 6.5)	2003 - 2009	12.8 (8.8 - 17.0)	1973 - 2005	7.8 (7.0 - 8.5)	2005 - 2009	14.8 (9.4 - 20.5)
Arms	1973 - 1998	4.2 (2.5 - 6.0)	1998 - 2009	11.2 (9.0 - 13.4)	1973 - 2009	8.7 (8.0 - 9.5)		
Legs	1973 - 2009	8.1 (6.9 - 9.4)			1973 - 2009	7.8 (7.0 - 8.6)		
Lip	1973 - 2009	0.5 (-0.8 - 1.9)			1973 - 2009	3.2 (2.3 - 4.1)		

[1]Period in years within joinpoint segment.
Abbreviations: CI, confidence interval; EAPC, estimated annual percentage change within joinpoint segment

increase in BCC incidence from 1973 to 1985, whereas after that period the EAPC rose to 4.5% (95% confidence interval [CI] 3.3 – 5.8). For women below forty years, no joinpoint was observed between 1973 and 2009 resulting in an annual linear increase of BCC incidence of 6.3% from 1973 to 2009 (figure 2). From 1973 onwards, the BCC incidence of men and women in age groups 40 – 64 and ≥ 65 years increased steadily over time, with EAPCs ranging from 2.3 to 4.6% (figure 2). Around the years 2002 – 2004, this pattern significantly altered according to the joinpoint analysis and trends in BCC incidence accelerated, with the highest EAPC of 7.9% (95% CI 5.2 – 10.6) found in women aged between 40 and 64 years (table 2).

Trends by site

All body sites exhibited significant increases in BCC rates, except for the lip in men (table 2). The head and neck region was the most commonly affected site for BCC during the whole study period, but showed the lowest annual increase in rates per year (4.7% in men and 5.8% in women). In the last 4 to 6 years prior to 2009, steep increases were especially seen for BCC on the trunk in men (EAPC 12.8%) and women (EAPC 14.8%). From 1998 onwards, a similar acceleration in rates was observed for BCCs on arms in men. For BCC located on the legs, there was a constant linear increase in rates (table 2).

BCC cumulative risk

In 2009, the cumulative risk for developing a first histologically confirmed BCC before the age of 40 years was higher in women (0.9%) than in men (0.4%) corresponding to 1 in 112 and 1 in 250 respectively. When expanding the risk set to 65 years, again women were more often

affected by BCC than men (7.0% [1 in 14] versus 5.5% [1 in 18]). However, the lifetime BCC risk for men was approximately 1 in 5 (21%) and 1 in 6 (18%) for women.

DISCUSSION

In 2009, more Dutch citizens were newly diagnosed with BCC than with any other cancer.[15] Elderly people were most often affected by BCC, but increases in BCC occurrence were steepest among young women, which is in line with other observational studies.[3, 10] Between 1973 and 2009, women aged forty years or less showed the most rapid increase in BCC rates compared to other age groups. Young women were also the only subgroup with a high constant linear increase in BCC rates over the last 37 years. Since 2002, accelerations in the speed of increase of incidence were also noted among older women and in men.

The continuous increment was not restricted to BCC incidence. The melanoma and SCC incidence increased significantly in young people but this is even more pronounced in elderly.[12,16] In accordance with previous studies, BCC were predominantly located in the chronically UV - exposed head and neck region.[13, 17] However, the steepest acceleration in site-specific BCC rates was detected on the trunk, most likely due to more frequent intermittent UV - exposure (e.g., more people travelling, wearing a bikini and practicing outdoor activities) of otherwise covered body parts.[18]

Accelerating increase in BCC rates

From 2002 onwards, we observe an acceleration in the increase in BCC rates. Interestingly, we also observed a jointpoint for SCC trends in the same year with an EAPC of 9.2% for women and 6.9% for men[19], but not in trends of melanoma incidence using nationwide cancer registry data.[2] This deviation from the trend in incidence of keratinocyte carcinomas (BCC and SCC) may be due to several factors. An increased awareness of cutaneous malignancies in the general population due to skin cancer prevention campaigns may have led to more skin checks and diagnoses of previously undiagnosed KCs. Also, the number of practicing dermatologists in the ECR region may have increased. This, together with the fact that clinicians are more aware of skin cancer and more often perform full body skin examinations, increases the likelihood of KCs being diagnosed.[20-21] The fact that the most marked increase in incidence is on the trunk is also consistent with increased surveillance as suggested previously.[21] Although the rise in melanoma incidence can partly be explained by overdiagnosis through improvement of histological diagnostic criteria, this is probably not the case for BCC.[22] An increased detection rate of BCC in cancer registries based on pathology reports may also be induced by changes in healthcare organization and/or reimbursement of care. The jointpoint for BCC was observed in 2002, however market forces were introduced much later in the Netherlands, namely in 2006, stimulating Dutch clinicians to treat non-life threatening BCCs

more rigorously than before (e.g. surgical excision instead of cryotherapy, curettage, electrodissection or a wait-and-see policy in elderly with multiple co-morbidities). This resulted in more histopathologically confirmed BCCs. It is unlikely that improved processes within the registry resulted in a higher capture rate and explain the changes in BCC and SCC incidence as there is substantial continuity in the registration staff (personal communication Eindhoven Cancer Registry). The demographic changes in the Dutch population (i.e., gender and age) were adjusted for in the analyses and therefore cannot explain the increase in BCC either. In fact, the proportion of people with dark skin, protective of skin cancer, increased during the study period which would in theory lead to dilution of risk.[23-25] The most plausible explanation is increased UV- exposure due to outdoor leisure activities and sports since the 1950's when weekly working hours were reduced and the number of holidays were increased.[18] In the early 1980's air travel became less expensive and more accessible to the general Dutch population encouraging people to travel to sunny destinations.[26] Furthermore in the last decade sunbed use has increased dramatically, particularly in younger populations.[27] In the Netherlands, the popularity of sunbed use started around 1990, but regulatory changes have only been introduced recently.

Implications

Knowledge about sun protective behaviour is considered to be relatively good among the European population, but informing people about adverse effects (of the sun) does not necessarily induce changes in risk behaviour[28-30] because despite multiple prevention campaigns the 'knowledge-behaviour gap' remains.[1, 28, 31-34] Therefore, more effective interventions focused on specific subgroups of the populations to influence skin cancer risk behaviour should be explored. More strict legislations should be considered, for example, restricting sunbed use to persons of eighteen years or older. The growing number of skin cancers will place increasing demands on health care providers, i.e., more dermatologists, nurse practitioners and physician assistants specialized in skin cancer may be required. Also, general physicians and (plastic-)surgeons might wish to be more informed about diagnosis and treatment of cutaneous (pre)malignancies.

Moreover, the fast growing number of (young) BCC patients emphasises the need to increase skin cancer awareness among all clinicians to improve the case-finding strategy among those involved in skin cancer care (e.g., general practitioners, dermatologists and [plastic-] surgeons). BCCs should be part of the differential diagnosis in persistent solitary skin lesion even in younger persons.

Strengths and limitations

The ECR reports the first histologically confirmed BCC per patient, ignoring BCCs that were clinically diagnosed and treated without histological confirmation. Therefore, the incidence rates provided within this study are probably an underestimation of the true BCC incidence.

The degree of underestimation is likely to be small as a previous Dutch study observed that 7% of all subsequent BCCs in patients with prior BCC were not histologically diagnosed.[35-36] Unfortunately, there is no information available on the proportion of non-histologically diagnosed BCC before this study of 2012.

It was assumed that the age-standardised BCC rates calculated with population-based data from the ECR were representative for the Netherlands as a whole[1], although other demographic factors such as socio-economic status and ethnicity that affect BCC risk may vary across the country. However, age-standardised incidence rates of melanoma based on nationwide data from 2009 differed only slightly from the rates calculated with data from ECR (22.8 versus 19.6, respectively), indicating a minor underestimation when extrapolating our BCC estimates).[15]

The non significant trend in rates observed among men under forty from 1973 to 1985 is probably due to the small number of men with BCC in this age category during that period.

CONCLUSION

In addition to the continuous increase in BCC incidence rates, an alarming acceleration in BCC rates was observed after 2002 in the southeast of The Netherlands. Besides emphasising the need for effective primary preventative skin cancer strategies, these results are a warning to our society. Governments together with health professionals need to respond more actively and differently to this 'BCC-epidemic' to stabilize and ultimately decrease BCC rates in the future.

MATERIAL AND METHODS

Data collection

For BCC incidence, we used patient-based data from ECR, which is part of the Netherlands Cancer Registry and located at the Comprehensive Cancer Centre South. ECR is the only population-based cancer registry in the Netherlands that routinely registers the first, histologically confirmed BCC per patient using PALGA, the nationwide network and registry of histo- and cytopathology as a signaling source.[1, 37] PALGA contains all excerpts of pathology reports and has nationwide coverage since 1991 based on all dutch laboratories which gave their excerpts to the cancer registry.[37] In this study, all individuals with a first, histologically confirmed BCC diagnosed between 1973 and 2009 were obtained from ECR.[38] During this period (January 1st 1973 to January 1st 2010), primarily due to expansion of the registry area, the number of inhabitants within the ECR catchment area increased from 591 916 to 2 261 967.[14]

Statistical analysis

First, the crude incidence of the first histologically confirmed BCC per patient was calculated. Numbers of BCC cases, subdivided by sex and eighteen 5-year age groups (0 – 4, 5 – 9, 10 – 15, etc), were divided by the number of inhabitants in the ECR catchment area in these same categories. Then, age-standardized incidence rates were calculated for sex by age group and site by direct standardization to the European Standard Population (European Standardized Rates [ESR]), expressed per 100 000 person-years.[1]

BCC site was coded according to the International Classification of Diseases for Oncology (ICD-O-3) and categorized into: head and neck, trunk, arms, legs, lips and other.[38] Given the small number of BCC cases within category 'other', these data have not been reported in this study. 'Age' at date of first histologically confirmed BCC was (a priori) subdivided into three groups, < 40 years, 40 – 64 years and ≥ 65 years.

Trends in BCC incidence rates were assessed, by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (CI), with the joinpoint regression model. The latter identifies the year in which a significant change in rates occurred.[12, 39] To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as a regressor variable (i.e., $y = ax + b$, where $y = \ln(\text{rate})$ and x = calendar year, then EAPC = $100 \times (e^a - 1)$). Trends in incidence rates were described for site and age group by sex. Statistical analyses were performed with Joinpoint version 3.5.2 obtained from the National Cancer Institute (http://surveillance.cancer.gov/joinpoint).

The cumulative risk of developing a BCC before ages 40, 65 and 85 years (the latter considered as BCC lifetime risk) was calculated for the year 2009. First, the cumulative incidence rates of BCC occurrence before ages 40, 65 and 85 years were calculated as the sum of the sex – and age - specific incidence rates for ages 0 – 39, 0 – 64 and 0 – 84, respectively and multiplied by the width of the age groups (5-years). Then, cumulative risks were calculated from the cumulative incidence rates using the following formula: cumulative risk = $100 \times (1 - \exp(\text{cumulative rate}/100))$.[1]

Acknowledgements

We thank all staff from Eindhoven Cancer Registry for dedicated data collection and disposition. We thank Loes Hollestein for statistical assistance.

REFERENCES

1. Flohil SC, de Vries E, Neumann HAM, Coebergh JW, Nijsten T. Incidence, Prevalence, and Future Trends of Primary Basal Cell Carcinoma in the Netherlands. Acta Derm-Venerol 2011;91:24 - 30.
2. Holterhues C, Vries E, Louwman MW, Koljenovic S, Nijsten T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989-2005. J Invest Dermatol 2010;130:1807-12.
3. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of non-melanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. Int J Cancer 2010;127:2190-8.
4. Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer 2007;121:2105-8.
5. Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. Arch Dermatol 1999;135:781-6.
6. Jensen AO, Bautz A, Olesen AB, Karagas MR, Sorensen HT, Friis S. Mortality in Danish patients with nonmelanoma skin cancer, 1978-2001. Br J Dermatol 2008;159:419-25.
7. Lewis KG, Weinstock MA. Trends in nonmelanoma skin cancer mortality rates in the United States, 1969 through 2000. J Invest Dermatol 2007;127:2323-7.
8. Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer 1999;81:555-9.
9. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. J Invest Dermatol 2004;123:634-8.
10. Christenson LJ, Borrowman TA, Vachon CM, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. Jama 2005;294:681-90.
11. Bivens MM, Bhosle M, Balkrishnan R, Camacho FT, Feldman SR, Fleischer AB, Jr. Nonmelanoma skin cancer: is the incidence really increasing among patients younger than 40? A reexamination using 25 years of U.S. outpatient data. Dermatol Surg 2006;32:1473-9.
12. Purdue MP, Freeman LE, Anderson WF, Tucker MA. Recent trends in incidence of cutaneous melanoma among US Caucasian young adults. J Invest Dermatol 2008;128:2905-8.
13. Flohil SC, Koljenovic S, de Haas ER, Overbeek LI, de Vries E, Nijsten T. Cumulative risks and rates of subsequent basal cell carcinomas in the Netherlands. Br J Dermatol 2011;165:874-81.
14. Coebergh JW, Neumann HA, Vrints LW, van der Heijden L, Meijer WJ, Verhagen-Teulings MT. Trends in the incidence of non-melanoma skin cancer in the SE Netherlands 1975-1988: a registry-based study. Br J Dermatol 1991;125:353-9.
15. Comprehensive Cancer Centre Netherlands. http://cijfersoverkanker.nl/selecties/dataset_2/img4f14099bd3b6c accessed at March 15th 2012.
16. Jemal A, Saraiya M, Patel P, et al. Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006. J Am Acad Dermatol 2011;65:S17-25 e1-3.
17. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 2002;147:41-7.
18. Randle HW. Suntanning: differences in perceptions throughout history. Mayo Clin Proc 1997;72:461-6.

19. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: Increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer 2012;48:2046-53.
20. Bastiaens MT, Hoefnagel JJ, Bruijn JA, Westendorp RG, Vermeer BJ, Bouwes Bavinck JN. Differences in age, site distribution, and sex between nodular and superficial basal cell carcinoma indicate different types of tumors. J Invest Dermatol 1998;110:880-4.
21. Valery PC, Neale R, Williams G, Pandeya N, Siller G, Green A. The effect of skin examination surveys on the incidence of basal cell carcinoma in a Queensland community sample: a 10-year longitudinal study. J Investig Dermatol Symp Proc 2004;9:148-51.
22. Weyers W. The 'epidemic' of melanoma between under- and overdiagnosis. J Cutan Pathol 2012;39:9-16.
23. Kiiski V, de Vries E, Flohil SC, et al. Risk factors for single and multiple Basal cell carcinomas. Arch Dermatol 2010;146:848-55.
24. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med 2005;353:2262-9.
25. Statistics Netherlands http://www.cbs.nl/ accessed at March 15th 2012
26. Statistics Netherlands http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=03770&D1=2&D2=a&VW=T accessed at July 2nd 2012.
27. Levine JA, Sorace M, Spencer J, Siegel DM. The indoor UV tanning industry: a review of skin cancer risk, health benefit claims, and regulation. J Am Acad Dermatol 2005;53:1038-44.
28. Suppa M, Cazzaniga S, Fargnoli MC, Naldi L, Peris K. Knowledge, perceptions and behaviours about skin cancer and sun protection among secondary school students from Central Italy. J Eur Acad Dermatol Venereol 2012 doi: 10.1111/j.1468-3083.2012.04484.x. [Epub ahead of print]
29. Paul C, Tzelepis F, Parfitt N, Girgis A. How to improve adolescents' sun protection behavior? Age and gender issues. Am J Health Behav 2008;32:387-98.
30. Peacey V, Steptoe A, Sanderman R, Wardle J. Ten-year changes in sun protection behaviors and beliefs of young adults in 13 European countries. Prev Med 2006;43:460-5.
31. Schneider S, Zimmermann S, Diehl K, Breitbart EW, Greinert R. Sunbed use in German adults: risk awareness does not correlate with behaviour. Acta Derm Venereol 2009;89:470-5.
32. Garbe C, Buettner PG. Predictors of the use of sunscreen in dermatological patients in Central Europe. Prev Med 2000;31:134-9.
33. Jones SE, Saraiya M, Miyamoto J, Berkowitz Z. Trends in sunscreen use among u.s. High school students: 1999-2009. J Adolesc Health 2012;50:304-7.
34. Devos SA, Baeyens K, Van Hecke L. Sunscreen use and skin protection behavior on the Belgian beach. Int J Dermatol 2003;42:352-6.
35. Flohil SC, van Tiel S, Koljenovic S, et al. Frequency of non-histologically diagnosed basal cell carcinomas in daily Dutch practice. J Eur Acad Dermatol Venereol 2012 doi: 10.1111/j.1468-3083.2011.04407.x. (Epub ahead of print).
36. Flohil SC, Proby CM, Forreset AD, et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. Br J Dermatol 2012; 167 (Suppl 2): 22-29.
37. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29:19-24.
38. Fritz A, Percy C, Jack A, et al. International Classification of Diseases for Oncology (ICD-O), Third Edition. Geneva, World Health Organisation (WHO) 2000.
39. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335-51.

CHAPTER 4

Cumulative risks and rates of subsequent basal cell carcinomas in The Netherlands

S.C. Flohil

S. Koljenović

E.R.M. de Haas

L.I.H. Overbeek

E. de Vries

T. Nijsten

Br J Dermatol 2011;165:874-81

ABSTRACT

Background

The incidence of multiple basal cell carcinomas (BCCs) is not well documented.

Objectives

To calculate the cumulative risks, rates and risk factors for the development of subsequent histology confirmed BCCs.

Methods

For this cohort study the Dutch nationwide network and registry of histo- and cytopathology (PALGA) was used. The first 2,483 patients diagnosed with a first histologically confirmed BCC in the year 2004 were followed for 5 years. Multifailure survival models were used to study whether gender or age affected the risk of developing subsequent tumors.

Results

During our observational period, the 2,483 patients developed a total of 3,793 histologically confirmed BCCs. The five year cumulative risk of developing one or more subsequent BCCs was 29.2%. Incidence rates were 25,318 per 100 000 person-years in the first half year after first BCC diagnosis, decreasing to 6,953 per 100 000 person-years after 5 years of follow-up. Males compared to females had a 30% (adjusted HR 1.30 [95% CI 1.11 – 1.53]) higher risk of developing multiple BCCs and those aged 65 – 79 years had more than 80% (adjusted HR 1.81 [95% CI 1.37 – 2.41]) higher risk of having subsequent tumors compared to patients younger than 50 years.

Conclusions

The high incidence rate of subsequent BCCs among patients with a first BCC is highest in the first months after diagnosis of the first BCC but persists long-term, indicating that BCC patients should undergo full body skin examinations at first presentation and subsequent follow-up visits. Special attention should be paid to males and persons of older age at index lesion.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer among Caucasians and is an increasing health problem.[1-4] In The Netherlands, the European age-standardized incidence rate increased more than threefold between 1973 and 2008. In 2008, about 30,000 of the 16 million Dutch citizens were diagnosed with a first primary histologically confirmed BCC.[4]

Currently, no internationally accepted follow-up guidelines for BCC patients are available. According to the Dutch guideline, only patients with two or more BCCs or a BCC located in a high risk zone (e.g. nose and surroundings of the eyes) should be followed.[5] The British guideline recommends follow-up for at least three years for patients treated for recurrent disease or with multiple BCCs.[6] In contrast, the German guideline suggests annual follow-up visits for all BCC patients for at least three years[7]. The guidelines of the USA and Australia are even more conservative, suggesting at least annual follow-up visits for all BCC patients for life.[8-9]

Previous studies have recognised that follow-up visits serve important purposes such as psychosocial support in patients and (early) detection of recurrent and/or second primary tumors.[10] In some studies, but not all, patients with prior BCC are at increased risk for second (invasive) primary cancers, such as keratinocytic cancers, melanoma, non-hodgkin lymphoma and cancers of the lip and salivary glands.[11-13]

Although epidemiological studies with selected and small populations from the USA, Australia and The Netherlands reported that about 30 - 40% of patients with prior BCC will develop further BCC(s) within 5 years after first diagnosis, no information from larger general population-based datasets is available because cancer registries do not record all multiple BCCs.[14-16] Such data is valuable, since it can bridge the gap between known incidence data and a full assessment of the public health burden of BCC in The Netherlands.

Limited reports have been published about risk factors for subsequent BCC(s) after a first BCC.[15, 17] A Dutch prospective cohort study observed that patients with red hair, those with higher socio-economic status, and those with a BCC located on their upper extremities have a higher risk of developing multiple BCCs. A recent study in Australia found that males and those aged 60 years or more are associated with the highest BCC counts among those affected.[15, 17]

More population-based research is needed, since the proportion of patients with multiple BCCs and the rate at which multiple BCCs occur has rarely been documented. Our aim was to reliably estimate the occurrence of subsequent histologically confirmed BCCs among 2,500 patients with a first histologically confirmed BCC in the year 2004. Here, we reported the cumulative risks, incidence rates and risk factors for the development of subsequent BCC(s) in The Netherlands, based on data of PALGA, the nationwide network and registry of histo- and cytopathology.

MATERIAL AND METHODS

Study population

In The Netherlands all histopathology and cytopathology reports are collected in PALGA. The PALGA database is an archive, which encompasses data from all 64 pathology laboratories in The Netherlands, and contains excerpts of all pathology reports with nationwide coverage from 1991 onwards. Each excerpt encloses encrypted patient data, a summary of the pathology report and a diagnosis line based upon standard pathology terminology similar to the Systematised Nomenclamenture of Medicine (SNOMED) issued by the College of American Pathologist.[18] Individuals in the database have an encrypted patient identification code, which enables linkage with all available pathology data within PALGA of this code. The latter allows us to follow individual patients for subsequent histology, irrespective of where (in which hospital in The Netherlands) biopsies or excisions were performed. Our search in PALGA was based on codes corresponding to all types of BCC (i.e. M80903, M80913, M80923, M80931, M80933, M80943, M80953, M80973 and M80983). We extracted the first 2,500 individuals of the year 2004 whose pathology reports were marked, for the first time in their lifetime, with one of the corresponding codes. Follow-up of subsequent BCC histology were obtained until 5 years after first BCC diagnosis. Since vital status is not registered by PALGA, we calculated for all patients the expected vital status based on the sex specific life-expectancy at age of first BCC diagnosis (data obtained from Statistics Netherlands).[19] Based on these population life-tables a fictive date of death was calculated; resulting in the expectation that during our 5 years of follow-up a total of 128 (5.1%) patients had died (of unknown cause).

Case definition

BCC case definitions were generated in cooperation with an experienced dermatopathologist. For most patients within the PALGA database anatomical location of BCC was mentioned in the reports. When the anatomical location was present, it was possible to distinguish between single and multiple tumors within a patient. However, in a small number of patients no tumor location was available in one or more subsequent pathological reports. In these cases we assumed that the biopsy followed by excision was the same tumor. In situations where the margins of the previous excision were tumor free, the next BCC reported was counted as a different tumor, irrespective of the location. When the margins of the preceding excision were not tumor free, the next reported tumor on the same/ adjacent location was considered the same BCC.

We assumed that subsequent BCCs reported within six months of the very first date of BCC diagnosis (index date), were already (clinically) present at index date. Therefore, we counted the date of the first reported BCC (index lesion) as the index date for all subsequently reported BCCs within the period of six months.[15] The BCC count was continuous; patients with multiple BCCs were defined as having 2 or more BCCs in the 5 years of study period. The body site of BCC was classified by dividing the body surface area into 20 distinct regions

(table 1). Histological subtypes were categorized into: infiltrative (including sclerosing and morpheaform), micronodular, nodular (including nodulocystic, adenoid and basosquamous types) and superficial. In mixed type BCC a superiority rule was used according to the most unfavourable subtype: infiltrative > micronodular > nodular > superficial.

Data analysis

The cumulative risks were estimated as the number of patients with 2 or more BCCs divided by the number of patients at risk, expressed in percentages. Person-based incidence rates were calculated as the number of people with multiple BCCs divided by the total number of person-years at risk, expressed per 100 000 person-years. Person-years were counted from date of diagnosis of the first BCC until either second BCC, date of death or the end date of observation (five years after BCC index date), whichever came first.
When estimating the annual number of patients with one or more additional BCC(s), patients could be counted more than once when having additional BCC(s) spread over the 5 observational years (table 3).
Differences in distribution of demographic factors between patients with one and multiple BCC(s) were compared, using the Pearson chi-square test (data not shown). The Andersen-Gill recurrent event survival analysis was performed to calculate the association between the risk factors and the development of subsequent BCC(s). This multifailure survival analysis has the advantage that it models the repeated occurrence of tumor episodes for each person as separate observations but adjusts for the relatedness of observations within one person.[20] Proportional hazard assumptions, tested by examining the interaction between the risk estimates (sex and age at index date) and event time, were not violated. BCCs occurring within six months of the index date, and therefore counted as additional BCCs at index date, were counted as separate BCCs in the multifailure analysis with one day time interval between occurrences compared to the index lesion. In the multivariate model, the risk estimates were adjusted for age at index BCC (continuous variable) and sex. For all data analyses, SPSS statistical software version 17.0 (SPSS Inc, Chicago, Illinois) was used, except for the Andersen-Gill recurrent event survival analysis, for which SAS statistical software version 9.2 (SAS institute Inc, Cary, North Carolina) was used.

RESULTS

Study population

Of the 2,500 Dutch patients with a first histological confirmed BCC in 2004 2,483 (99.3%) were included in our study population. BCC cases were excluded from our study when the pathology reports were incomplete (n=2) or when the PALGA code did not correspond to the PALGA excerpt (n=15). The date of first diagnosis of BCC was between January 1st 2004 and March 29th 2004. Of the 2,483 included patients, 1,224 (49.3%) were males and 1,259 (50.7%)

Table 1. Characteristics of the 3,793 basal cell carcinomas developed in 2,483 patients during a total follow-up time of 12,297 person-years

Number of tumors (total follow-up time of 12,297 persons-years)	**Number of patients (%) (n=2483)**
1	1796 (72.3%)
≥ 2	687 (27.7)
Number of tumors at index date*	**Number of patients (%) (n=2483)**
1	2204 (88.8)
≥ 2	279 (11.2)

Tumor site	**Total study population number of tumors (%)†**	**Patients with 1 BCC number of tumors (%)†**	**Patients with multiple BCCs number of tumors (%)†**
	(n= 3793)	**(n= 1796)**	**(n = 1997)**
Head and neck	**2296 (60.5)**	**1225 (68.2)**	**1071 (53.6)**
Scalp	60 (1.6)	28 (1.6)	32 (1.6)
Temporal areas	293 (7.7)	138 (7.7)	155 (7.8)
Forehead	341 (9.0)	176 (9.8)	165 (8.3)
Retro- and preauriculair areas	122 (3.2)	57 (3.2)	65 (3.3)
Cheeks	238 (6.3)	131 (7.3)	107 (5.4)
Nose / surroundings of the nose	441 (11.6)	263 (14.6)	178 (8.9)
Nasolabial fold and upper lip	129 (3.4)	68 (3.8)	61 (3.1)
Lower lip and chin	37 (1.0)	13 (0.7)	24 (1.2)
Jaw	26 (0.7)	12 (0.7)	14 (0.7)
Ears	97 (2.6)	55 (3.1)	42 (2.1)
Eyebrow areas / eye surroundings	286 (7.5)	180 (10.0)	106 (5.3)
Head, specific location unkown	58 (1.5)	34 (1.9)	24 (1.2)
Neck	168 (4.4)	70 (3.9)	98 (4.9)
Trunk	**935 (24.7)**	**327 (18.2)**	**608 (30.4)**
Back and shoulders	530 (14.0)	169 (9.4)	361 (18.0)
Thorax	310 (8.2)	120 (6.7)	190 (9.5)
Abdomen	89 (2.3)	36 (2.0)	53 (2.7)
Trunk, specific location unkown	6 (0.2)	2 (0.1)	4 (0.2)
Upper extremities	**157 (4.1)**	**66 (3.7)**	**91 (4.6)**
Lower extremities	**247 (6.5)**	**95 (5.3)**	**152 (7.6)**
Other (pelvic/anogenital area, buttocks)	**19 (0.5)**	**15 (0.8)**	**4 (0.2)**
Missing	**139 (3.7)**	**68 (3.8)**	**71 (3.6)**
Tumor histology	**Number of tumors (%)**	**Number of tumors (%)**	**Number of tumors (%)**
	(n= 3793)	**(n= 1796)**	**(n = 1997)**
Nodular	2214 (58.4)	1140 (63.5)	1074 (53.8)
Superficial	674 (17.7)	187 (10.4)	487 (24.4)
Infiltrative	542 (14.3)	298 (16.6)	244 (12.2)
Micronodular	38 (1.0)	17 (0.9)	21 (1.0)
Basal cell carcinoma, unspecified	325 (8.6)	154 (8.6)	171 (8.6)

* Basal cell carcinomas occurring within 6 months of the first date of BCC diagnosis (index date) were counted as additional tumors at index date.

† Total may not equal 100% due to rounding.

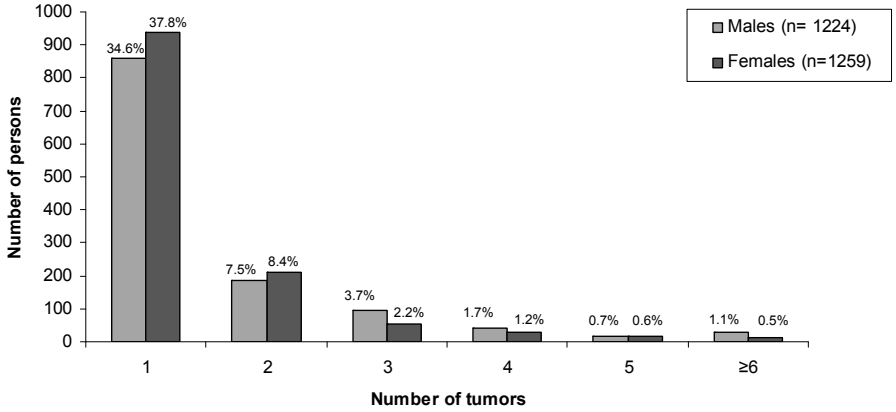


Figure 1. Absolute number of basal cell carcinomas among the 2,483 cohort members with at least one histologically confirmed basal cell carcinoma, stratified for sex and expressed in percentages

were females; in total they developed 3,793 pathology-confirmed BCCs during 5-years of follow-up. They contributed 12,297 person-years of follow-up during our study period of five years. The mean age at BCC index date was 65.1 years (range 16 – 100 years); two persons were under the age of eighteen.

BCC description

During our observational period, 1,796 (72.3%) patients had one BCC; 394 (15.9%) patients developed two and 293 (11.8%) three or more BCCs (figure 1). The mean and median numbers of BCCs were 1.52 (standard deviation 1.20) and 1.0 (interquartile range [IQR] 1), respectively. In the total study population, the most frequently affected body site was head and neck (60.5%), followed by trunk (24.7%), lower extremities (6.5%) and upper extremities (4.1%). Of the 3,793 BCCs, 19 (0.5%) tumors were located in the pelvic/anogenital region or buttocks and for 139 (3.7%) tumors a location was not registered in the PALGA database. Among patients with one or multiple BCCs, the distribution of tumor site was similar (table 1). Overall, most BCCs were of nodular histological subtype (58.4%), followed by superficial (17.7%), infiltrative (14.3%) and micronodular subtype (1.0%). Among patients with multiple BCCs, the distribution of histological subtype was similar. In contrast with the total study population and patients with multiple BCCs, the proportion of infiltrative BCCs was higher than the proportion of superficial BCCs in patients with a single BCC (table 1).

Cumulative risk of multiple BCCs

The cumulative risk of a BCC after the first 6 months from BCC index date was 11.2% (table 2). As expected, this risk increased with follow-up time. After three years, 546 patients had developed subsequent BCCs, and based on the expected life-expectancies 15 patients had died, resulting in a cumulative risk of 22.0%. Five years after BCC index date 687 patients had

developed subsequent BCCs and more than 5% was expected to have died; the cumulative risk was almost 30% (table 2).

Incidence rate of multiple BCCs

The incidence rate for the development of additional BCC(s) was the highest in the first 6 months after BCC index date: 25,318 per 100 000 person-years. After one year of follow-up this rate decreased with almost 40% compared to the first six months. Three years after diagnosis (follow-up time 6,239 person-years), the incidence rate was reduced to 8,752 per 100 000 person-years. Five years after index date the rate declined to 6,953 per 100 000 person-years, which was almost a fourfold lower than the incidence rate in the first 6 months after index date (table 2).

Table 2. Cumulative risks and incidence rates of the development of subsequent basal cell carcinomas (≥ 2 tumors in total) after index basal cell carcinoma

Years	Number of patients with subsequent BCC (%)	Deaths during follow-up (%)**	Total follow-up time (person-years)	Cumulative risk (%)	Incidence rate (*100 000 person-years)
0.5*	279 (11.2)	0 (0.0)	1102.0	11.2	25318
1	345 (13.9)	0 (0.0)	2192.2	13.9	15737
2	460 (18.5)	1 (0.04)	4267.6	18.5	10779
3	546 (22.0)	15 (0.6)	6238.9	22.1	8752
4	618 (24.9)	60 (2.4)	8110.1	25.5	7620
5	687 (27.7)	128 (5.2)	9881.2	29.2	6953

* Basal cell carcinomas occurring within 6 months of the first date of BCC diagnosis (index date) were counted as additional tumors at index date

** Expected vital status of patients was calculated based on sex-specific life expectancy at age of Index BCC (data from Statistics Netherlands)

Abbreviation: BCC, basal cell carcinoma

Table 3. Number of patients with subsequent basal cell carcinomas and total number of subsequent basal cell carcinomas per year after index basal cell carcinoma

Year	Number of patients with subsequent BCC (%) (n=687)**	Total number of subsequent BCCs (%) (n=1310)	Percentage of patients with two or more subsequent BCCs
0 - 0.5*	279 (40.6)	377 (28.8)	25.5%
0.5 - 1	95 (13.8)	119 (9.1)	20.0%
1 - 2	179 (24.0)	232 (17.7)	17.3%
2 - 3	165 (26.1)	210 (16.0)	20.0%
3 - 4	132 (19.2)	181 (13.8)	20.5%
4 – 5	151 (22.0)	191 (14.6)	20.5%

* Basal cell carcinomas occurring within 6 months of the first date of BCC diagnosis (index date) were counted as additional tumors at index date

** Patients can be counted more than once, when having additional BCC(s) spread over several years

Abbreviation: BCC, basal cell carcinoma

The median time to develop a second BCC was 11 months (IQR 32). When excluding those patients who had their second BCC at index date or within the first 6 months after index date (n = 279) the median time to develop a second BCC increased to 26 months (IQR 25.75).

Subsequent BCC per year

Of the 2,483 patients, 687 developed two or more BCC(s) during our study period. About 40% of these patients had one or more subsequent BCC(s) at index date or within the first 6 months after index date, suggesting simultaneous development of BCCs (table 3). In the years thereafter, about a quarter of the patients with multiple BCCs developed at least one BCC irrespective of what occurred in the years before or after the study year. In total, the 687 patients developed 1,310 (median 1 [IQR 1]) subsequent tumors. In line with the unique number of patients who developed subsequent BCCs, the absolute number of BCCs (and its proportion) was the highest in the first 6 months after index date. For each of the 5 years since index date, approximately 15% of all subsequent BCCs were recorded. The proportion of patients with multiple BCCs that developed two or more BCCs per follow-up year was limited (≤ 25.5%; see table 3), suggesting that if patients developed a subsequent BCC it was likely to be one per year (median number of subsequent BCCs was 1.0 [IQR = 1] for each of the follow-up years).

The number of patients with additional BCC(s), and their corresponding total number of subsequent BCCs, was overall higher for men than for women (figure 2). The distribution of the four age categories at index data, showed that the oldest age-group (≥ 80 years) had the

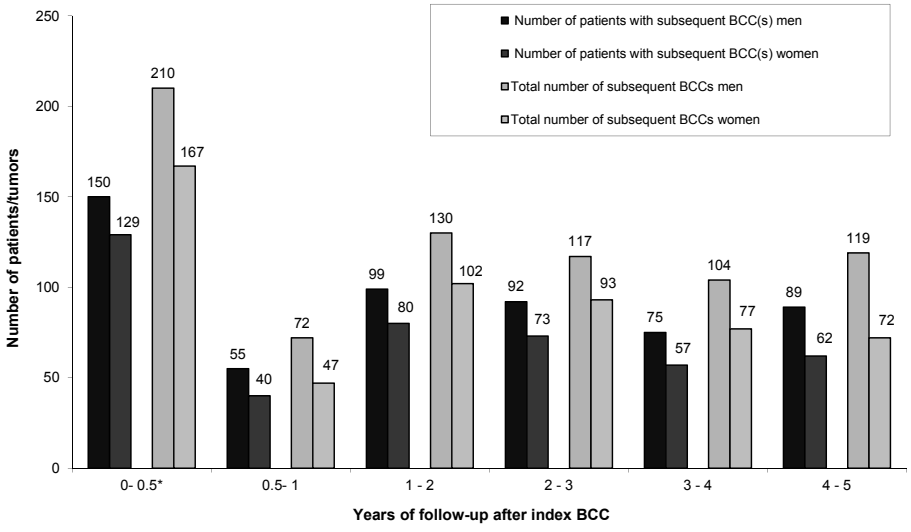


Figure 2. Number of patients with, and the absolute number of subsequent basal cell carcinomas by sex and years after index basal cell carcinoma

Table 4. Risk factors associated with the development of subsequent basal cell carcinomas

	Patient with one BCC (n=1796)	Patients with multiple BCC (n=687)	Univariate Andersen-Gill for multiple BCCs (95% CI)	Multivariate Andersen-Gill for multiple BCCs (95% CI)*
Person-years of follow-up	8890	3407	NA	NA
Mean follow-up per patient (years)	4.95	4.96	NA	NA
Sex				
Female	938 (52.2)	321 (46.7)	1.00 (ref)	1.00 (ref)
Male	858 (47.8)	366 (53.3)	**1.29 (1.10 - 1.51)**	**1.30 (1.11 - 1.53)**
Age, mean (min. max in years)	64.5 (16-100)	66.6 (28-95)		
Age at index lesion (years)				
< 50	280 (15.6)	64 (9.3)	1.00 (ref)	1.00 (ref)
50 - 64	589 (32.8)	219 (31.9)	**1.68 (1.26 - 2.26)**	**1.67 (1.25 - 2.24)**
65 - 79	644 (35.9)	296 (43.1)	**1.84 (1.39 - 2.44)**	**1.81 (1.37 - 2.41)**
≥ 80	283 (15.8)	108 (15.7)	**1.53 (1.11 - 2.11)**	**1.54 (1.12 - 2.13)**

* Multivariate Andersen-Gill: adjusted for sex and age at index date
Abbreviations: BCC, basal cell carcinoma; CI, confidence interval

highest percentage (13.6%) of patients with subsequent BCC(s) on index date or within the first six months after their index BCC, followed by age-groups 65 – 79 years (11.4%), 50 – 64 years (10.9%) and the youngest age-group (9.0%) (data not shown).

Age, sex and multiple BCCs

In the univariate Andersen-Gill multi failure analyses male sex and higher age at index BCC were significantly associated with the development of multiple BCCs. After inclusion of sex and age at index date in the multivariate model, both factors remained statistically significant. Males had almost 30% (adjusted HR 1.30 [95% CI 1.11 – 1.53]) more risk of developing multiple BCCs compared to females. Patients within age-group 65 until 79 years had more than 80% (adjusted HR 1.81 [95% CI 1.37 – 2.41]) higher risk of having subsequent BCC(s) in comparison with patients younger than 50 years (table 4).

DISCUSSION

This is the first Dutch study investigating the risk of subsequent BCC development in a large population-based cohort of BCC patients, including almost 2,500 patients with a first BCC. We observed a cumulative risk of approximately 30% of developing subsequent BCC(s) in first 5 years following diagnosis of the first BCC. The observed incidence rates for further BCC(s) were especially high in the first six months after BCC index date. In total, 2,483 patients developed 3,793 histologically confirmed BCCs, of which about two third were located in the head and neck region and were of the nodular subtype.

Our five-year cumulative risk is in accordance with a previous Dutch cohort study of middle-aged and elderly people (i.e. Rotterdam Study), but considerably lower than that of studies of selected populations from the USA or Australia.[15] The USA based New Hampshire Skin Cancer Study Group, observed a 5-year cumulative probability of 41% of further BCC(s) after prior BCC.[21] In Australia, The Nambour Skin Cancer Study showed that 46% of the 301 patients with a prior BCC developed subsequent BCCs after a follow-up period of 10-years.[16] The lower cumulative risks in The Netherlands were to be expected; since Australia and the USA have different climates/latitudes compared to The Netherlands with many more hours of sunshine per year and are primarily inhabited by people of primary Northern European descent. Other high risk populations, such as transplant patients and PUVA recipients had also 20% higher 5-year cumulative risks of subsequent BCC(s) than our group of patients with prior BCC.[22-24]
The rate of developing a subsequent BCC was almost fourfold higher in the first 6 months post-diagnosis compared to year 5 after diagnosis. Increased skin cancer awareness and self-detection are likely to have caused part of the high incidence rate observed in the first half year of our study period. However, the main cause is probably similar to what occurs in organised mass-screening programs with the 'prevalence screen', i.e. the first time a population is screened for a specific disease and many cases are identified due to a case finding effect, causing incidence rates to be high.[25] Although no formal screening took place in our study, after first BCC diagnosis, patients had probably several follow-up visits at their (dermatological) clinic, concerning patient reassuring, treatment and follow-up. When several pre-existing (prevalent) BCCs existed among these patients, they were detected by the patients and/or physicians during this period. Consequently, the number of patients with primary additional BCC(s) in the second half year after index date decreased rapidly compared to the first half year, as observed in our data and depicted in table 3 and figure 2.
The characteristics of the 3,793 studied BCC tumors are in concordance with previous published results, in which the most prominent tumor site was head and neck, followed by trunk, lower and upper extremities.[15, 26] The distribution of histological subtypes were in accordance with previous studies in which nodular subtype was the most common, followed by superficial, infiltrative and micronodular subtype.[26-27]

Full body skin examination

Approximately one third of people diagnosed with subsequent BCC(s) had these tumors within the first half year of follow-up emphasizing the need for full body skin examination (FBSE), especially at date of first diagnosis. The 'prevalence screen-effect' observed in our study indicated that patients had multiple BCCs at date of first diagnosis. For example, as most BCCs are located in head and neck region, physicians confronted with such a patient, may disregard the less visible parts of the body whilst missing possible other (already existing) BCC(s) hidden under the patients' clothes.[26] On the other side, patients and/or their relatives have after first skin cancer diagnosis and probably associated biopsy, treatment and

sun protecting advices, increased skin cancer awareness. They become concerned about other suspected skin lesions, return to their physician, possibly presenting with additional BCC(s), which were probably already present at date of first BCC diagnosis.

FBSE should especially be recommended for males and elderly people since we observed that these patients were at greater risk of developing additional BCC(s), which is in accordance with some, but not all, previously published studies.[15, 17, 21, 28] Older age at index lesion was related with an increased risk of subsequent BCC(s), which is different than reported in a Dutch cohort study among elderly (aged >55 years) inhabitants.[15] Variations in the age distribution pattern between the two studies probably account for part of the dissimilarity observed, especially since in the current study we included patients of all ages.

Follow-up

The necessity of follow-up visits, their frequency and duration need to be assessed. Follow-up has several important aims; however, there is no clear (inter)national consensus about a suitable follow-up regime of patients with BCC(s).[5-6, 8]

In our study the incidence rates of developing subsequent BCC(s) were particularly high in the first years of follow-up; however, with time these rates decreased rapidly, although they remained high. In contrast with recommendations from the current Dutch national guideline, we recommend follow-up visits for (early) detection of subsequent BCC(s).[28] Early stage BCCs are often asymptomatic and may not be noticed by the patient until the tumor becomes larger and is in a more advanced stage. Early BCC detection by a physician during follow-up may therefore reduce patient morbidity by preventing growth in vital structures and mutilating local tissue destruction. When the tumor is relatively small, more (less-invasive) treatment options (e.g. nonsurgical therapies such as photodynamic therapy and 5-fluorouracil cream) are available, often resulting in a better aesthetic outcome. When surgical excision is the treatment of choice, less cosmetic disfigurement is induced and less time for reconstruction is needed when operating a smaller compared to a larger tumor, and concurrently, costs will be reduced.

Based on our data, annual follow-up visits for at least three years appear to be recommended, particularly paying special attention to men and persons of older age at index lesion. Implementing such a strict follow-up regime implicates large numbers of patients to be seen by physicians. However, this number will not differ that much from the current situation; since a majority of the patients are already followed at least once a year after first BCC diagnosis due to the regular occurrence of multiple BCCs and recurrences of treated BCCs.

Strengths and limitations

PALGA contains primary histologically confirmed BCCs with nationwide coverage from 1991 and onwards.[18] However, we have probably underestimated the true incidence and risk of subsequent BCC(s) in our study since some patients may have been diagnosed and/ or

treated on clinical diagnosis alone and to a lesser extent some may have been diagnosed and/or treated abroad.

We did not have data on vital status of the BCC patients included in our study. However, previous studies estimated a relative survival of almost 100% of BCC(s)[19, 29] and therefore, we considered it appropriate to predict vital status based on sex and age specific life-expectancy.

CONCLUSION

The 'BCC epidemic' in The Netherlands still continues and it is estimated that 1 in 6 Dutch citizens will develop a BCC in his/her lifetime.[4] Patients with a prior BCC are, with a 5-year cumulative risk of almost 30%, among the highest risk groups of developing another BCC. Ideally, annual FBSE seems to be appropriate for at least three years. However, the (Dutch) health care system has to adjust to the huge workload BCC patients put on time and resources of physicians who take care of these patients.

REFERENCES

1. Holterhues C, Vries E, Louwman MW, Koljenovic S, Nijsten T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989-2005. J Invest Dermatol 2010;130:1807-12.
2. Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer 2007;121:2105-8.
3. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of non-melanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. Int J Cancer 2010;127:2190-8.
4. Flohil SC, de Vries E, Neumann HAM, Coebergh JW, Nijsten T. Incidence, Prevalence, and Future Trends of Primary Basal Cell Carcinoma in the Netherlands. Acta Derm-Venerol 2011;91:24 - 30.
5. Dutch Society for Dermatology and Venereology. Evidence-based guideline Treatment of the basal cell carcinoma. http://www.huidarts.info/documents/?v=2&id=69 accessed at August 2nd 2010.
6. Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. Br J Dermatol 2008;159:35-48.
7. Hauschild A, Breuninger H, Kaufmann R, et al. Short German guidelines: basal cell carcinoma. J Dtsch Dermatol Ges 2008;6 Suppl 1:S2-4.
8. NCCN Clinical Practice Guidelines in Oncology. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp accessed at January 28th 2011.
9. Clinical practice guide: basal cell carcinoma, squamous cell carcinoma (and related lesions) - a guide to clinical management in Australia. http://www.cancer.org.au/File/BasalcellcarcinomaSquamouscellcarcinomaGuideNov2008Final.pdf. accessed at April 21th 2011.
10. Fields RC, Coit DG. Evidence-based follow-up for the patient with melanoma. Surg Oncol Clin N Am 2011;20:181-200.
11. Milan T, Pukkala E, Verkasalo PK, et al. Subsequent primary cancers after basal-cell carcinoma: A nationwide study in Finland from 1953 to 1995. Int J Cancer 2000;87:283-8.
12. Karagas MR, Greenberg ER, Mott LA, Baron JA, Ernster VL. Occurrence of other cancers among patients with prior basal cell and squamous cell skin cancer. Cancer Epidemiol Biomarkers Prev 1998;7:157-61.
13. Levi F, La Vecchia C, Te VC, Randimbison L, Erler G. Incidence of invasive cancers following basal cell skin cancer. Am J Epidemiol 1998;147:722-6.
14. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524-30.
15. Kiiski V, de Vries E, Flohil SC, et al. Risk factors for single and multiple Basal cell carcinomas. Arch Dermatol 2010;146:848-55.
16. Richmond-Sinclair NM, Pandeya N, Ware RS, et al. Incidence of basal cell carcinoma multiplicity and detailed anatomic distribution: longitudinal study of an Australian population. J Invest Dermatol 2009;129:323-8.
17. Richmond-Sinclair NM, Pandeya N, Williams GM, Neale RE, van der Pols JC, Green AC. Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: a 16-year longitudinal study. Int J Cancer 2010;127:2622-9.

18. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29:19-24.
19. de Vries E, Nijsten T, Louwman MW, Coebergh JW. [Skin cancer epidemic in the Netherlands]. Ned Tijdschr Geneeskd 2009;153:A768.
20. Pandeya N, Purdie DM, Green A, Williams G. Repeated occurrence of basal cell carcinoma of the skin and multifailure survival analysis: follow-up data from the Nambour Skin Cancer Prevention Trial. Am J Epidemiol 2005;161:748-54.
21. Karagas MR, Stukel TA, Greenberg ER, Baron JA, Mott LA, Stern RS. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin Cancer Prevention Study Group. Jama 1992;267:3305-10.
22. Bruynzeel I, Bergman W, Hartevelt HM, et al. 'High single-dose' European PUVA regimen also causes an excess of non-melanoma skin cancer. Br J Dermatol 1991;124:49-55.
23. Katz KA, Marcil I, Stern RS. Incidence and risk factors associated with a second squamous cell carcinoma or basal cell carcinoma in psoralen + ultraviolet a light-treated psoriasis patients. J Invest Dermatol 2002;118:1038-43.
24. Wisgerhof HC, Edelbroek JR, de Fijter JW, et al. Subsequent squamous- and basal-cell carcinomas in kidney-transplant recipients after the first skin cancer: cumulative incidence and risk factors. Transplantation 2010;89:1231-8.
25. Steele RJ, Kostourou I, McClements P, et al. Effect of repeated invitations on uptake of colorectal cancer screening using faecal occult blood testing: analysis of prevalence and incidence screening. BMJ 2010;341:c5531.
26. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 2002;147:41-7.
27. Arits A, Schlangen M, Nelemans P, Kelleners-Smeets N. Trends in the incidence of basal cell carcinoma by histopathological subtype. J Eur Acad Dermatol Venereol 2010.
28. van Iersel CA, van de Velden HV, Kusters CD, et al. Prognostic factors for a subsequent basal cell carcinoma: implications for follow-up. Br J Dermatol 2005;153:1078-80.
29. de Vries E, Steliarova-Foucher E, Spatz A, Ardanaz E, Eggermont AM, Coebergh JW. Skin cancer incidence and survival in European children and adolescents (1978-1997). Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42:2170-82.

CHAPTER 5

Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis

S.C. Flohil

R.J.T. van der Leest

L.R. Arends

E. de Vries

T. Nijsten

Submitted

ABSTRACT

Background

Patients with a keratinocyte carcinoma (KC) are at increased risk of developing subsequent malignancies of the skin. In this systematic review and meta-analysis the risk of a subsequent BCC, SCC or melanoma in patients with a previous KC was investigated.

Methods

A comprehensive literature search was performed in Pubmed, Embase, Web of Science and the Cochrane library to find studies published before January 1st 2012 that reported risks (i.e. proportions, cumulative risks or standardized incidence ratios [SIR]) of developing a subsequent BCC, SCC or melanoma in patients with prior KC. Pooled estimates for proportion and SIR with 95% confidence intervals (95% CI) were calculated using a random-effects meta-analysis.

Findings

45 articles fulfilled the inclusion criteria. In BCC patients, the pooled proportion for a subsequent BCC, SCC or melanoma was respectively 29.2% (95% CI: 24.6 – 34.3%), 4.3% (1.7 – 10.1%) and 0.5% (0.4 – 0.8%). The pooled proportion of a subsequent SCC, BCC or melanoma in SCC patients was respectively 13.3% (95% CI: 7.4 – 22.8%), 15.9% (5.6 – 37.6%) and 0.5% (0.3 – 0.6%). The pooled proportion for KC after KC was 37.0% (29.0 – 45.8%). The pooled SIRs for a subsequent BCC, SCC or melanoma were respectively 17.4 (95% CI 0.0 – 37.4), 3.2 (0.0 – 6.5) and 2.4 (2.3 – 2.6) in BCC patients and 4.2 (95% CI 2.0 – 6.5), 15.0 (14.0 – 16.0) and 2.7 (2.3 – 3.2) in SCC patients. In the subgroup analyses (i.e. stratification by study quality, study design and continent) of the pooled proportion and SIR, strongest differences in risks were found in the continent strata (risks Australia > North America > Europe).

Interpretation

A prior KC is among the highest risk factors for developing another cutaneous malignancy, especially for a subsequent tumor of the same origin. This risk is comparable to that of transplant and radiotherapy recipients and patients with genodermatoses.

Funding

The Netherlands Organization for Health Research and Development (ZonMw), project numbers 152001013 / VIDI 91711315.

INTRODUCTION

Keratinocyte carcinoma (KC), comprising basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, is the most common cancer in Caucasian populations with increasing incidence rates across North America, Australia and Europe.[1] Currently, KC patients are putting a heavy burden on (dermatological) health services.[1-3] Although associated mortality rates are relatively low, KC may induce significant cosmetic and functional morbidity because the majority of these lesions are located in the head and neck region.[4]

Patients with prior KC are at increased risk of developing subsequent cutaneous (pre-)malignancies.[2, 5-47] The number of population-based studies investigating risks of subsequent KC is low, because KC are often not or partially included in national or regional cancer registries. In 2000, Marcil and Stern estimated the risk of a subsequent BCC and SCC in patients with a history of KC in a meta-analysis including 17 studies.[48] A 3-year cumulative risk of 44% for BCC after BCC and 18% for SCC after SCC was observed. However, these analyses were not based on a systematic review, studies were not critically appraised, and melanoma was excluded. After 2000, multiple new studies on risk of subsequent cutaneous malignancies among patients with prior cutaneous malignancies have been published.

In this systematic review and meta-analysis the risk of developing a subsequent BCC, SCC or melanoma in patients with previous KC was investigated to give a complete view on the currently available data regarding this topic. It may serve as a guide for patients and clinicians and form a basis for (future) skin cancer care and guidelines, health care policy makers and public health campaigns.

METHODS

This study was conducted to examine risk estimates of developing a subsequent BCC, SCC or melanoma in patients with a history of BCC, SCC or melanoma. This systematic review and meta-analysis is limited to the risk of developing a subsequent BCC, SCC or melanoma patients in patients with previous KC and excluded risks of these cutaneous malignancies amongst melanoma patients. Results were reported according to the PRISMA statement for reporting systematic reviews and meta-analyses of epidemiological studies.[49]

Search strategy

A comprehensive literature search strategy was performed assisted by a medical librarian of the Erasmus MC University Medical Center, Rotterdam, The Netherlands. On May 5th 2011, Pubmed, Embase, Web of Science and the Cochrane library were searched with database-specific search strings (appendix table 1). On January 18th 2012, an update of the search query (May 1st 2011 until January 1st 2012) was performed. In figure 1, the selection process of included articles is shown. No relevant articles were found within the Cochrane database. To have insight in grey literature internet search engines were also searched and one ad-

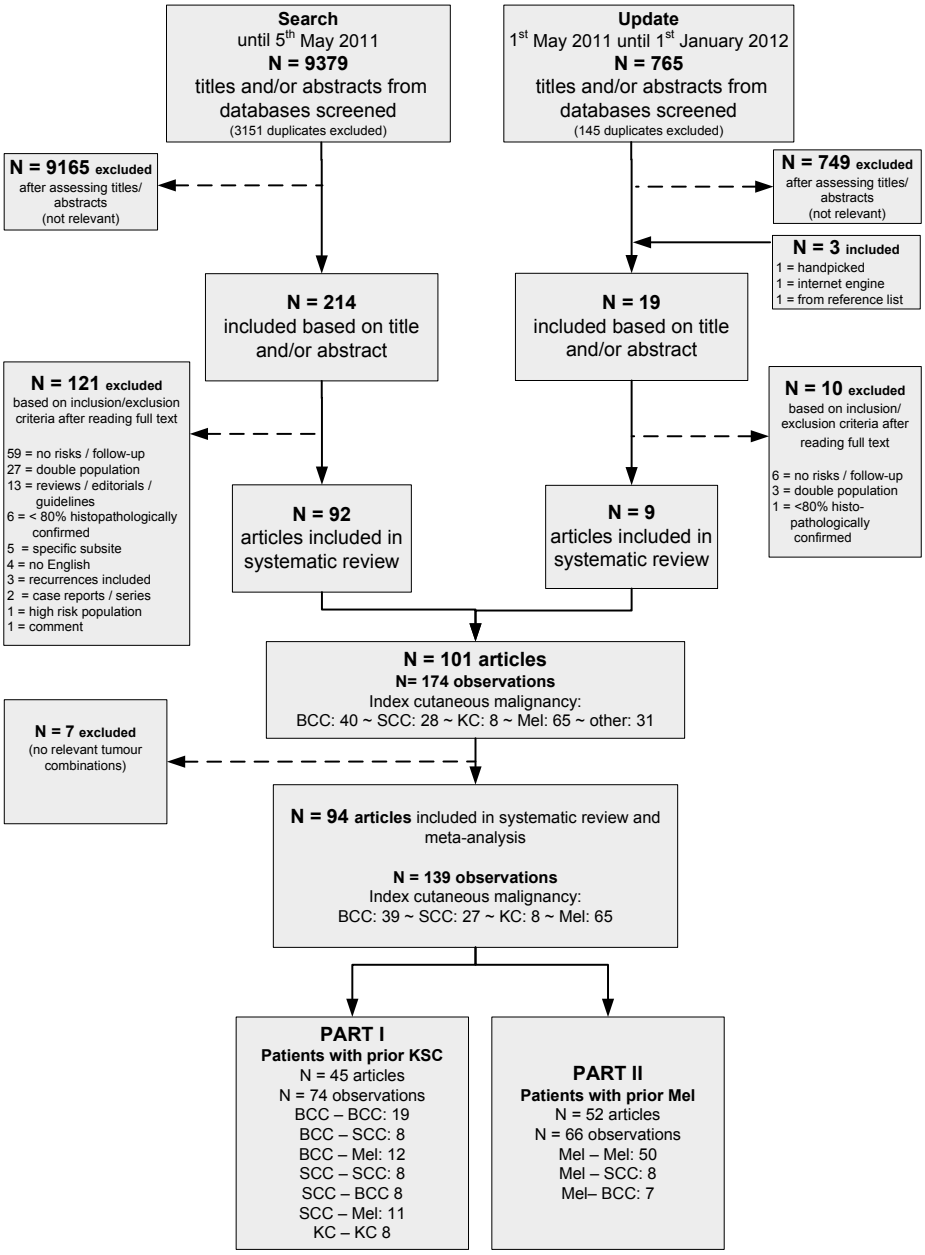


Figure 1. Selection process of included articles

Abbreviations: BCC, basal cell carcinoma; KC, keratinocyte carcinoma; Mel; melanoma; N, number; SCC, squamous cell carcinoma

ditional article was included.[50] Two other articles were handpicked; one after manually checking cross-references[51] and another recent study conducted within our department.[52]
Two authors (S.F. and R.L.) reviewed independently all titles and/or abstracts (n = 10 147, including 3 handpicked). When an article fulfilled the inclusion criteria, data extraction and quality assessment were independently performed by S.F. and R.L. Disagreements were discussed and solved together in consensus with authors E.V. and T.N.

Inclusion and exclusion criteria

Studies were included when meeting the following inclusion criteria: (1) patients with a previous BCC or SCC were followed over time for the development of a subsequent BCC, SCC or melanoma and an associated proportion, standardized incidence ratio (SIR) or cumulative risk (CR) was provided; (2) skin cancer diagnoses were histopathologically confirmed in more than 80% of the cases; (3) reported in English.
Of the above mentioned eligible risk estimates, proportion was the most frequently reported in literature, however, in contrast with CR and SIR, this estimate is little informative as it is not time-specific, does not account for the competing risk 'death' and does not compare to the risk in the non-KC population.
Studies were excluded when meeting the following exclusion criteria: (1) specific patient populations who were at extreme risk of developing cutaneous malignancies (e.g. transplant patients or genodermatoses); (2) more than 10% of the first or subsequent cutaneous malignancies were recurrences or no adequate case definition was made (e.g. no distinction between recurrences and first or subsequent cutaneous malignancies); (3) animal studies; (4) review, editorial, meta-analysis, consensus, guideline, case-reports or case – series; (5) only reporting cutaneous malignancies on specific anatomical sites.

Study selection

The following 7 tumor combinations of interest were extracted: BCC after BCC, SCC after BCC, melanoma after BCC, BCC after SCC, SCC after SCC, melanoma after SCC and KC after KC.
The majority of the included articles reported separate observations for multiple tumor combinations.
If identical populations were described in several publications within the same or overlapping time period, these publications were compared and the study with the most extensive results was included. An exception was made for two studies with an overlapping study population, which provided different risks measurements.[40-41]

Data extraction

The following information was extracted from each study: (1) study design (retrospective, prospective, population-based, hospital-based or cancer registry); (2) in - and exclusion criteria of the study; (3) abstract or full text; (4) the number of followed patients with a (first)

BCC, SCC or KC (the latter, when only combined data on BCC and SCC were available); (5) characteristics of study population (sex, mean [SD; standard deviation] or median age in years, mean [SD] or median follow-up time in years, total number of person-years); (6) risk estimate of developing a second or subsequent BCC, SCC, melanoma or KC (i.e. proportion, cumulative risk [CR], standardized incidence ratio [SIR]); (7) first cutaneous malignancy within patient (yes, no or unknown); (8) inclusion of *in situ* cutaneous malignancies (yes, no or unknown); (9) study location and continent; (10) year of publication.

In studies providing a CR for men and women separately without an overall CR, these numbers were averaged. Different nomenclature in medical literature is used for the risk measure 'Standardised Incidence Ratio' (SIR), therefore 'relative risk' (RR) and observed divided by expected (O:E) were also considered a SIR.

Quality assessment

The study quality was assessed by using adapted criteria (appendix table 2) from the Newcastle-Ottawa quality assessment scale (NOS) which is a quality assessment tool for cohort and case-control studies in systematic reviews and meta-analyses.[53] The NOS is divided within three grouping items: selection (4 points), comparability (2 points) and outcome (3 points). The maximum score of an article was 9 points. The risk of bias was considered moderate or low when the overall sum was 5 points or higher.[54]

Statistical methods

The primary outcome of interest of this meta-analysis was the proportion of BCC, SCC or KC patients that developed a subsequent cutaneous malignancy (i.e., BCC, SCC, melanoma or KC separately). This proportion was calculated by dividing the number of patients with a subsequent skin cancer by the total number of followed patients. The second outcome of interest was SIR, calculated as the observed number of patients that developed a subsequent cutaneous malignancy by the expected number of patients in the general population (i.e. background incidence). CR was calculated by dividing the number of patients that developed a subsequent cutaneous maligancy by the total number of patients alive after a certain time period.

Pooled estimates for proportion and SIR with 95% confidence intervals (95% CI) were calculated with a random effects model as proposed by DerSimonian and Laird because of high study heterogeneity (I^2 index > 75%).[55,56] In this model, the inverse of standard errors of proportion and SIR from the individual studies combined with the between study variation were used as weights. Only a limited number of studies provided a CR and most of them provided a 5 – years CR. In addition, confidence intervals and lifetables were often lacking. Therefore, it was not possible to calculate a pooled CR. However, to give an overview of the available CR data, the available 5 – year CR were averaged.

Subgroup analyses (only performed when number of separate observations per tumor combination ≥ 5) and sensitivity analyses were performed to understand the 'robustness' of the data and to find possible sources for study heterogeneity.[57] In the subgroup analyses the following study characteristics were compared, overall NOS score < 5 versus ≥ 5, population- versus hospital-based, in- versus exclusion of *in situ* cutaneous malignancies, studies that explicitly stated to follow patients with a 'first' BCC, SCC or KC versus studies without this statement (i.e., unknown if the patients under study were 'new' skin cancer patients or not). Stratification by study continent (i.e., Australia, North America and Europe) was also performed. Publication bias was statistically assessed by funnel plots and the Eggers' test (appendix figure 1).[58] All statistical analyses were performed using the software package Comphrensive meta-analysis (version 2.2) and SPSS statistical software (version 18 for Windows, SPCC Inc, Chicago, Illinois).

Role of the funding source

The Netherlands Organization for Health Research and Development (ZonMw project numbers 152001013 / VIDI 91711315) had no role in study design, data collection, data analysis, data interpretation or writing of the article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

The literature search identified 10 147 articles of which 233 were found potentially eligible based on title or abstract. Of the 233 fully read articles, 45 were eligible in the prior KC analysis (figure 1). In these 45 articles (appendix table 3), a total of 74 separate observations (i.e., in most cases one article contained information on multiple tumor combinations) were reported for the 7 possible tumor combinations. Of these 74 separate observations, 39 had BCC as index tumor, 27 SCC and 8 KC.

The 45 articles in this meta-analysis included 43 cohort and 2 case – control studies. More than half of the articles were population-based (n = 24), of which 15 included cancer registry data. In total, 11 articles had a prospective, while 34 had a retrospective study design. Of 41 articles the full text was available, whereas for 4 only abstracts[5, 18, 35, 38] were retrieved. Fourteen countries were represented in the articles, corresponding to three continents (i.e. Australia, North America and Europe). Of the full articles, 44% was appraised with a high quality score (≥ 5 NOS score); 47% of the 74 separate observations also received this score.

BCC as index tumor

29 articles [6, 8-9, 12, 14-18, 20, 22-24, 27-28, 31-33, 35-38, 40-42, 45, 47, 59-60], corresponding to 39 separate observations, included patients with a BCC as index tumor. In these patients, the pooled proportion for a subsequent BCC, SCC or melanoma was respectively 29.2% (95% CI 24.6 – 34.3%; n =

Table 1 Overview of pooled estimates of proportion with subgroup analyses for all observations

	BCC after BCC (%, 95% CI)	SCC after BCC (%, 95% CI)	Mel after BCC (%, 95% CI)	BCC after SCC (%, 95% CI)	SCC after SCC (%, 95% CI)	Mel after SCC (%, 95% CI)	KC after KC (%, 95% CI)
N studies	**19**	**7**	**11**	**6**	**5**	**9**	**7**
Pooled proportion	**29.2 (24.6-34.3)**	**4.3 (1.7- 10.1)**	**0.5 (0.4-0.8)**	**15.9 (5.6-37.6)**	**13.3 (7.4-22.8)**	**0.5 (0.3-0.6)**	**37.0 (29.0-45.8)**
NOS ≥5 N studies	6	4	9	4	3	8	1
Pooled proportion	31.1 (23.0-40.6)	7.0 (2.3-19.6)	0.5 (0.3-0.8)	17.9 (4.6-49.5)	11.3 (5.3-22.5)	0.4 (0.3-0.5)	50.0 (48.8-51.2)
NOS <5 N studies	13	3	2	2	2	1	6
Pooled proportion	27.8 (21.9-34.6)	1.7 (0.9-3.4)	0.7 (0.5-1.2)	11.5 (9.0-14.3)	18,4 (12.3-26.7)	1.2 (0.6-2.3)	34.9 (25.0-46.3)
Population-based N studies	8	4	9	4	4	8	2
Pooled proportion	29.7 (22.0-38.7)	7.0 (2.3-19.6)	0.5 (0.3-0.8)	17.9 (4.6-49.5)	11.8 (6.1-21.6)	0.4 (0.3-0.5)	44.2 (33.3-55.6)
Hospital based N studies	11	3	2	2	1	1	5
Pooled proportion	29.0 (23.6-35.0)	1.7 (0.9-3.4)	0.7 (0.5-1.2)	11.5 (9.1-14.3)	21.2 (14.3-30.1)	1.2 (0.7-2.3)	34.2 (19.7-52.3)
Excluding in situ N studies	15	4	6	5	5	4	7
Pooled proportion	29.7 (24.1-35.9)	5.1 (1.5-15.6)	0.6 (0.3-1.1)	17.2 (5.1-44.0)	13.0 (7.4-22.8)	0.4 (0.2-0.7)	37.0 (29.0-45.8)
Including in situ N studies	0	1	0	1	0	1	0
Pooled proportion	NA	0.9 (0.3-2.9)	NA	10.8 (8.9-13.1)	NA	1.2 (0.7-2.3)	NA
In situ, unknown included N studies	4	2	5	0	0	4	0
Pooled proportion	27.8 (20.1-37.1)	6.0 (1.3-23.4)	0.5 (0.3-0.6)	NA	NA	0.5 (0.4-0.5)	NA
First tumor yes N studies	9	4	7	4	3	9	1
Pooled proportion	25.8 (22.7-29.2)	4.5 (2.5-7.9)	0.4 (0.3-0.5)	12.0 (6.0-22.5)	9.7 (6.0-15.5)	0.5 (0.3-0.6)	39.3 (34.9-44.0)
First tumor no N studies	7	3	2	1	1	0	6w
Pooled proportion	42.9 (36.7-49.4)	3.9 (0.5-27.9)	1.5 (0.4-5.2)	43.0 (40.9-45.1)	17.3 (15.8-19.0)	NA	36.7 (27.9-46.4)
First tumor unknown N studies	3	0	2	1	1	0	0
Pooled proportion	20.6 (14.5-28.4)	NA	0.5 (0.3-1.0)	14.4 (8.9-22.6)	21.2 (14.4-30.1)	NA	NA
Europe N studies	12	5	9	3	2	7	3
Pooled proportion	27.3 (23.8-31.2)	2.7 (1.7 – 4.2)	0.4 (0.3-0.5)	7.2 (5.2-9.8)	12.1 (3.8-32.7)	0.4 (0.3-0.5)	23.3 (19.5-27.5)
USA N studies	6	2	2	3	3	2	2
Pooled proportion	32.5 (24.0-42.2)	14.8 (8.3-25.2)	1.7 (0.8-3.8)	29.1 (11.0-57.7)	15.3 (11.7-19.7)	1.3 (0.8-2.3)	44.8 (34.7-55.4)
Australia N studies	1	0	0	0	0	0	2
Pooled proportion	57.9 (53.0-62.6)	NA	NA	NA	NA	NA	53.3 (25.9-78.9)

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; KC, keratinocyte carcinoma; Mel, melanoma; N, number; NA, not applicable; NOS, Newcastle – Ottawa scale; Pr, proportion; SCC, squamous cell carcinoma; USA, United States of America.

Table 2. Overview of pooled estimates of standardised incidence ratios (SIR)

	BCC after BCC (95% CI)	SCC after BCC (95% CI)	Mel after BCC (95% CI)	BCC after SCC (95% CI)	SCC after SCC (95% CI)	Mel after SCC (95% CI)	KC after KC (95% CI)
N studies	2	3	6	3	1	5	0
Pooled estimate SIR	17.4 (0.0-37.4)	3.2(0.0-6.5)	2.4 (2.3-2.6)	4.2 (2.0-6.5)	15.0 (14.0-16.0)	2.8 (2.3-3.2)	NA

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; KC, keratinocyte carcinoma; Mel, melanoma; NA, not applicable; N, number; SCC, squamous cell carcinoma; SIR, standardised incidence ratio

Table 3. Mean 5 – year cumulative risks

	Number of studies	Mean 5-year cumulative risk (range)
BCC after BCC	7; [2, 11, 22-23, 32, 35, 41]	36.2% (11.0 – 49.9)
SCC after BCC	0	NA
Mel after BCC	0	NA
BCC after SCC	2; [13, 19]	39.3% (6.0 – 72.5)
SCC after SCC	3; [11, 19, 26]	37.0% (30.0 – 50.0)
Mel after SCC	0	NA
KC after KC	2; [11,30]	36.2% (22.4 – 50.0)

Abbreviations: BCC, basal cell carcinoma; CR, cumulative risk; Mel, melanoma; NA, not applicable; SCC, squamous cell carcinoma

19), 4.3% (1.7 – 10.1%; n = 7) and 0.5% (0.4 – 0.8%; n = 11) (figure 2 A-C). Pooled estimates within the subgroup analyses (i.e., study quality, study design, *in situ* cutaneous malignancies in- or excluded, 'first' cutaneous malignancy yes / no, continents) showed similar results with overlapping confidence intervals (table 1).

In the forrest plots, the Australian study by Richmond Sinclair *et al.*[42] was an outlier, with almost 58% of the BCC patients developing another BCC, compared to the other 18 studies (figure 2A). Two studies conducted in North America[17, 20] presented relatively high proportions of patients developing a subsequent SCC (after BCC) compared to the other European studies (figure 2B). Also, melanoma risk after BCC was higher in United States (US) studies[20,27], compared to the European and one Canadian study[15] (figure 2C).

The previous observations were confirmed within the subgroup analyses by continent (table 1). For BCC after BCC, the highest pooled proportion for BCC after BCC was found in Australia (n=1, 57.9%), followed by North America (n = 6, 32.5%) and Europe (n = 12, 27.3%). For SCC and melanoma after BCC the highest pooled proportion was observed in North America followed by Europe (table 1). In the latter two tumor combinations, no data from Australia was available.

In addition, two studies explicitly stated to have age restrictions (Cox *et al.*[24] and Kiiski *et al.*[31]) and two studies only contained data on low risk BCC (McLoone *et al.*[14] and Pulido *et al.* [38]). After excluding these 4 articles in a sensitivity analysis, the pooled proportion increased to 32.5% (95% CI 27.2 – 38.3).

Pooled SIRs, which compares the observed incidence to the expected incidence in the general population, showed that patients with a BCC had a seventeen fold (SIR 17.4 [0.0 – 37.4; n = 2] increased risk of a subsequent BCC compared to the general population. This was followed by SCC (3.2 [0.0 – 6.5]; n = 3) and melanoma (2.4 [2.3 – 2.6]; n = 5) after BCC (table 2).
The mean 5–year cumulative risk (CR) for BCC after BCC[2, 11, 22-23, 32, 35, 41] was 36.2% (n = 7, range 11.0 – 49.9%). No 5-year CR were available for the other tumor combinations with BCC as index tumor (table 3).

SCC as index tumor

17 articles[5, 8, 10-11, 13, 15-19, 21, 26, 29, 34, 46, 61-62], corresponding to 27 separate observations, described patients with SCC as index tumor. The pooled proportion of a subsequent SCC, BCC or melanoma in SCC patients was respectively, 13.3% (95% CI 7.4 – 22.8; n = 5), 15.9% (5.6 – 37.6; n = 6) and 0.5% (0.3 – 0.6; n = 9) (figure 2 D-F). In the 5 subgroup analyses, similar results with overlapping CI compared to the overall pooled proportions were observed (table 1). The continent with the highest pooled proportion for SCC, BCC and melanoma after SCC was North America [15.3% (11.7 – 19.7; n = 3), 29.1% (11.0 – 57.7; n = 3) and 1.3% (0.8 – 2.2; n = 2), respectively]. No data was available for Australia.
The studies performed in the USA (Schreiber *et al.*[17] and Chuang *et al.*[21], except the study by Efird *et al.*[10]) had with 43% the highest proportions for BCC after SCC and seemed outliers compared to the other four studies in this tumor combination. After excluding these two studies in a sensitivity analysis, the pooled proportion for BCC after SCC decreased to 8.0% (5.8 – 11.4). In melanoma after SCC, the highest proportions were found by relatively small studies such as Chuang *et al*.[21] (n = 189) and Efird *et al.*[10] (n = 822), whereas others had study sizes of more than 1000 patients, except Troyanova *et al.*[18] (n = 741) (appendix table 3B). After excluding Chang *et al.*[21] and Efird *et al.*[10] in the sensitivity analysis, the pooled proportion for melanoma after SCC decreased to 0.4% (0.3 – 0.5).
A high SIR of 15.0 (14.0 – 16.0) was observed for SCC after SCC, however based on just one study (table 2). The SIRs for BCC and melanoma after SCC were also increased, respectively (4.2 [95% CI 2.0 – 6.5]; n = 3) and (2.7 [95% CI 2.3 – 3.2]; n = 5).

The mean 5–year CR for SCC after SCC was 37.0%[11, 19, 26] (n = 3, range 30.0 – 50.0%) and comparable to the mean 5-year CR of BCC after SCC[13, 19] (39.3% [n = 2, range 6.0 – 72.5%]). No 5 – year CR was available for tumor combination melanoma after SCC (table 3).

KC as index tumor

Seven articles[7, 11, 17, 30, 39, 43, 63], including 8 separate observations, investigated KC (BCC and SCC combined) after KC. This resulted in a pooled proportion of 37.0% (95% CI 29.0 – 45.8; n = 7). Czarnecki *et al.*[25] from Australia, the study with the longest mean follow-up time (i.e. 10 years), had with 67.8% a high proportion of KC patients developing another KC compared

to another Australian study (Raasch *et al.*[39] with 38.5%) and studies from North America and Europe (figure 2G).
Although based on one study, subgroup analysis by continent (table 1) showed that the highest pooled proportion was found in Australia with 53.3% (n=2), followed by North America (44.8%; n = 2) and Europe (23.3%; n = 3). No studies reported SIR as risk measurement for KC after KC. The mean 5 – year CR for KC after KC was 36.2% (n = 2, range 22.4 – 50.0%).[11,30]

DISCUSSION

This systematic review and meta-analysis emphasizes that a KC history is among the strongest risk factors of developing another BCC, SCC or melanoma. The highest risk estimates were found for subsequent cutaneous malignancies of the same type, especially for BCC in which 29% of patients had subsequent BCCs. The increased risk of developing subsequent BCC, SCC and melanoma after a first KC suggests a partially common aetiology of UV-induced field cancerization and genetic predisposition among these three types of skin cancer.[64-65] In contrast, the observation that people were most likely to develop an identical type of malignancy suggest that there are differences in carcinogenesis and associated risk factors among the three most common skin cancers.
A KC history seems to be among the highest risk factors for developing a subsequent KC, and almost comparable to the risk of transplant recipients, radiotherapy treated patients and those exposed to high doses of PUVA.[66-70] Compared to these specific patient populations with an iatrogenic risk of developing skin cancer, the number of patients with a history of KC is enormous and constantly increasing implying a huge impact on health care services. Since primary prevention appears to be unsuccessful in reducing the incidence of skin cancer, secondary prevention strategies in which patients with a KC are informed about future risk, motivated to perform self examinations and have annual total body skin examinations for 3 to 5 years by trained physicians or nurse practitioners in order to detect new lesions early seems appropriate. Both BCC and SCC patients also had increased SIRs for developing melanoma (2.4 and 2.7 respectively), which is in accordance with a previous systematic review.[71] Unfortunately, in this review, KC were not included as second primary cancers.[71] These increased risks should alert clinicians and KC patients because early detection of a subsequent melanoma may decrease melanoma-associated mortality.

Subgroup analyses

BCC, SCC and melanoma are all strongly associated with UV exposure and the incidence rates of a primary skin cancer depends on geographic latitude.[72-73] After stratifying for continent, effect sizes of developing subsequent skin cancers after a first KC were the highest for Australia, followed by North America and Europe as expected by the decreasing UV-levels among primarily Caucasian populations. Therefore, the pooled risk estimates of all studies combined should be

interpreted with caution because it is biased by geographic location limiting the generalizability of the results. To maximize external validity of this meta-analysis, ideally, it would be necessary to include many studies with identical study designs and large study populations for each tumor combination in each continent to provide location-specific estimates.[74] Here, only a limited number of countries (n = 14) and continents (n = 3) were available and the number of studies in some geographic areas was low. Although we performed subgroup analyses by continents, differences in the distribution of people's characteristics such as pigmentation status (i.e. eye-, hair- and skin color) were not accounted for further affecting the generalizibility. No pooled estimates could be calculated for Africa, Asia and inhabitants of the Middle-East. However, considering the darker pigmentation status of these inhabitants, primary and multiple cutaneous malignancies might be a smaller public health problem in these regions.

Consequences and follow-up

Recently, the US preventative task force recommended a case-finding approach in the screening of skin cancer.[75] Although total body skin examinations of all patients visiting a physician may not be feasible in clinical practice, it is warranted in patients with a history of KC because of their extremely high risk. Other important reasons of following patients with cutaneous malignancies are for psychosocial support, (early) detection of a local recurrence for BCC and to a lesser extent of SCC and progression of SCC and melanoma to the draining lymph nodes and visceral organs.[76] Frequency and duration of follow-up of KC patients remains controversial, but from the perspective of developing subsequent cutaneous malignancies follow-up seems desirable for at least 3-5 years annually.[59]

Strengths and limitations

This is the largest systematic review and meta-analysis available on risk of subsequent skin cancer after a BCC or SCC. To ensure high quality reporting, the PRISMA guidelines were used.[49] The pooled risk estimates presented for all tumor combinations are probably underestimated, because some BCCs may be diagnosed clinically without histological confirmation.[77] This problem is almost non-existent for melanoma and SCC, because these cutaneous malignancies have a higher metastatic potential than BCC and are usually surgically treated and histologically confirmed. A recent Dutch study observed that during a mean follow-up of 6 years only 7% of the subsequent BCC in patients with a prior histologically confirmed BCC were clinically diagnosed, indicating that the degree of underestimation of our data is relatively limited.[78]

The risk estimate proportion was the most frequently reported estimate in the literature describing risks of subsequent cutaneous malignancies, but has the disadvantage that is not time-specific nor does it account for the competing risk 'death'. A relative risk that is much more informative about the risk in the study population compared to the general population (SIR) and an unbiased risk over time (CR) that controls for the number of patients that died

during follow-up (i.e. competing risks) are preferred in subsequent (cutaneous) malignancy research.[79] Unfortunately, the number of studies providing SIRs of the tumor combinations of interest was low, which may be a KC specific problem. Most cancer registries do not register BCCs and those that do reliably report the first but not the subsequent BCCs because of the required resources and 'coding' difficulties.[59, 80] Therefore, the risk of a subsequent BCC or SCC was mostly based on smaller studies that may have inflated the pooled proportions by selection bias. Also, no pooled CR estimates were calculated because only a few studies reporting the risk of BCC and SCC after a first KC provided this risk measurement. In contrast, studies investigating the risks of subsequent melanomas were more often larger cancer registry studies than studies that investigated the risk of a subsequent BCC or SCC in patients with prior KC limiting the aforementioned limitations.

Publication bias is likely to be minimal because the risk estimates of developing a subsequent cutaneous malignancy are probably increased in all studies, as illustrated in this review, minimizing negative findings and thus publication bias.[74] Furthermore, publication bias was unlikely due to symmetrical funnel plots and non-significant Egger's tests. The systematic literature search was done by a medical librarian using a string and included congress abstracts and monographs (i.e., 'grey literature').[81] However, language bias may have had an effect because only studies reported in English were eligible. To control for multiple publication bias, only the study that presented the most extensive results or had the longest follow-up was included.

CONCLUSION

A history of a prior KC is a very strong predictor for developing a subsequent BCC and SCC and to a lesser extent melanoma. Secondary prevention (early detection of subsequent episodes of the disease) is pivotal in patients with a prior KC. Patients should be well informed about future risk and require adequate follow up by physicians.

ACKNOWLEDGEMENTS

We would like to thank Louis Volkers (medical librarian) from the Erasmus MC University Medical Center Rotterdam, The Netherlands for assistance in developing an accurate search strategy.

REFERENCES

1. Lomas A, Leonardi-Bee J, Bath-Hextall F. A Systematic Review of worldwide incidence of Non-melanoma skin cancer. Br J Dermatol 2012;166:1069-80.
2. Flohil SC, Koljenovic S, de Haas ER, Overbeek LI, de Vries E, Nijsten T. Cumulative risks and rates of subsequent basal cell carcinomas in The Netherlands. Br J Dermatol 2011;165:874-81.
3. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in The Netherlands: Increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer 2012;48:2046-53.
4. Lewis KG, Weinstock MA. Trends in nonmelanoma skin cancer mortality rates in the United States, 1969 through 2000. J Invest Dermatol 2007;127:2323-7.
5. Kemmett D, Chan C. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of squamous cell carcinoma. Br J Dermatol 2004;151:30-1.
6. Revenga F, Paricio JF, Vasquez MM, del Villar V. Risk of subsequent non-melanoma skin cancer in a cohort of patients with primary basal cell carcinoma [5]. J Eur Acad Dermatol Venereol 2004;18:514-5.
7. Veien K, Veien NK. Risk of developing subsequent nonmelanoma skin cancers. Arch Dermatol 2001;137:1251.
8. Cantwell MM, Murray LJ, Catney D, et al. Second primary cancers in patients with skin cancer: a population-based study in Northern Ireland. Br J Cancer 2009;100:174-7.
9. Di Landro A, Zaccaria E, Naldi L, et al. Risk of developing a new basal cell carcinoma or other skin neoplasms in patients already treated for a basal cell carcinoma. G Ital Dermatol Venereol 2004;139:507-14.
10. Efird JT, Friedman GD, Habel L, Tekawa IS, Nelson LM. Risk of subsequent cancer following invasive or in situ squamous cell skin cancer. Ann Epidemiol 2002;12:469-75.
11. Karagas MR, Stukel TA, Greenberg ER, Baron JA, Mott LA, Stern RS. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin Cancer Prevention Study Group. Jama 1992;267:3305-10.
12. Levi F, La Vecchia C, Te VC, Randimbison L, Erler G. Incidence of invasive cancers following basal cell skin cancer. Am J Epidemiol 1998;147:722-6.
13. Levi F, Randimbison L, La Vecchia C, Erler G, Te VC. Incidence of invasive cancers following squamous cell skin cancer. Am J Epidemiol 1997;146:734-9.
14. Mc Loone NM, Tolland J, Walsh M, Dolan OM. Follow-up of basal cell carcinomas: an audit of current practice. J Eur Acad Dermatol Venereol 2006;20:698-701.
15. Nugent Z, Demers AA, Wiseman MC, Mihalcioiu C, Kliewer EV. Risk of second primary cancer and death following a diagnosis of nonmelanoma skin cancer. Cancer Epidemiol Biomarkers Prev 2005;14:2584-90.
16. Pring A, Verne J, De Berker DAR. The incidence of second primary skin cancer in an English region. Br J Dermatol 2010;163:7.
17. Schreiber MM, Moon TE, Fox SH, Davidson J. The risk of developing subsequent nonmelanoma skin cancers. J Am Acad Dermatol 1990;23:1114-8.
18. Troyanova P, Danon S, Ivanova T. Nonmelanoma skin cancers and risk of subsequent malignancies: a cancer registry-based study in Bulgaria. Neoplasma 2002;49:81-5.
19. Yoong C, De'Ambrosis B. Cutaneous invasive squamous cell carcinoma: 10-year experience and recommendations for follow up. Australas J Dermatol 2009;50:261-5.

20. Chuang TY, Popescu A, Su WP, Chute CG. Basal cell carcinoma. A population-based incidence study in Rochester, Minnesota. J Am Acad Dermatol 1990;22:413-7.
21. Chuang TY, Popescu NA, Su WP, Chute CG. Squamous cell carcinoma. A population-based incidence study in Rochester, Minn. Arch Dermatol 1990;126:185-8.
22. Lear JT, Smith AG, Heagerty AH, et al. Truncal site and detoxifying enzyme polymorphisms significantly reduce time to presentation of further primary cutaneous basal cell carcinoma. Carcinogenesis 1997;18:1499-503.
23. van Iersel CA, van de Velden HV, Kusters CD, et al. Prognostic factors for a subsequent basal cell carcinoma: implications for follow-up. Br J Dermatol 2005;153:1078-80.
24. Cox NH. Basal cell carcinoma in young adults. Br J Dermatol 1992;127:26-9.
25. Czarnecki D, Sutton T, Czarnecki C, Culjak G. A 10-year prospective study of patients with skin cancer. J Cutan Med Surg 2002;6:427-9.
26. Frankel DH, Hanusa BH, Zitelli JA. New primary nonmelanoma skin cancer in patients with a history of squamous cell carcinoma of the skin. Implications and recommendations for follow-up. J Am Acad Dermatol 1992;26:720-6.
27. Friedman GD, Tekawa IS. Association of basal cell skin cancers with other cancers (United States). Cancer Causes Control 2000;11:891-7.
28. Frisch M, Hjalgrim H, Olsen JH, Melbye M. Risk for subsequent cancer after diagnosis of basal-cell carcinoma. A population-based, epidemiologic study. Ann Intern Med 1996;125:815-21.
29. Frisch M, Melbye M. New primary cancers after squamous cell skin cancer. Am J Epidemiol 1995;141:916-22.
30. Graells J. The risk and risk factors of a second non-melanoma skin cancer: a study in a Mediterranean population. J Eur Acad Dermatol Venereol 2004;18:142-7.
31. Kiiski V, de Vries E, Flohil SC, et al. Risk factors for single and multiple basal cell carcinomas. Arch Dermatol 2010;146:848-55.
32. Levi F, Randimbison L, Maspoli M, Te VC, La Vecchia C. High incidence of second basal cell skin cancers. Int J Cancer 2006;119:1505-7.
33. Lindelof B, Sigurgeirsson B, Wallberg P, Eklund G. Occurrence of other malignancies in 1973 patients with basal cell carcinoma. J Am Acad Dermatol 1991;25:245-8.
34. Maitra SK, Gallo H, Rowland-Payne C, Robinson D, Moller H. Second primary cancers in patients with squamous cell carcinoma of the skin. Br J Cancer 2005;92:570-1.
35. Marghoob A, Kopf AW, Bart RS, et al. Risk of another basal cell carcinoma developing after treatment of a basal cell carcinoma. J Am Acad Dermatol 1993;28:22-8.
36. Bower CP, Lear JT, Bygrave S, Etherington D, Harvey I, Archer CB. Basal cell carcinoma and risk of subsequent malignancies: A cancer registry-based study in southwest England. J Am Acad Dermatol 2000;42:988-91.
37. Milan T, Pukkala E, Verkasalo PK, et al. Subsequent primary cancers after basal-cell carcinoma: A nationwide study in Finland from 1953 to 1995. Int J Cancer 2000;87:283-8.
38. Pulido A, Bellon JM, Carretero F, et al. Epidemiological trends in non melanoma skin cancer in a Mediterranean population. Melanoma Res 2010;20:e69-e70.
39. Raasch BA, Buettner PG. Multiple nonmelanoma skin cancer in an exposed Australian population. Int J Dermatol 2002;41:652-8.
40. Ramachandran S, Fryer AA, Smith AG, et al. Basal cell carcinomas: association of allelic variants with a high-risk subgroup of patients with the multiple presentation phenotype. Pharmacogenetics 2001;11:247-54.

41. Ramachandran S, Rajaratnam R, Smith AG, Lear JT, Strange RC. Patients with both basal and squamous cell carcinomas are at a lower risk of further basal cell carcinomas than patients with only a basal cell carcinoma. J Am Acad Dermatol 2009;61:247-51.
42. Richmond-Sinclair NM, Pandeya N, Williams GM, Neale RE, van der Pols JC, Green AC. Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: a 16-year longitudinal study. Int J Cancer 2010;127:2622-9.
43. Schinstine M, Goldman GD. Risk of synchronous and metachronous second nonmelanoma skin cancer when referred for Mohs micrographic surgery. J Am Acad Dermatol 2001;44:497-9.
44. Wassberg C, Thorn M, Yuen J, Hakulinen T, Ringborg U. Cancer risk in patients with earlier diagnosis of cutaneous melanoma in situ. Int J Cancer 1999;83:314-7.
45. Reizner GT, Chuang TY, Elpern DJ, Stone JL, Farmer ER. Basal cell carcinoma in Kauai, Hawaii: the highest documented incidence in the United States. J Am Acad Dermatol 1993;29:184-9.
46. Chuang TY, Reizner GT, Elpern DJ, Stone JL, Farmer ER. Squamous cell carcinoma in Kauai, Hawaii. Int J Dermatol 1995;34:393-7.
47. Biro L, Price E, MacWilliams P. Basal-cell carcinoma in office practice. N Y State J Med 1975;75:1427-33.
48. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524-30.
49. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
50. Karahalios E. Second primary cancers in Victoria. Second primary cancers in Victoria Victorian Cancer Registry 2009.
51. Garbe C, Paul A, Kohler-Spath H, et al. Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy. J Clin Oncol 2003;21:520-9.
52. van der Leest RJT, Liu L, Coebergh JWW, et al. Risk of second primary in situ and invasive melanoma in Dutch population-based cohort: 1989 - 2008. Br J Dermatol 2012 *(accepted for publication)*.
53. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M. The Newcastla-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp accessed at May 6th 2011.
54. Aung K, Htay T. Thiazide diuretics and the risk of hip fracture. Cochrane Database Syst Rev 2011:CD005185.
55. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
56. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
57. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21:589-624.
58. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
59. Flohil SC, de Vries E, Neumann HA, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in The Netherlands. Acta Derm Venereol 2011;91:24-30.
60. Karagas MR. Occurrence of cutaneous basal cell and squamous cell malignancies among those with a prior history of skin cancer. The Skin Cancer Prevention Study Group. J Invest Dermatol 1994;102:10S-3S.
61. Dong C, Hemminki K. Second primary neoplasms in 633,964 cancer patients in Sweden, 1958-1996. Int J Cancer 2001;93:155-61.

62. Wassberg C, Thorn M, Yuen J, Ringborg U, Hakulinen T. Second primary cancers in patients with squamous cell carcinoma of the skin: a population-based study in Sweden. Int J Cancer 1999;80:511-5.
63. Czarnecki C, Czarnecki D. Patients who have multiple skin cancers develop new skin cancers at a constant rate. Arch Dermatol 2002;138:125.
64. Gudbjartsson DF, Sulem P, Stacey SN, et al. ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat Genet 2008;40:886-91.
65. Stacey SN, Gudbjartsson DF, Sulem P, et al. Common variants on 1p36 and 1q42 are associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits. Nat Genet 2008;40:1313-8.
66. Tessari G, Naldi L, Boschiero L, et al. Incidence and clinical predictors of a subsequent nonmelanoma skin cancer in solid organ transplant recipients with a first nonmelanoma skin cancer: a multicenter cohort study. Arch Dermatol 2010;146:294-9.
67. Jensen P, Hansen S, Moller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol 1999;40:177-86.
68. Stern RS. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. J Am Acad Dermatol 2012;66:553-62.
69. Jemec GB, Holm EA. Nonmelanoma skin cancer in organ transplant patients. Transplantation 2003;75:253-7.
70. Watt TC, Inskip PD, Stratton K, et al. Radiation-related risk of Basal cell carcinoma: a report from the childhood cancer survivor study. J Natl Cancer Inst 2012;104:1240-50.
71. Wheless L, Black J, Alberg AJ. Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. Cancer Epidemiol Biomarkers Prev 2010;19:1686-95.
72. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005;41:45-60.
73. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet 2010;375:673-85.
74. Egger M, Smith GD, Sterne JA. Uses and abuses of meta-analysis. Clin Med 2001;1:478-84.
75. United States Preventative Services Task Force http://archive.ahrq.gov/clinic/ajpmsuppl/skcarr.htm accessed at August 18th 2012.
76. Holterhues C, van de Poll-Franse LV, de Vries E, Neumann HA, Nijsten TE. Melanoma patients receive more follow-up care than current guideline recommendations: a study of 546 patients from the general Dutch population. J Eur Acad Dermatol Venereol 2011 doi: 10.1111/j.1468-3083.2011.04297.x. [Epub ahead of print].
77. Flohil SC, Proby CM, Forrest AD, et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. Br J Dermatol 2012;167:22-9.
78. Flohil SC, van Tiel S, Koljenovic S, et al. Frequency of non-histologically diagnosed basal cell carcinomas in daily Dutch practice. J Eur Acad Dermatol Venereol 2012 doi: 10.1111/j.1468-3083.2011.04407.x [Epub ahead of print].
79. Boyle P, Parkin DM. Chapter 11 Statistical methods for registries. In: Cancer registration: principles and methods (IARC Scientific Publication no 95) Lyone, France: International Agency for Research on Cancer 1991:126-58.
80. de Vries E, Micallef R, Brewster DH, et al. Population-based estimates of the occurrence of multiple vs first primary basal cell carcinomas in 4 European regions. Arch Dermatol 2012;148:347-54.
81. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. BMJ 2012;344:d7762.

Appendix Table 1. Search strings

Database	Search string[a]	Number of articles (first search performed on May 5th 2012)	Number of articles (update from May 1st until January 1st 2012)[b]
Pubmed	(cancer*[tw] OR tumor[tw] OR tumors[tw] OR tumou*[tw] OR carcinom*[tw] OR neoplas*[tw] OR squam*[tw] OR epitheliom*[tw] OR melanom*[tw]) AND (multiple[tw] OR subsequen*[tw] OR second*[tw] OR metachron*[tw]) AND (skin*[tw] OR dermatol*[tw] OR basal[tw] OR baso*[tw] OR cutan*[tw] OR cutis*[tw] OR rodent ulcer*[tw] OR melanom*[tw]) AND (risk[mesh] OR risk*[tw] OR incidence*[tw] OR prevalence*[tw] OR epidemiol*[tw]) AND eng[la] NOT (animals[mesh] NOT humans[mesh])	7076	409
EMbase	(((cancer* OR tumo* OR carcinom* OR neoplas* OR melanom*) NEAR/3 (multiple OR subsequen* OR another OR further OR more OR second* OR metachron*)):ti,ab,de OR 'second cancer'/syn) AND (((cancer* OR tumo* OR carcinom* OR neoplas* OR squam* OR epitheliom*) NEAR/3 (skin* OR derma* OR basal OR baso* OR cutan* OR cutis*)):ti,ab,de OR 'skin tumor'/syn OR (rodent NEAR/1 ulcer*):ti,ab,de OR melanom*:ti,ab,de) AND (risk* OR incidence* OR prevalence* OR epidemiol*):ti,ab,de AND [english]/lim NOT ([animals]/lim NOT [humans]/lim)	3155	304
Web of Science	((cancer* OR tumo* OR carcinom* OR neoplas* OR melanom*) SAME (multiple OR subsequen* OR another OR further OR more OR second* OR metachron*)) AND (((cancer* OR tumo* OR carcinom* OR neoplas* OR squam* OR epitheliom*) SAME (skin* OR derma* OR basal OR baso* OR cutan* OR cutis*)) OR rodent-ulcer* OR melanom*) AND (risk* OR incidence* OR prevalence* OR epidemiol*)	2299	
Web of Science[a]	((cancer* OR tumo* OR carcinom* OR neoplas* OR melanom*) NEAR/1 (multiple OR subsequen* OR another OR further OR more OR second* OR metachron*)) AND (((cancer* OR tumo* OR carcinom* OR neoplas* OR squam* OR epitheliom*) NEAR/3 (skin* OR derma* OR basal OR baso* OR cutan* OR cutis*)) OR (rodent NEAR/1 ulcer*) OR melanom*) AND (risk* OR incidence* OR prevalence* OR epidemiol*)		200
Total		**12530**	**913**
Deduplication		-3151	-148
Total (after deduplication)		**9379**	**765**

[a] Identical search strings were used for the update within Pubmed and Embase databases. The search string for Web of Science was adjusted due to changes of this database and time was restricted to 2011 and 2012.

[b] Literature search was updated until January 1st 2012, but was performed on January 18th 2012

Appendix 2A. Adapted Newcastle – Ottawa quality assessment scale for cohort studies

	NOS[a]		Adapted NOS[b]	
Selection				
1	**Representativeness of the exposed cohort**		**Representativeness of the cohort**	
a)	truly representative of the average … (describe) in the community	*	population-based study	**
b)	somewhat representative of the average … in the community	*	population-based study with restrictions (e.g. age limits)	*
c)	selected group of users eg nurses, volunteers	-	hospital-based study	-
d)	no description of the derivation of the cohort	-	no description of the derivation of the cohort	-
2	**Selection of the non exposed cohort**		*Question removed, not applicable in our research question*	
a)	drawn from the same community as the exposed cohort	*		NA
b)	drawn from a different source	-		
c)	no description of the derivation of the non exposed cohort	-		
3	**Ascertainment of exposure**		**Ascertainment of completeness of the studied cohort**	
a)	secure record (eg surgical records)	*	nationwide pathology lab, Cancer Registry	*
b)	structured interview	*	hospital-based	-
c)	written self report	-	written self report	-
d)	no description	-	no description	-
4	**Demonstration that outcome of interest was not present at start of study**		**Certainty of the first skin cancer**	
a)	Yes	*	yes, truly first skin cancer, explicitly mentioned in text	*
b)	No	-	no / unknown	-
Comparability				
1	**Comparability of cohorts on the basis of the design or analysis**		**Comparability of cohorts on the basis of the design or analysis**	
a)	study controls for … (select the most important factor)	*	risk of developing another skin cancer is stratified for sex	*
b)	study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)	*	study controls for any additional factor (e.g. follow-up, age)	*
Outcome				
1	**Assessment of outcome**		**Ascertainment of another skin cancer**	
a)	independent blind assessment	*	record linkage (e.g. cancer registry, nationwide pathology database)	*
b)	record linkage	*	hospital pathology database	*
c)	self report	-	NA (exclusion criteria nr. …)	-
d)	no description	-	no description	-
2	**Was follow-up long enough for outcomes to occur**		**Was follow-up long enough for outcomes to occur**	
a)	yes (select an adequate follow up period for outcome of interest)	*	yes (mean/median follow-up time is at least 3 years)	*
b)	No	-	no or unknown	-
3	**Adequacy of follow up of cohorts**		**Adequacy of follow up of cohorts**	
a)	complete follow up - all subjects accounted for	*	complete follow up - all subjects accounted for	*
b)	subjects lost to follow up unlikely to introduce bias - small number lost - > … % (select an adequate %) follow up, or description provided of those lost)	*	subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % (select an adequate %) follow up, or description provided of those lost)	*
c)	follow up rate < … % (select an adequate %) and no description of those lost	-	follow up rate < 80 % (select an adequate %) and no description of those lost	-
d)	no statement	-	no statement	-

[a] A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

[b] A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories (except Selection question 1, two stars can be given to population-based studies). A maximum of two stars can be given for Comparability.

Abbreviations: 'NOS'=Newcastle - Ottawa Scale; 'NA'= not applicable

Appendix 2B. Adapted Newcastle – Ottawa quality assessment scale for case-control studies

	NOS[a]		Adapted NOS[b]	
Selection				
1	**Is the case definition adequate**		**Is the case definition (skin cancer patients who developed another skin cancer) adequate**	
a)	yes, with independent validation	*	secure record (e.g. cancer registry, nationwide pathology database)	*
b)	yes, e.g. record linkage or based on self reports	-	hospital-based database	-
c)	no description	-	no description	-
2	**Representativeness of the cases**		**Representativeness of the cases (skin cancer patients who developed another skin cancer)**	
a)	consecutive or obviously representative series of cases	*	population-based study	*
b)	potential for selection biases or not stated	-	population-based study with restrictions (e.g. age limits)	*
c)			hospital-based study	-
d)			no description of the derivation of the cohort	-
3	**Selection of Controls**		**Selection of Controls (skin cancer patients who did not develop another skin cancer)**	
a)	community controls	*	population-based study	*
b)	hospital controls	*	population-based study with restrictions (e.g. age limits)	*
c)	no description	-	hospital-based study	-
d)			no description of the derivation of the cohort	-
4	**Definition of Controls**		**Definition of Controls (skin cancer patients who did not develop another skin cancer)**	
a)	no history of disease (endpoint)	*	no development of another skin cancer	*
b)	no description of source	-	not described / unknown	-
Comparability				
1	**Comparability of cases and controls on the basis of the design or analysis**		**Comparability of cases and controls on the basis of the design or analysis**	
a)	study controls for … (Select the most important factor.)	*	study controls for age	*
b)	study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)	*	study controls for any additional factor (e.g. sex)	*
Exposure				
1	**Assessment of outcome**		**Ascertainment of another skin cancer**	
a)	secure record (e.g. surgical records)	*	secure record (e.g. cancer registry, nationwide pathology database)	**
b)	structured interview where blind to case/control status	*	hospital pathology database	*
c)	interview not blinded to case/control status	-	NA	-
d)	written self report or medical record only	-	NA	-
e)	no description	-	no description	-
2	**Same method of ascertainment for cases and controls**		*Question removed, not applicable in our research question*	
a)	yes	*		NA
b)	No	-		
3	**Non-Response rate**		**Non-Response rate**	
a)	same rate for both groups	*	same rate for both groups	*
b)	non respondents described	-	non respondents described	-
c)	rate different and no designation	-	rate different and no designation	-

[a] A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

[b] A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories (except Exposure question 1, two stars can be given to a secure record). A maximum of two stars can be given for Comparability.

Abbreviations: 'NOS'=Newcastle - Ottawa Scale; 'NA'= not applicable

Appendix Table 3. Study characteristics

A. Basal cell carcinoma (BCC) as index tumor

	First author	Year	Country	Time Period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Sub- group	No. of patients	% sub-sequent tumor	Mean age (years)	Mean follow-up (years)	Person years (total)	S	C	O	T
BCC after BCC (n = 19)	Biro [47]	1975	USA	1966 - 1971	Retrospective	Cohort	No	H	-	628	21.5	-	-	-	0	0	0	0
	Chuang [20]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	657	26.0	65	5	-	4	0	2	6
	Cox [24]	1992	UK	1979 - 1989	Retrospective	Cohort	Yes	H	15 - 34 year of age	54	7.4	30	1	-	3	0	1	4
	Di Landro [9]	2004	Italy	1994 - 2002	Retrospective	Cohort	No	H	-	322	37.6	68	6	-	0	1	1	2
	Flohil [2]	2011	Netherlands	2004 - 2009	Retrospective	Cohort	No	P	-	2483	27.7	65	5	12297	4	2	3	9
	Karagas [11]	1992	USA	1980 - 1989	Prospective	Cohort	No	H	Multi - center trial	1735	37.5	-	5	-	0	2	1	3
	Kiiski [31]	2010	Netherlands	1990 - 2007	Prospective	Cohort	No	P	> 55 year of age	524	31.1	69	12	6274	3	2	2	7
	Lear [22]	1997	UK	1991 - 1995	Retrospective	Cohort	No	H	-	856	33.9	68	-	-	1	0	0	1
	Levi [32]	2006	Switzerland	1976 - 2003	Retrospective	Cohort	Yes	P	-	1868	27.1	69	-	20261	4	2	2	8
	Marghoob [35]	1993	USA	-	Retrospective	Cohort	No	H	Whites	260	52.7	59	7	-	0	1	2	3
	McLoone [14]	2006	UK	1999 - 2000	Retrospective	Cohort	No	H	Only low risk BCC	114	16.7	67	-	196	0	0	1	1
	Pulido [38]	2010	Spain	1997 - 2007	Retrospective	Cohort	No	H	Only solid BCC	106	10.4	66	10	-	0	0	2	2
	Ramachandran [40]	2001	UK	1991 - 1998	Prospective	Cohort	No	H	-	926	27.8	-	-	-	0	0	0	0
	Ramachandran [41]	2009	UK	1991 - 1998	Prospective	Cohort	No	H	-	174	48.9	-	5	-	0	0	2	2
	Reizner [45]	1993	USA	1983 - 1987	Prospective	Cohort	No	P	-	242	16.9	57	5	71888	2	0	1	3
	Revenga [6]	2004	Spain	1998 - 2001	Prospective	Cohort	No	H	-	85	5.9		3	-	1	0	2	3
	Richmond-Sinclair [42]	2010	Australia	1992 - 2007	Prospective	Cohort	No	P / field trial	-	401	57.9	60	-	-	1	1	1	3
	Schreiber [17]	1990	USA	1985 - 1988	Retrospective	Cohort	Yes	P	-	4670	46.9	-	-	-	3	1	1	5
	van Iersel [23]	2005	Netherlands	1993 - 1998	Retrospective	Cohort	No	H	-	237	29.5	-	3.1	-	1	2	2	5

SCC after BCC (n = 8)	Cantwell [8]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P	-	14442	2.4	68	4	-	4	1	3	8
	Chuang [20]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	657	11.0	65	-	-	4	0	1	5
	Di Landro [9]	2004	Italy	1994 - 2002	Retrospective	Cohort	No	H	-	322	0.9	68	6	-	0	1	1	2
	Levi [12]	1998	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P	-	11878	4.2	68	-	76510	4	2	2	8
	McLoone [14]	2006	UK	1999 - 2000	Retrospective	Cohort	No	H	Only low risk BCC	114	2.6	67	-	196	0	0	1	1
	Pring [16]	2010	UK	1998 - 2007	Retrospective	Cohort	Yes	P	-	-	-	-	-	-	2	0	1	3
	Revenga [6]	2004	Spain	1998 - 2001	Prospective	Cohort	No	H	-	85	2.4	-	3	-	1	0	2	3
	Schreiber [17]	1990	USA	1985 - 1988	Retrospective	Cohort	Yes	P	-	4670	19.4	-	-	-	3	1	1	5
Melanoma after BCC (n = 12)	Bower [36]	2000	UK	1981 - 1995	Retrospective	Cohort	Yes	P	-	13961	0.5	-	-	117939	4	1	2	7
	Cantwell [8]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P	-	14442	0.3	68	4	-	4	1	3	8
	Chuang [20]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	657	1.1	65	-	-	4	0	1	5
	Di Landro [9]	2004	Italy	1994 - 2002	Retrospective	Cohort	No	H	-	322	0.6	68	6	-	0	1	1	2
	Friedman [27]	2000	USA	1974 - 1997	Retrospective	Case - control	No	P	-	3164	2.4	-	11	-	2	2	2	6
	Frisch [28]	1996	Denmark	1978 - 1991	Retrospective	Cohort	Yes	P	-	37674	0.4	68	4	190945	4	2	3	9
	Levi [12]	1998	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P	-	11878	0.5	68		76510	4	2	2	8
	Lindelof [33]	1991	Sweden	1971 - 1983	Retrospective	Cohort	Partly	H	-	1973	0.8	68	7	12867	1	1	2	4
	Milan [37]	2000	Finland	1953 - 1995	Retrospective	Cohort	Yes	P	-	71924	0.4	-	-	625144	4	2	2	8
	Nugent [15]	2005	Canada	1956 - 2000	Retrospective	Cohort	Yes	P	-	28956	0.5	67	-	282814	4	2	1	7
	Pring [16]	2010	UK	1998 - 2007	Retrospective	Cohort	Yes	P	-	-	-	-	-	-	2	0	1	3
	Troyanova [18]	2002	Bulgaria	1993 - 2000	Retrospective	Cohort	Yes	P	-	1820	0.1	-	-	15856	4	1	2	7

B. Squamous cell carcinoma (SCC) as index tumor

	First author	Year	Country	Time Period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Sub-group	No. of patients	% sub-sequent tumor	Mean age (years)	Mean follow-up (years)	Person years (total)	S	C	O	T
SCC after SCC (n=8)	Chuang [21]	1990	USA	1976 – 1984	Retrospective	Cohort	No	P	-	169	11.8	71	4	-	4	0	1	5
	Chuang [46]	1995	USA	1983 – 1987	Prospective	Cohort	No	P	-	58	13.8	66	5	71888	2	0	1	3
	Dong [61]	2001	Sweden	1958 – 1996	Retrospective	Cohort	Yes	P	-	17438	6.9	72	-	-	4	2	1	7
	Frankel [26]	1992	USA	1980 – 1988	Retrospective	Cohort	No	H	Only those who had MMS	101	-	67	5	-	0	2	1	3
	Karagas [11]	1992	USA	1980 – 1989	Prospective	Cohort	No	H	Multi-center trial	189	-	-	5	-	0	2	1	3
	Kemmett [5]	2004	Scotland	1999 – 2003	Retrospective	Cohort	No	H	-	104	21.2	77	4	-	0	1	1	2
	Schreiber [17]	1990	USA	1985 – 1988	Retrospective	Cohort	Yes	P	-	2192	17.3	-	-	-	3	1	1	5
	Yoong [19]	2009	Australia	1996 – 2006	Retrospective	Cohort	No	H	-	40	-	65	8	-	0	0	3	3
BCC after SCC (n=8)	Cantwell [8]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P	-	6401	5.2	74	4	-	4	1	3	8
	Chuang [21]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	169	43.2	71	-	-	4	0	1	5
	Efird [10]	2002	USA	1974 - 1989	Retrospective	Case - control	No	H	-	822	10.8	-	8	-	2	0	2	4
	Kemmett [5]	2004	Scotland	1999 - 2003	Retrospective	Cohort	No	H	-	104	14.4	77	4	-	0	1	1	2
	Levi [13]	1997	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P	-	4639	6.8	74	-	23152	4	2	2	8
	Pring [16]	2010	UK	1998 - 2007	Retrospective	Cohort	Yes	P	-	-	-	-	-	-	2	0	1	3
	Schreiber [17]	1990	USA	1985 - 1988	Retrospective	Cohort	Yes	P	-	2192	43.0	-	-	-	3	1	1	5
	Yoong [19]	2009	Australia	1996 - 2006	Retrospective	Cohort	No	H	-	40	-	65	8	-	0	0	3	3
Melanoma after SCC (n=11)	Cantwell [8]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P	-	6401	0.2	74	4	-	4	1	3	8
	Chuang[21]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	169	1.8	71	-	-	4	0	1	5
	Efird [10]	2002	USA	1974 - 1997	Retrospective	Case - control	No	H	-	822	1.2	-	8	-	2	0	2	4
	Frisch [29]	1995	Denmark	1978 - 1989	Retrospective	Cohort	Yes	P	-	5100	0.3	75	-	22916	4	2	2	8
	Levi [13]	1997	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P	-	4639	0.5	74	-	23152	4	2	2	8
	Maitra [34]	2005	UK	1961 - 2000	Retrospective	Cohort	Yes	P	-	25731	0.3		-		4	1	1	6

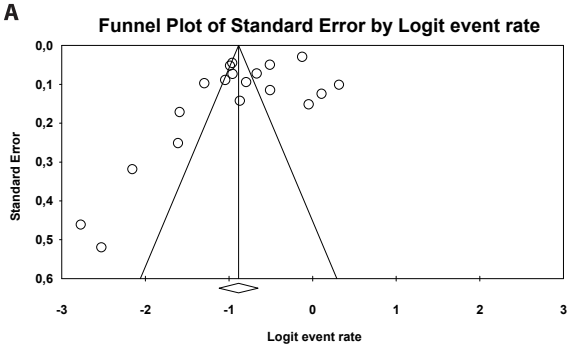
Nugent [15]	2005	Canada	1956 - 2000	Retrospective	Cohort	Yes	P	-	7833	0.5	73	-	61416	4	2	1		7
Pring [16]	2010	UK	1998 - 2007	Retrospective	Cohort	Yes	P	-	-	-	-	-		2	0	1		3
Troyanova [18]	2002	Bulgaria	1993 - 2000	Retrospective	Cohort	Yes	P	-	741	0.5	-	-	15856	4	1	2		7
Wassberg [44]	1999	Sweden	1985 - 1992	Retrospective	Cohort	Yes	P	-	25947	0.4	75	5	137312	4	2	3		9
Yoong [19]	2009	Australia	1996 - 2006	Retrospective	Cohort	No	H	-	40	-	65	8	-	0	0	3		3

C. Keratinocyte carcinoma (KC) as index tumor

	First author	Year	Country	Time Period	Study Design		Cancer registry	Hospital -(H) or population (P) -based	Sub- group	No. of patients	% sub-sequent tumor	Mean age (years)	Mean follow-up (years)	Person years (total)	S	C	O	T
KC after KC (n = 8)	Czarnecki [25]	2002	Australia	1988 – 1989	Prospective	Cohort	No	H	-	481	67.8	-	10	-	0	1	2	3
	Graells [30]	2004	Spain	1995 – 2001	Retrospective	Cohort	No	H	-	535	22.4	68	2	-	0	0	1	1
	Karagas [11]	1992	USA	1980 – 1989	Prospective	Cohort	No	H	Multi- center trial	1805	-	-	5	-	0	2	1	3
	Raasch [39]	2002	Australia	1997 – 1999	Prospective	Cohort	No	P	-	6708	38.5	-	-	-	2	0	1	3
	Schinstine [43]	2001	USA	1996 – 1998	Retrospective	Cohort	No	H	96% on head and neck	440	39.3	-	2	-	1	0	2	3
	Schreiber [17]	1990	USA	1985 – 1988	Retrospective	Cohort	Yes	P	-	6310	50.0	69	-	-	3	1	1	5
	Veien [7]	2001	Denmark	1995 – 1998	Prospective	Cohort	No	H	-	638	27.1	-	2	-	0	0	0	0
	Veien [7]	2001	Denmark	1990 – 1993	Prospective	Cohort	No	H	-	526	20.3	-	2	-	0	0	0	0

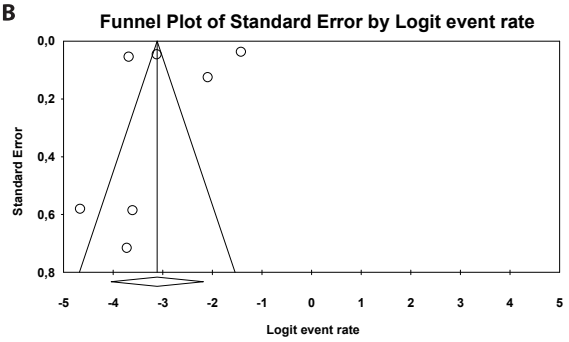
Abbreviations: BCC, basal cell carcinoma; H, hospital-based; KC, keratinocyte carcinoma; N, number; NA, not applicable; NOS, Newcastle – Ottawa scale; P, Population-based; SCC, squamous cell carcinoma; SCOT, Selection Comparibility Outcome Total NOS; USA, United States of America.

A



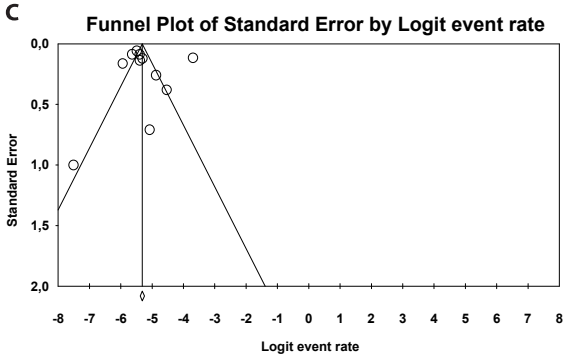
p value 0.6

B



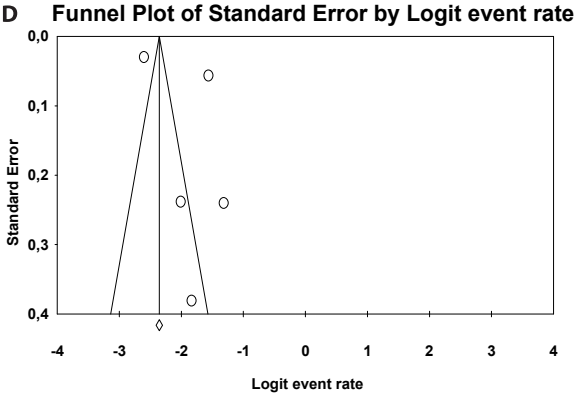
p value 0.6

C

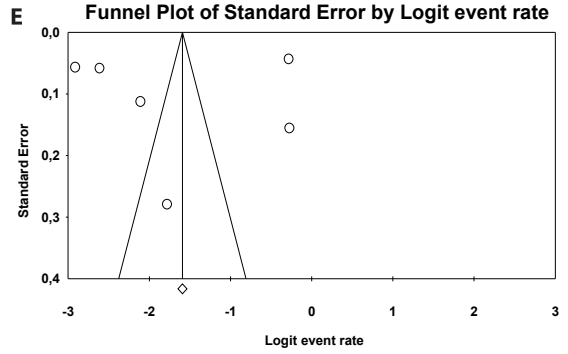


p value 0.7

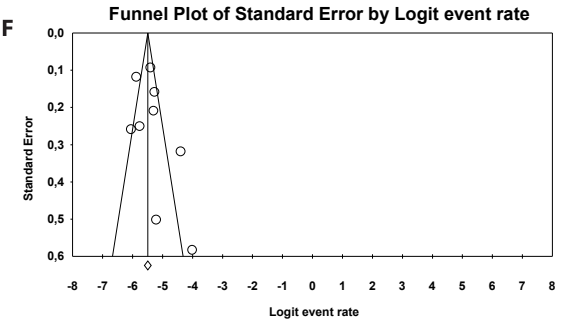
D



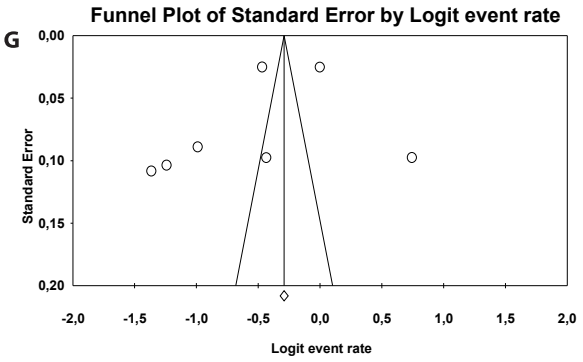
p value 0.4



p value 0.8



p value 0.3



p value 0.4

Appendix figure 1 Risk (%) of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma

A Basal cell carcinoma (BCC) after BCC (n = 19)
B Squamous cell carcinoma (SCC) after BCC (n = 7)
C Melanoma after BCC (n = 11)
D SCC after SCC (n = 5)
E BCC after SCC (n = 6)
F Melanoma after SCC (n = 9)
G Keratinocyte carcinoma (KC) after KC (n = 7)

Abbreviations : BCC, basal cell carcinoma; CI, confidence interval; LB, lower bound, KC, keratinocyte carcinoma; SCC, squamous cell carcinoma; UB, upper bound.

CHAPTER 6

Frequency of non-histologically diagnosed basal cell carcinomas in daily Dutch practice

S.C. Flohil

S. van Tiel

S. Koljenović

G. Jaanen-van der Sanden

L.I.H. Overbeek

E. de Vries

T. Nijsten

J Eur Acad Dermatol Venereol 2012 doi: 10.1111/j.1468-3083.2011.04407.x [Epub ahead of print]

ABSTRACT

Background

Population-based basal cell carcinoma (BCC) incidences are based on cancer registry data, however these only include histologically diagnosed tumors.

Objectives

First, to investigate the number of subsequent non-histologically diagnosed BCC(s) in patients with a first histologically diagnosed BCC in 2004. Secondly, to observe differences in tumor characteristics between subsequent histologically and subsequent non-histologically diagnosed BCC(s).

Methods

All patients, from four hospitals located in the serving area of the Eindhoven Cancer Registry, with a first histologically diagnosed BCC in 2004 (n=1,290) were selected. A linkage was made with PALGA, the nationwide network and registry of histo- and cytopathology, to obtain pathology reports of subsequent histologically diagnosed BCC(s) up to November 1st 2010. Patient records were extracted from the participating dermatology departments and reviewed up to November 1st 2010 to identify non-histologically diagnosed BCC(s).

Results

Overall, 33.2% of the 1,089 followed patients developed subsequent histologically and/or non-histologically diagnosed BCCs. In total, 1,974 BCCs were observed of which 1,833 were histologically and 141 were non-histologically diagnosed BCCs. The distribution of tumor site and subtype differed significantly between subsequent histologically and subsequent non-histologically diagnosed BCCs.

Conclusions

The total burden of BCC is underestimated by the absence of data on the occurrence of non-histologically diagnosed BCCs in daily dermatological practice. It is pivotal for Dutch health care policy makers to acknowledge this in order to make accurate BCC-related cost estimates.

INTRODUCTION

The incidence of basal cell carcinoma (BCCs) of the skin is increasing worldwide and is becoming a growing public health problem. Population-based basal cell carcinoma (BCC) incidences are based on data from a few cancer registries that collect BCC information and in most cases only report the first or limited number of subsequent histologically diagnosed BCC(s) per patient (to limit registration costs).[1-3] About one third of the people with a first BCC develop subsequent histologically diagnosed BCC(s), but the occurrence of non-histologically diagnosed BCCs is not known.[4-5]

This study's objective was to investigate the frequency of BCCs that have not been examined histologically in patients with a prior BCC and to compare tumor characteristics between subsequent histologically and subsequent non-histologically diagnosed BCCs.

METHODS

This study was primarily conducted to examine the health care consumption of patients with a first histologically diagnosed BCC in 2004 for a report to the Dutch Ministry of Health. Data were obtained from the Dutch Eindhoven Cancer Registry (ECR) and four dermatology departments in that area.[1, 6] All 1,290 patients from the participating hospitals with a first histologically diagnosed BCC in 2004 were extracted from ECR. These patients were linked to PALGA, the Dutch nationwide network and registry of histo- and cytopathology.[4, 6] Twenty-nine patients were not found within PALGA and twenty-three patients had already a histologically diagnosed BCC prior to 2004. These 52 patients were excluded (figure 1). Therefore, 1,238 of the 1,290 patients were eligible for this study. BCC case definition has been described previously.[4]

Between January 14th and March 28th 2011, the dermatology records were reviewed until November 1st 2010 to identify subsequent histologically and non-histologically diagnosed BCCs. When a BCC was described in the dermatology record and no pathology record of this tumor was present, it was considered a non-histologically diagnosed BCC. Based on these dermatology records, another 149 patients were excluded because their dermatology records were incomplete and/or missing, or because they were not seen by a dermatologist for their first histologically diagnosed BCC in 2004 (figure 1).

The Pearson chi-square or Fisher's exact test was used for categorical and the unpaired T-test for continuous variables. In table 2, all patients (n=71) with multiple BCCs at date of first BCC diagnosis were excluded, since it would have been an arbitrary decision to choose which one was the initial index tumor. Person-years were counted from date of diagnosis of the first histologically diagnosed BCC in 2004 until the end date of observation (November 1st, 2010) or date of death (n= 196), whichever came first.

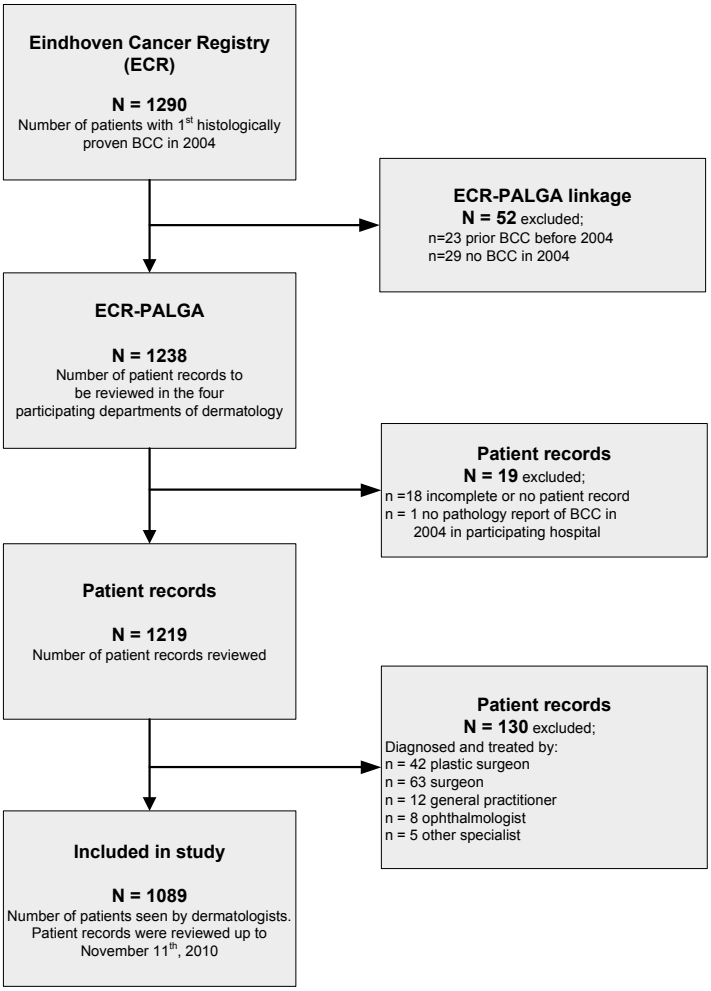


Figure 1. Description of the study population
Abbreviations: BCC, basal cell carcinoma; ECR, Eindhoven Cancer Registry; PALGA; the nationwide network and registry of histo- and cytopathology.

RESULTS

In total, 1,089 patients were included. Overall, they contributed 6,253 person-years of follow-up (table 1). The mean age at date of first histologically confirmed BCC was 65.0 (standard deviation 14.0). The male-female ratio was 1:1. During our study period, 33.2% of the 1,089 followed patients developed one or more subsequent

BCCs (table 1). More than a quarter of all eligible cases (27.1%) developed subsequent histologically diagnosed BCCs, of which 171 (57.8%) had one and 125 (42.2%) two or more. Sixty-six (6.1%) patients had subsequent non-histologically diagnosed BCCs of which 42 (63.6%) had one and 24 (36.4%) had two or more subsequent BCCs. Sixteen of these sixty-

six patients had only subsequent non-histologically diagnosed BCCs, while the remaining fifty patients also had subsequent histologically diagnosed BCCs. In total, 1,974 BCCs were diagnosed in 1,089 patients of which 1,833 (92.9%) were histologically and 141 (7.1%) were non-histologically diagnosed.

There were significant (p = 0.02) more females (n=40; 60.6%) with subsequent non-histologically diagnosed BCCs (twelve of the forty females also had subsequent histologically diagnosed BCCs) than there were females (n= 131; 44.3%) with subsequent histologically diagnosed BCCs (table 1). When comparing the dermatology departments (p=0.002) between patients with subsequent histologically diagnosed BCCs (n=296) and those (n=66) with subsequent non-histologically diagnosed BCCs (fifty persons also had subsequent histologically diagnosed BCCs), there was a significant difference (p = 0.002).

Almost 70% of the first histologically diagnosed BCCs in 2004 were located in the head and neck area, followed by trunk (20.1%) (table 2). More than half were nodular BCCs, followed by infiltrative (14.1%), superficial (13.7%) and micronodular (0.4%). The distribution of tumor

Table 1. Characteristics of the study population including 1,089 patients with a first, histologically diagnosed basal cell carcinoma in 2004

Characteristics	Total study population (n=1089)[1]	Patients with one BCC (%) (n=727)[1]	Patients with subsequent histologically diagnosed BCC(s) (%) *(n=296)*[1]	Patients with subsequent non-histologically diagnosed BCC(s) (%) *(n=66)*[1,2]	p-value[3]
Total follow-up time (years)	6252.5	4127.1	1733.9	391.4	
Mean follow-up per patient (years)	5.7	5.7	5.9	5.9	
Age at date of first BCC (years)					
Mean (±SD)	65.0 (14.0)	64.8 (14.2)	65.7 (13.4)	64.2 (± 14.5)	0.42
Median (IQR)	66.1 (19.2)	65.6 (20.0)	67.4 (18.6)	66.4 (15.7)	
Sex					
Female	544 (50.0)	373 (51.3)	131 (44.3)	40 (60.6%)	**0.02**
Male	545 (50.0)	354 (48.7)	165 (55.7)	26 (39.4%)	
Dermatology department					
1	374 (34.3)	243 (33.4)	119 (40.2)	12 (18.2%)	**0.002**
2	159 (14.6)	106 (14.6)	44 (14.9)	9 (13.6%)	
3	337 (30.9)	221 (30.4)	90 (30.4)	26 (39.3%)	
4	219 (20.1)	157 (21.6)	43 (14.5)	19 (28.8%)	

[1] Percentages may not equal 100% due to rounding.

[2] Of the 66 patients with subsequent non-histologically diagnosed BCC(s), 50 patients also had subsequent histologically diagnosed BCC(s).

[3] Differences in distribution between patients with subsequent histologically diagnosed BCC(s) (n=296) and patients with subsequent non-histologically diagnosed BCC(s) (n=66) were compared, using the unpaired T-test and Pearson chi-square test. P-value was two-tailed and statistically significant when p-value < 0.05.

Abbreviations: BCC, basal cell carcinoma; IQR, interquartile range; N, number; SD, standard deviation

Table 2. Distribution of tumor site and subtype of subsequent (non-)histologically diagnosed basal cell carcinomas

Tumor site	Number of first histologically diagnosed BCC (%) in 2004 *(n=1018)*[1,3]	Number of subsequent histologically diagnosed BCCs (%) *(n=551)*[1]	Number of subsequent non-histologically diagnosed BCCs (%) *(n=121)*[1]	p-value[2,5]
Head and neck	**711 (69.8)**	**308 (55.9)**	**14 (11.6)**	**< 0.001**
Scalp	18 (1.8)	16 (2.9)	-	
Temporal areas	77 (7.6)	40 (7.3)	3 (2.5)	
Forehead	93 (9.1)	58 (10.5)	-	
Retro- and preauriculair areas	31 (3.0)	20 (3.6)	1 (0.8)	
Cheeks	90 (8.8)	27 (4.9)	1 (0.8)	
Nose / surroundings of the nose	163 (16.0)	54 (9.8)	2 (1.7)	
Nasolabial fold and upper lip	40 (3.9)	15 (2.7)	-	
Lower lip and chin	10 (1.0)	9 (1.6)	-	
Jaw	7 (0.7)	2 (0.4)	-	
Ears	33 (3.2)	8 (1.5)	1 (0.8)	
Eyebrow areas / eye surroundings	94 (9.2)	23 (4.2)	-	
Head, specific location unkown	13 (1.3)	7 (1.3)	-	
Neck	42 (4.1)	29 (5.3)	6 (5.0)	
Trunk	**205 (20.1)**	**178 (32.3)**	**66 (54.5)**	**< 0.001**
Back and shoulders	112 (11.0)	92 (16.7)	49 (40.5)	
Thorax	74 (7.3)	64 (11.6)	17 (14.0)	
Abdomen	16 (1.6)	21 (3.8)	-	
Trunk, specific location unkown	3 (0.3)	1 (0.2)	-	
Upper extremities	**38 (3.7)**	**21 (3.8)**	**21 (17.4)**	**< 0.001**
Lower extremities	**55 (5.4)**	**37 (6.7)**	**18 (14.8)**	**0.003**
Other (anogenital area, buttocks)	**4 (0.4)**	**4 (0.7)**	**-**	
Missing	**5 (0.5)**	**3 (0.5)**	**2 (1.7)**	

Tumor subtype[4]	Number of first histologically diagnosed BCC (%) in 2004 *(n=1018)*[1]	Number of subsequent histologically diagnosed BCCs (%) *(n=551)*[1]	Number of subsequent non-histologically diagnosed BCCs (%) *(n=121)*[1]	p-value[2,5]
Nodular	601 (59.0)	257 (46.6)	-	**< 0.001**
Superficial	139 (13.7)	161 (29.2)	76 (62.8)	**< 0.001**
Infiltrative	144 (14.1)	72 (13.1)	-	**< 0.001**
Micronodular	4 (0.4)	8 (1.5)	-	0.36
Basal cell carcinoma, unspecified	130 (12.8)	53 (9.6)	45 (37.2)	**< 0.001**

[1] Percentages may not equal 100% due to rounding.

[2] Differences in distribution between subsequent histologically and non-histologically diagnosed BCCs were compared using the Pearson chi-square test or Fisher's exact test. P-value was two-tailed and statistically significant when p-value < 0.05.

[3] Seventy-one patients were excluded from this table since they had multiple BCCs at date of diagnosis of first histologically confirmed BCC in 2004.
[4] Tumor subtype of histologically confirmed BCCs was based on pathology reports and for non-histologically diagnosed BCCs on clinical suspicion.
[5] Reference category in statistical analyses: all other tumor sites or subtypes combined.
Abbreviations: BCC, basal cell carcinoma; N, number

site was similar for subsequent histologically confirmed BCCs, but differed for tumor subtype (table 2). Subsequent non-histologically diagnosed BCCs were predominantly located on trunk, while the head and neck area was the least affected. Almost two-third (n=76) of the non-histologically diagnosed BCCs were suspected to be superficial, whereas in 45 cases (37.2%) the BCC subtype was not described.

When comparing tumor sites, there were significant more subsequent histologically diagnosed BCCs than subsequent non-histologically diagnosed BCCs located on the head and neck ($p < 0.001$). Compared to histologically diagnosed BCCs, there were significant more subsequent non-histologically diagnosed BCCs located on trunk ($p < 0.001$), upper extremities ($p < 0.001$) and lower extremities ($p = 0.003$). There were significantly more clinically suspicious superficial BCCs in the group of subsequent non-histologically diagnosed BCCs than there were in the group of subsequent histologically diagnosed BCCs ($p < 0.001$).

DISCUSSION

Among Dutch patients with a prior BCC receiving dermatological care, 7% of all subsequent BCCs were not histologically diagnosed, which is higher than a small Scottish study (3.8%) and lower than a French estimate based on a survey among dermatologists (14.1%).[7-8] In addition to multiple BCCs, non-histologically diagnosed BCCs explain the underreporting of the absolute BCC number based on cancer registry data.[5, 9] Non-histologically diagnosed BCCs are often suspected to have a superficial subtype and are most often located on the trunk. In contrast, the head and neck area is the most prominent site for subsequent histologically diagnosed BCCs.

The present study has certain limitations that need to be taken into account when interpreting the data. We studied patients with a prior histologically diagnosed BCC only and included four Dutch centers, which may limit the generalizability of our findings. In contrast to histologically diagnosed BCCs (identified in PALGA), we may have missed non-histologically diagnosed BCCs (e.g., patients moved outside the catchment area which was not recorded in dermatology record). Non-histologically diagnosed BCCs may have been misdiagnosed by dermatologists, inducing a differential misclassification bias leading to an overestimation of the frequency.[7, 10] In this study, almost all non-histologically diagnosed BCCs were classified as a superficial subtype, which was supported by the location (i.e. trunk) on which the majority of these BCCs were observed.[11] Therefore, we expect the extent of this bias to be limited.

In conclusion, the occurrence of BCCs is underestimated when solely based on cancer registry data. It is important for health care policy makers to acknowledge this in order to make accurate BCC-related cost estimates.

ACKNOWLEDGEMENTS

This study was funded by The Netherlands organisation for health research and development, ZonMw (project number 152001013).The authors would like to thank all staff from the participating dermatology departments, ECR and PALGA for the data collection and data disposition. We would especially like to thank Danielle Kuijpers from Amphia Hospital Breda, Maarten Bastiaens from TweeSteden Hospital Tilburg, Monique Andriessen from Jeroen Bosch Hospital 's Hertogenbosch and Karin van der Wegen - Franken from Elkerliek Hospital Helmond.

REFERENCES

1. Flohil SC, de Vries E, Neumann HAM, Coebergh JW, Nijsten T. Incidence, Prevalence, and Future Trends of Primary Basal Cell Carcinoma in the Netherlands. Acta Derm-Venerol 2011;91:24 - 30.
2. Brewster DH, Bhatti LA, Inglis JH, Nairn ER, Doherty VR. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992-2003. Br J Dermatol 2007;156:1295-300.
3. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. Int J Cancer 2010;127:2190-8.
4. Flohil SC, Koljenovic S, de Haas ER, Overbeek LI, de Vries E, Nijsten T. Cumulative risks and rates of subsequent basal cell carcinomas in the Netherlands. Br J Dermatol 2011;165:874-81.
5. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524-30.
6. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29:19-24.
7. Lucke TW, Hole DJ, Mackie RM. An audit of the completeness of non-melanoma skin cancer registration in Greater Glasgow. Br J Dermatol 1997;137:761-3.
8. Bernard P, Dupuy A, Sasco A, et al. Basal cell carcinomas and actinic keratoses seen in dermatological practice in France: a cross-sectional survey. Dermatology 2008;216:194-9.
9. Raasch BA, Buettner PG. Multiple nonmelanoma skin cancer in an exposed Australian population. Int J Dermatol 2002;41:652-8.
10. Bernard P, Dupuy A, Brun P, et al. [Therapeutic modalities and economic assessment in the treatment of superficial basal cell carcinomas and multiple actinic keratoses by French dermatologists]. Ann Dermatol Venereol 2007;134:527-33.
11. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 2002;147:41-7.

CHAPTER 7

Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions

S.C. Flohil

C.M. Proby

A.D. Forrest

S. van Tiel

O. Saksela

S. Pitkänen

T. Ahti

R. Micallef

E. de Vries

and members of the EPIDERM group

Br J Dermatol 2012;167(Suppl 2):22-9

ABSTRACT

Background

Limited data is available on how often basal cell carcinomas (BCC) are clinically diagnosed without histological confirmation and how they are treated.

Objectives

Within the framework of the EPIDERM project, an audit was conducted in four European countries to study the occurrence of clinically diagnosed BCC without histological confirmation and to investigate how these are treated.

Methods

In The Netherlands, Scotland, Finland and Malta studies were performed within different timeframes. Patients with one or more BCC(s) were selected and the number of clinically diagnosed BCC without histological confirmation and their treatment was investigated by (manually) reviewing the (electronic) patient records and checking the (hospital) pathology databases to find evidence of histological confirmation.

Results

In The Netherlands, 1,089 patients with a first histologically confirmed BCC developed 1,974 BCCs of which 1,833 (92.9%) were histologically confirmed and 141 (7.1%) were not. The four months retrospective study conducted in Scotland selected 294 patients with 344 BCC; 306 (89.0%) were histologically confirmed and 38 (11.0%) were not. The three months prospective study performed at the same centre in Scotland identified 44 patients who developed 58 BCC, 44 (75.9%) of these were histologically confirmed and 14 (24.1%) were not. In Finland, they included 701 patients who developed 977 BCC, of which 807 (82.6%) were histologically and 170 (17.4%) non-histologically confirmed. In Malta, there were 420 patients with 477 BCCs. Only three (0.7%) of them were clinically diagnosed without histological confirmation. In The Netherlands and Finland, clinically diagnosed BCC without histological confirmation were most often treated with cryotherapy, whereas in Scotland 5% Imiquimod cream was the preferred treatment modality.

Conclusions

Although the frequency of clinically diagnosed BCC without histological confirmation differed between the four European regions (range 0.7%-24.1%), it confirms that the burden of BCC in Europe is underestimated when based on data from pathology and/or cancer registries.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer among Caucasians and its incidence is increasing worldwide.[1-5] The growing number of patients with a history of BCC and/or multiple BCC, together with the costs related to treatment and follow-up, make this skin cancer an increasingly important public health problem.[6-7]

Most incidence and prevalence rates reported in the literature for BCC are based on data from cancer registries. However, only a few population-based cancer registries register BCC information and most of them only collect the first histologically-confirmed BCC per patient.[3, 8] The large numbers involved, the high prevalence of multiple BCCs within one patient on day of diagnosis, the practical problems in coding 'multiple BCCs', the number of cancer registry clerks needed and the difficulties in accessing private clinics, all prevent many cancer registries from collecting (additional) BCC information.

Therefore, the exact size of the BCC problem is largely unknown as a significant proportion of BCC patients develop multiple BCC over time and physicians may treat clinically diagnosed BCC without histological confirmation. In the last decade, the latter has become more common with the introduction of new non-invasive treatments such as photodynamic therapy and 5% imiquimod cream, which often have better cosmetic outcome than standard surgery.[9] Besides a previous Dutch report, there is limited data on how often BCC(s) get diagnosed and treated without histological verification and whether there are differences across Europe.[10] Lack of histological confirmation impedes registry of BCC in cancer registries and consequently BCC incidence and prevalence data will be lower than experienced by dermatologists.

Within the framework of the EPIDERM project, an audit was conducted in four European countries (The Netherlands, Scotland, Finland and Malta) to investigate the occurrence of clinically diagnosed BCC without histological confirmation.[11]

METHODS

The Netherlands

This study has been described before.[10] In short, a retrospective study was performed. All 1,290 patients from four participating hospitals with a first histologically diagnosed BCC in 2004 were extracted from Eindhoven Cancer Registry (ECR).[2] These patients were linked to PALGA, the Dutch nationwide network and registry of histo- and cytopathology.[12] The 1,290 extracted patients were followed for subsequent histologically-confirmed BCCs until November 1st 2010 or date of death, whichever came first. BCC case definition has been described before.[7] Twenty-nine patients could not be retrieved from PALGA, 24 already had a histologically-confirmed BCC prior to 2004, 149 had incomplete or missing patients records or were never seen by a dermatologist; therefore 1,089 patients were considered eligible for this study. Among these patients, the number of non-histologically confirmed BCCs and the

treatment methods for histologically and non-histologically confirmed BCCs were registered by manually reviewing the patient records of these individuals between January 14th and March 28th 2011.

Scotland

A four months retrospective and a three months prospective study was carried out in the dermatology department of Ninewells Hospital, Dundee, to estimate the proportion of BCCs seen that were clinically diagnosed without histological confirmation and therefore never recorded on a histopathology or cancer registry database. Clinical details in the form of a general practitioner letter are registered in an electronic clinical database (Dermabase) for all patients attending the department of Dermatology. A Dermabase record is generated after every dermatology appointment and therefore an individual patient may have multiple Dermabase records. This Dermabase record includes a diagnosis recorded either as "Active Diagnosis" or "Inactive Diagnosis". In case there were deficiencies in tracking all BCCs using Dermabase, a prospective study was conducted as well, whereby all patients attending a selection of out-patient clinics were audited over a three month period.

Four months retrospective study

Electronic patient records in Dermabase with an active diagnosis of "Basal Cell Carcinoma" were identified between September 1st 2009 and December 31st 2009, representing 310 patients. For each patient, the hospital pathology database was searched from September 1st 2009 until May 31st 2010, allowing five additional months to accommodate delays in surgical treatment. Nine patients were excluded because neither pathology data nor Dermabase letters were available, or because the Dermabase entries represented first appointments that were not attended. Two patients were excluded because the diagnosis of BCC was in fact "inactive" and five patients because they were recorded under 'basal cell carcinoma' when they had a diagnosis of basal cell papilloma. In total, 294 patients with an active diagnosis of BCC were included in this study. For those with and without evidence of histological confirmation, Dermabase was interrogated to find the method of treatment. No information was collected on the histopathological subtypes and anatomical localisation of the included BCCs.

Three months prospective study

Seventy-seven patients attending dermatology clinics at Ninewells Hospital, Dundee between January 11th and April 11th 2010 and identified as presenting with a BCC were studied. Forty-four of these 77 had one or more BCC(s) correctly diagnosed at that clinic appointment and were included in the audit, whereas the remainder had the initial clinical diagnosis of BCC made prior to the study period and were therefore excluded. For each patient, the pathology database was searched between January 10th and May 31st 2010 to look for receipt of a BCC specimen after the appointment at which the clinical diagnosis of BCC was made. For those

with and without evidence of histological confirmation, Dermabase was interrogated to find the method of treatment. No information was collected on the histopathological subtypes and anatomical localisation of the included BCCs.

Finland

Between October 1st and December 31st 2009 a retrospective and between January 1st and March 31st 2010 a prospective study was performed at the department of dermatology of the Skin and Allergy Hospital, Helsinki University Central Hospital in Helsinki (the regional centre for dermato-oncology). All skin cancer patients who visited the department of dermatology during these six months were included. During this study period, 701 patients were diagnosed or treated for one or more BCC(s). In June 2010 the hospital pathology database was checked to verify histologically-confirmed BCCs, allowing two additional months to accommodate delays in surgical treatment. In the retrospective part of the study the patient records were investigated to find the method of treatment, in the prospective part the method of treatment was recorded after the appointment. No information was collected on the histopathological subtypes and anatomical localisation of the included BCCs.

Malta

Between October 1st 2009 and March 31st 2010, all hospitals and clinics both public and private (Mater Dei Hospital, St. James Hospital, St. Philips Hospital, Dr. Deguara's lab, the oncology department and St. Mark's lab) were visited to collect and count all patients with a BCC between January 1st 2009 and December 31st 2009, by going through all hospital pathology databases, patient records, oncology reports and notifications. When a BCC was mentioned in the patient record, oncology report or in a notification, but not found in the pathology database, it was considered a clinically diagnosed BCC without histological confirmation. When a patient presented him/herself with multiple BCC on the day of diagnosis, only the localisation of one BCC was registered in the Maltese Cancer Registry. If available within the hospital pathology database, the histopathological subtype of the BCC was registered.

RESULTS

The Netherlands

After combining the data from PALGA, ECR and the hospital patient records, a total of 1,974 BCC were diagnosed among 1,089 patients.[10] Overall, the patients contributed 6,253 person-years of follow-up. The mean age at date of first histologically confirmed BCC was 65.0 (standard deviation [SD] 14.0). The male-female ratio was 1:1. In total, 1,974 BCCs were diagnosed in 1,089 patients of which 1,833 (92.9%) were histologically and 141 (7.1%) were non-histologically confirmed (Table 1).

Surgical excision (83.6%) was the most performed treatment modality, followed by cryotherapy (6.1%) and photodynamic therapy (2.8%). This distribution was the same for histologically-confirmed BCCs (Table 2a). For non-histologically confirmed BCCs, cryotherapy (65.2%) was the predominant treatment, followed by photodynamic therapy (23.4%), 5-fluourouracil (4.3%) and imiquimod cream (4.3%).

Scotland

Four months retrospective study

In total, 344 BCCs were recorded belonging to 294 patients, of which 156 (53.1%) were males and 138 (46.9%) were females. The mean age at date of diagnosis was 70.5 years (SD 12.4). Of the 344 BCCs, 306 (89.0%) were histologically-confirmed and 38 (11.0%) were not confirmed histologically (Table 1).

Most BCCs were treated surgically (87.2%), followed by imiquimod cream (4.9%) and cryotherapy (2.3%). All but one histologically confirmed BCC were treated with simple surgical excision or Mohs micrographic surgery. One was treated with radiotherapy. For non-histologically confirmed BCC, imiquimod cream (44.7%) was the preferred treatment method, followed by cryotherapy (21.1%) and 5-fluorouracil cream (Table 2b).

Three months prospective study

The 44 patients diagnosed with a BCC between January 11th and April 11th 2010 had a total of 58 BCCs. Among the patients, there were 24 (54.5%) males and 20 (45.5%) females. The mean age at diagnosis was 71.2 years (SD 10.7). Of the 58 BCCs, 44 (75.9%) were histologically and 14 (24.1%) were not histologically confirmed (Table 1). The mean number of BCC diagnosed at the date of appointment was 1.3 (SD 0.82), ranging from 1 to 5.

Taking the retrospective and prospective audits together, the majority of BCC were treated surgically (86.8%), followed by imiquimod cream (7.0%) (data not shown). All histologically-confirmed BCC were treated with surgical excision. For BCC without histological confirmation, imiquimod cream (53.8%) was the preferred treatment, followed by cryotherapy (15.4%) and overall for ten BCC it was decided to observe and not to treat because the patients were elderly and frail.

Finland

Among the 701 included patients, there were 327 (46.6%) males and 374 (53.4%) females. In total, they developed 977 BCCs during the study period. The mean age at diagnosis was 72.3 (SD 12.8). Of the total 977 BCCs, 807 were histologically confirmed (82.6%) and 170 (17.4%) were non-histologically confirmed BCCs (Table 1).

The majority of BCC were treated with standard surgical excision (57.1%), followed by cryotherapy (28.4%) and photodynamic treatment (11.8%). For three patients the therapy was missing because they died before they were treated. For histologically-confirmed BCC, the

distribution was similar. Non-histologically confirmed BCCs were most often treated with cryotherapy (77.1%) and the remainder with photodynamic therapy (22.9%) (Table 2c).

Malta

Of the 420 included patients, there were 256 (61.0%) males and 264 (39.0%) females. In total, they developed 447 BCCs. The mean age at diagnosis was 65.9 (SD 13.8). Only 3 (0.7%) of the 447 tumors were diagnosed clinically without histological confirmation (Table 1). The most common site was the head and neck area (n =256), followed by trunk (n=67), upper extremities and shoulders (n=28) and lower extremities (n=22). This excluded 47 BCC for whom site was not registered. The histopathological subtype was unspecified in 442 (98.9%) BCC. Of the remainder, 30 BCCs (6.7%) were superficial, while 5 (1.1%) had infiltrative growth pattern. No detailed information was available on the treatments used.

DISCUSSION

The frequency of clinically diagnosed BCC treated without histological confirmation differed between the four European regions (range 0.7% -24.1%), the highest proportion being observed in the small prospective study in Dundee, Scotland. This contrasts with the findings of a previous study in 1997 from Glasgow (3.8%), which suggested that dermatologists rarely treat clinically suspicious tumors without histological proof of diagnosis.[13] Either practice varies significantly across Scotland or (more likely) dermatological practice has changed with the advent and greater availability of non-surgical treatments such as imiquimod cream and photodynamic therapy. A previous study among French dermatologists found that 14.1% of the clinically suspicious BCCs were not histologically confirmed, which is not dissimilar from the percentages observed in Finland (17.4%) and in the retrospective study performed in Dundee, Scotland (11.0%).[14]

Malta, with less than 1%, had the lowest percentage of BCCs diagnosed without histological confirmation. After interviewing the Maltese dermatologists (n= 12) about their practices of treating patients, they all confirmed that it was custom to verify all clinically suspicious BCCs histologically with biopsy and/or surgical excision. In The Netherlands, the number of subsequent clinically diagnosed BCCs without histological confirmation (developed during a mean follow-up period of almost six years) was investigated in patients with a prior histologically confirmed BCC. This differs from the study design of the other three European regions in which there was no selection of patients who already had a first, histologically confirmed BCC. Besides dissimilarities in practice and study design, also differences in insurance reimbursements between the European regions may account for the wide variation found in the percentage of clinically diagnosed BCC. However, the latter should not be such a large factor as in all four European regions BCC do not need histological confirmation for patients to receive insurance reimbursements (based on personal communications with S.P., R.M and E.V).

Table 1. Number of histologically and non-histologically confirmed basal cell carcinomas in four European regions

Country	Study design	Time period patient selection	Total number of patients	Total number of BCCs	Histologically confirmed BCCs	Non-histologically confirmed BCCs	Percentage non-histologically confirmed BCCs	Specifics
Netherlands	Retrospective	January 1st 2004 - December 31st 2004	1,089	1,974	1,833	141	7.1%	The first 1,089 patients with a first histologically confirmed BCC in 2004 were selected in four hospitals and followed until November 1st 2011 or date of death.
Scotland	1. Retrospective	September 1st 2009 - December 31st 2009	294	344	306	38	11.0%	All patients with a Dermabase electronic record giving 'active diagnosis' of BCC were selected.
	2. Prospective	January 11th 2010 - April 11th 2010	44	58	44	14	24.1%	All patients attending the Monday morning dermatology clinic at Ninewells Hospital were audited. All audited patients with a diagnosis of BCC were selected.
Finland	Retrospective/ prospective	October 1st 2009 - March 31st 2010	701	977	807	170	17.4%	Three months retrospective and three months prospective study was conducted. All patients with a diagnosis of BCC who visited the department of dermatology were selected.
Malta	Retrospective	January 1st 2009 – December 31st 2009	420	447	444	3	0.7%	All hospitals and clinics in Malta were visited to collect and count all patients with a BCC.

Abbreviation: BCC, basal cell carcinoma

Table 2. Treatment modalities of basal cell carcinoma in The Netherlands, Scotland and Finland

A. Dutch study: treatment per basal cell carcinoma

Treatment	Total number BCCs (%) *n=1974*	Histologically confirmed BCCs (%) *n=1833*	Non-histologically confirmed BCCs (%) *n=141*
Surgical excision	1650 (83.6%)	1650 (90.0%)	-
Mohs micrographic surgery	20 (1,0%)	20 (1.1%)	-
Cryotherapy	121 (6,1%)	29 (1.6%)	92 (65.2%)
Photodynamic therapy	56 (2.8%)	23 (1.3%)	33 (23.4%)
5-Fluorouracil cream	10 (0.5%)	4 (0.2%)	6 (4.3%)
Imiquimod cream	8 (0.4%)	2 (0.1%)	6 (4.3%)
Diclofenac gel	-	-	-
Curettage	14 (0.7%)	14 (0.8%)	-
Tretinoin	-	-	-
Radiotherapy	-	-	-
Expectative / not treated	4 (0.2%)	2 (0.1%)	2 (1.4%)
Missing	91 (4.6%)	89 (4.9%)	2 (1.4%)

B. Scottish four months retrospective study: treatment per basal cell carcinoma

Treatment	Total number BCCs (%) *n=344*	Histologically confirmed BCCs (%) *n=306*	Non-histologically confirmed BCCs (%) *n=38*
Surgical excision	300 (87.2)	300 (98.1)	-
Mohs micrographic surgery	5 (1.5)	5 (1.6)	-
Cryotherapy	8 (2.3)	-	8 (21.1)
Photodynamic therapy	-	-	-
5-Fluorouracil cream	5 (1.5)	-	5 (13.2)
Imiquimod cream	17 (4.9)	-	17 (44.7)
Diclofenac gel	1 (0.3)	-	1 (2.6)
Curettage	-	-	-
Tretinoin	-	-	-
Radiotherapy	1 (0.3)	1 (0.3)	-
Expectative / not treated	7 (2.0)	-	7 (18.4)
Missing	-	-	-

C. Finnish study: treatment per basal cell carcinoma

Treatment	Total number BCCs (%) *n=977*	Histologically confirmed BCCs (%) *n=807*	Non-histologically confirmed BCCs (%) *n=170*
Surgical excision	558 (57.1)	558 (69.1)	-
Mohs micrographic surgery	23 (2.4)	23 (2.9)	-
Cryotherapy	278 (28.4)	147 (18.2)	131 (77.1)
Photodynamic therapy	115 (11.8)	76 (9.4)	39 (22.9)
5-Fluorouracil cream	-	-	-
Imiquimod cream	-	-	-
Diclofenac gel	-	-	-
Curettage	-	-	-
Tretinoin	-	-	-
Radiotherapy	-	-	-
Expectative / not treated	-	-	-
Missing	3 (0.3)	3 (0.4)	-

Abbreviation: BCC, basal cell carcinoma

This study confirms an underestimate of the absolute BCC number based on histologically-confirmed BCC alone and illustrates that previous studies based on cancer registries and/or pathology databases will have underestimated the true BCC burden. Therefore, health care policy makers (especially in The Netherlands, Scotland and Finland) should incorporate the proportion of BCC treated without histological confirmation into their calculations (in Malta this seems to be a less of a problem). Especially, since in all four European regions the ratio of dermatologists to the total population is dramatically low, ranging from 1 to 3.6 per 100.000 inhabitants.

In The Netherlands, Scotland and Finland, the preferred treatment modality for histologically-confirmed BCC is standard surgical excision, followed by cryotherapy (The Netherlands and Finland) and imiquimod cream (Scotland). No detailed data was available for Malta, however it seems that the majority are surgically excised (based on personal communication). In The Netherlands and Finland, for clinically diagnosed BCC without histology, cryotherapy was the treatment used most often followed by photodynamic therapy. In Scotland, Imiquimod was the preferred treatment, then cryotherapy.

A limitation of this study was the methodological differences between the sub-studies performed in the four European regions. The study design was notably different in The Netherlands, where patients with a first histologically confirmed BCC in 2004 from four dermatology departments were followed for subsequent clinically diagnosed BCCs. In Scotland and Finland, the audits were performed at hospital level, while in Malta all hospitals and clinics were investigated for clinically diagnosed BCC. This was possible for Malta because of its small size and contained geographic region. In addition, the cancer registry in Malta recorded all BCC for whom there was a histological diagnosis. Another important variation was the size of the study populations. Although the prospective Scottish study observed the highest percentage of BCC diagnosed clinically without histology, this study also had the smallest study population, which may have inflated the proportion. Nonetheless, the greater proportion of BCC without histological diagnosis that were identified in this prospective study compared with the retrospective study from the same department, does demonstrate the importance of prospective investigation. This potential problem of missed BCC in retrospective studies was largely avoided by interrogating hospital case notes for all included patients in the other sub-studies.

A French medical cost analysis study described that when histological confirmation was performed in a clinical suspicious superficial BCC; the BCC diagnosis was confirmed in 85% of the cases.[15] Additionally, a study from the United States suggested that the positive predictive value of the clinical diagnosis of a BCC is only 80%, and that is when the dermatologist is reasonably confident about the diagnosis.[16] Therefore, the observed percentages of clinically diagnosed BCC without histological confirmation within this study may be an overestimate. These limitations and the differences identified between the sub-studies from four different

European regions suggest that our data are an estimate for the number of clinically diagnosed BCC and may not be representative for Europe as a whole.

CONCLUSION

Limited data is available about the frequency of clinically diagnosed BCCs without histological confirmation and their treatment. Although the percentage of non-histological confirmed BCCs differed between the four European regions, our findings do confirm that the burden of BCCs is underestimated when based solely on data from pathology records and/or cancer registries.

ACKNOWLEDGEMENTS

This publication arises from the EPIDERM project which was co-funded by the European Commission's Executive Agency for Health and Consumers (EPIDERM project: PHEA 2007–A/100994 HI). In Finland, Meri Övermark, MD, Tiina Karppinen, MD, Suvi Cajanus, MD, and Terhi Lemetti, Pirkko-Liisa Nurmela, Mira Pantzar, Anne Penttinen, Marja Saarinen and Catherine Wettenstrand are acknowledged for assisting in the data collection. In The Netherlands we would like to thank all staff from the participating dermatology departments, ECR and PALGA for the data collection and data disposition. We would especially like to thank Dr Danielle Kuijpers from Amphia Hospital Breda, Dr Maarten Bastiaens from TweeSteden Hospital Tilburg, Dr Monique Andriessen from Jeroen Bosch Hospital 's Hertogenbosch and Dr Karin van der Wegen - Franken from Elkerliek Hospital Helmond. In Scotland, Dr Ross Hearn, Dr Alyson Bryden, Dr Andrew Affleck, Dr Robert Dawe, Dr Sally Ibbotson, Dr John Foerster, Dr Cathy Green and Dr Sue Lewis Jones are thanked for their help with the BCC audit at Ninewells Hospital, Dundee.

REFERENCES

1. Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer 2007;121:2105-8.
2. Flohil SC, de Vries E, Neumann HAM, Coebergh JW, Nijsten T. Incidence, Prevalence, and Future Trends of Primary Basal Cell Carcinoma in the Netherlands. Acta Derm-Venerol 2011;91:24 - 30.
3. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of non-melanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. Int J Cancer 2010;127:2190-8.
4. Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer 1999;81:555-9.
5. Buettner PG, Raasch BA. Incidence rates of skin cancer in Townsville, Australia. International journal of cancer 1998;78:587-93.
6. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524-30.
7. Flohil SC, Koljenovic S, de Haas ER, Overbeek LI, de Vries E, Nijsten T. Cumulative risks and rates of subsequent basal cell carcinomas in the Netherlands. Br J Dermatol 2011;165:874-81.
8. Brewster DH, Bhatti LA, Inglis JH, Nairn ER, Doherty VR. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992-2003. Br J Dermatol 2007;156:1295-300.
9. Rhodes LE, de Rie MA, Leifsdottir R, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol 2007;143:1131-6.
10. Flohil SC, van Tiel S, Koljenović S, et al. Frequency of non-histologically diagnosed basal cell carcinomas in daily Dutch practice. J Eur Acad Dermatol Venereol 2012 doi: 10.1111/j.1468-3083.2011.04407.x. [Epub ahead of print].
11. de Vries E, Micaleff R, Brewster DH, et al. Population-based estimates of the occurrence of multiple versus first primary basal cell carcinomas in 4 European regions. Arch Dermatol 2012;148:347-54.
12. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29:19-24.
13. Lucke TW, Hole DJ, Mackie RM. An audit of the completeness of non-melanoma skin cancer registration in Greater Glasgow. Br J Dermatol 1997;137:761-3.
14. Bernard P, Dupuy A, Sasco A, et al. Basal cell carcinomas and actinic keratoses seen in dermatological practice in France: a cross-sectional survey. Dermatology 2008;216:194-9.
15. Bernard P, Dupuy A, Brun P, et al. [Therapeutic modalities and economic assessment in the treatment of superficial basal cell carcinomas and multiple actinic keratoses by French dermatologists]. Ann Dermatol Venereol 2007;134:527-33.
16. Schwartzberg JB, Elgart GW, Romanelli P, Fangchao M, Federman DG, Kirsner RS. Accuracy and predictors of basal cell carcinoma diagnosis. Dermatol Surg 2005;31:534-7.

CHAPTER 8

Risk factors for single and multiple basal cell carcinomas

V. Kiiski

E. de Vries

S.C. Flohil

M.J. Bijl

A. Hofman

B.H.Ch. Stricker

T. Nijsten

Arch Dermatol. 2010;146:848-55

ABSTRACT

Objective

To investigate the incidence of (multiple) basal cell carcinomas (BCC) and associated risk factors.

Design

A prospective population-based cohort study.

Setting

Two cohorts of altogether 10,994 Dutch people, aged ≥55 years, were included since 1991 (1st cohort) and 1999 (2nd cohort).

Patients

Patients with BCC were identified from the Dutch national pathology laboratories network, hospitals and general practices.

Main Outcome Measures

The associations between determinants and first and multiple BCCs were studied by estimating odds ratios and hazard ratios, using multivariable logistic regression and Andersen-Gill models, respectively.

Results

Of the eligible 10,820 cohort members, 524 (4.8%) had a BCC of whom 361 had one and 163 patients had multiple lesions (31.1%). Age and red hair were significant risk factors for a first BCC in a multivariable model. In the Anderson-Gill model, people who developed a first BCC after 75 years of age were significantly less likely to develop multiple BCCs (≥75 years adjusted OR 0.58; 95% CI 0.47 – 0.71). Red hair (adjusted OR 1.43; 95% CI 1.05 – 1.94), high educational level (adjusted OR 1.42; 95% CI 1.12 – 1.81) and a first BCC located on the upper extremities (adjusted OR 1.49; 95% CI 1.02 – 2.15) were associated with a significantly increased risk of developing multiple BCCs.

Conclusion

Patients who are relatively young at their first BCC diagnosis, those with red hair, higher socioeconomic status and/or those who had a BCC on their upper extremities have a higher risk of developing multiple BCCs and require more close follow-up over time.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in people with European ancestry and its incidence continues to increase steeply.[1-5] The BCC incidence varies geographically. For instance, in The Netherlands, the incidence rate is approximately 100 per 100 000 person-years which is about one-tenth of the high risk in areas such as Australia.[6] More than a million people in the United States develop a BCC annually.[7] Although BCC therapy is relatively straightforward and BCC mortality is extremely low, its high incidence and high risk of developing multiple BCC put a major burden on limited health care resources, placing BCC on the 5th place of most expensive cancers in the USA.[8]

Individual risk factors for BCC include age, male sex, race, phenotypic characteristics and genetic predisposition. These factors may interact with environmental exposures such as ultraviolet light or iatrogenic exposures.[9-14] In contrast to risk factors associated with incident BCC, the risk factor profile of those who develop multiple BCC among patients with a prior BCC is not well documented. Most observational BCC studies were performed with data from a few cancer registries that record incident BCC without detailed data on risk factors (except for basic demographics). Specialized centers include specific subgroups of patients, with detailed risk factor information but their results are often not generalizable due to selection processes with potential bias or confounding.[12, 15-17] The strongest risk factor for developing multiple BCCs appears to be a personal history of a prior BCC, representing the accumulation of gene-environmental interactions. It has been estimated that 40% to 50% of patients with a BCC develop subsequent tumors.[12-13] Previous studies have suggested that BCC patients who had a truncal and/or superficial BCC, a sun sensitive skin type and who were unable to tan are at an increased risk of developing subsequent tumors.[12, 16-18]

Identification of BCC patients at high risk of developing subsequent BCCs may assist physicians in the adequate selection of individuals from the large number of BCC patients who should be followed more closely over time. Currently, national BCC guidelines are ambiguous concerning follow-up, but often advise patients to be followed annually for several years (often a 5-year period)[19-21] leading to an overwhelming workload for (medical) dermatologists, of whom there is a shortage in several countries such as The Netherlands, USA and UK.
Therefore, the study objective was to investigate incidence and risk factors associated with development of (multiple) BCC in a population-based study of almost 11,000 middle-aged and elderly people from the general Dutch population.

METHODS

Study population

The Rotterdam Study is a well-established prospective population-based cohort study in the Ommoord district in Rotterdam, The Netherlands, which was designed to study diseases in elderly people.[22] In January 1990, the first inception cohort of 7,983 people aged ≥55 years (78% of invitees) was established. In 1999, an additional 3,011 participants who had turned 55 or moved into the district were added to the cohort (67% of invitees). The Medical Ethics Committee of the Erasmus Medical Center has approved the Rotterdam Study and written informed consent was obtained from each participant.

Case definition

All pathology-confirmed cases of BCC in the Rotterdam Study were extracted from the Dutch national pathology laboratories network PALGA between the start of the cohort study and December 2007. Patients with a BCC diagnosis prior to study entry were excluded from the analyses (Figure 1). BCC reports with pathology sample dates 6 months or less apart with the same location and/or pathology report summary including the words 'biopsy' or 'punch biopsy' at first date and 'excision' on second/following dates were considered as the same BCC and therefore counted as one lesion. If no further description was available, BCC reports in cases appearing within 3 months with the same location were combined assuming that it was a biopsy followed by an excision. Subsequent lesions occurring in the same location with 'recurrence' or 're-excision' mentioned in the pathology report were considered as recurrent tumors and were not counted as subsequent BCC. Lesions occurring within six months of the very first date of BCC diagnosis (index date) were counted as additional tumors at the date of the first diagnosis (index lesions) because they probably were present at index date as well; they were counted as separate BCCs with a zero time interval between occurrence compared to the index lesion.Tumor specific information was extracted from the SNOMED abstract available in PALGA. The body site of BCC was classified by dividing the body surface area into 20 parts. Histological subtypes were categorized into: nodular (including nodulocystic and basosquamous types), infiltrative, superficial, micronodular and adenoid type. In mixed type lesions a superiority rule was used according to aggressiveness, namely: infiltrative > nodular > micronodular > superficial. When inconsistent, the pathology report of the excision overruled the biopsy report. The BCC count was continuous, multiple BCC was defined as having had ≥ 2 BCCs. Patients were counted only once per histological subtypes or body sites in analyses that stratified for these two characteristics. Cohort participants without a pathology-based diagnosis of BCC were used as a reference group.

Co-variables

Baseline data of determinants and potential risk factors for BCC included gender, age, hair color (fair, red and brown/black) and eye color (blue, intermediate and brown), educational

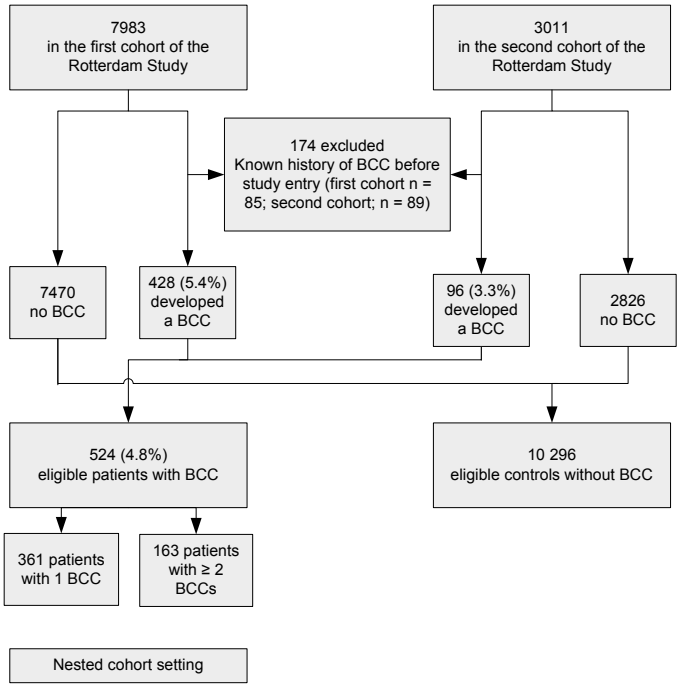


Figure 1. Schematic overview of study population

level (classified into 3 categories: low [primary education], medium [lower-level general education, intermediate-level general education, and lower-level vocational education], and high [higher-level general education, intermediate-level vocational education, higher-level vocational education and university]), alcohol consumption (<10, 10-20 and >20 g/day), smoking history (never, former or current smoker) and body mass index (BMI: <25, 25-29,99 and ≥30) at cohort entry. Four questions assessing ultraviolet (UV) exposure were available including tendency for sunburns, history of more than 25 years of outdoor work, having lived more than one year in sunny countries, and sun-protective behavior (i.e., wearing sunglasses and/or a rimmed hat in the sunshine). The first three UV items had binary responses and the latter was categorized into no, often and always.

Statistical analyses

Differences in the distribution of demographic and BCC characteristics were compared using Student's *t*-test or Mann–Whitney *U* test for continuous variables, as appropriate, and Pearson's χ^2 for categorical variables. Due to violation of the proportional hazards assumption, logistic regression models were used to calculate crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) for the development of the either a single BCC or multiple BCCs. In addition to gender, if a vari-

able showed an association with BCC occurrence with a p-value <0.20 in the univariable analyses, it was included in the multivariable logistic regression model.[23] No significant interactions were observed between variables that were eligible for the multivariate logistic regression model.

The Andersen-Gill multifailure survival model, which assesses the recurrence of multiple events, was used to estimate hazard ratios (HR) and 95% CIs for multiple BCC. The advantage of this method of analysis is that it includes all BCCs that patients developed after their initial BCC and not just the second lesion, which makes it more appropriate for depicting a phenomenon with a repeated character such as BCC occurrence.[15] To increase the stability of the Andersen-Gill analysis, patients were censored at a maximum of 5 BCCs because of the small number of patients with more than 5 BCCs (n=12). Variables showing an association with $p < 0.20$ were included in the adjusted model. Hazard ratios for lesion subtype and lesion site were analysed making dummies by subcategory, resulting in analyses comparing one subtype/site with all other subtypes/sites as a reference group. SPSS15.0 for Windows (SPSS Inc., Chicago, IL) was used for data analyses, except for the Andersen-Gill multifailure survival model for which SAS 9.13 for Windows (SAS institute Inc., Cary, NC) was used.

RESULTS

Study population

Of the total of 10,994 persons who participated in the Rotterdam Study, 174 (1.6%) were excluded because they had a BCC prior to cohort entry (Figure 1). The remaining 10,820 patients were included and contributed 102,171 person-years of follow-up, with a mean follow-up duration of 9.5 years (SD 4.8). The mean age at study entry was 69 years (Table 1). Approximately 60% of our study population was female and 98% was Caucasian. Characteristics of the study population are presented in Table 1.

BCC data

1,556 pathology reports containing information on BCCs of the cohort members of the Rotterdam Study from 1982 to 2007 were extracted from PALGA. Of the 10,820 eligible cohort members, 524 (4.8%) had at least one recorded pathology-confirmed BCC of whom 68.9% had one, 18.1% two and 12,9% persons had three or more tumors (Figure 2). The mean and median numbers of pathology-confirmed BCCs were 1.63 and 1, respectively, and ranged between 1 and 11. In total, 854 unique BCCs (recurrences excluded) were identified of which about two thirds were located on the head and neck (Table 2). More than half of the BCCs were nodular and about a quarter were of infiltrating histological subtype. Of all BCC patients 63.9% had at least one cancer lesion of nodular, 31.5% an infiltrating and 14.7% a superficial subtype.

In the group of patients with multiple BCC, 79.4% had one or more nodular lesion, 43.6% had infiltrating lesions and 30.9% superficial lesions. Most BCCs were located on the head and neck area, followed by trunk and upper and lower extremities (60.4%, 17.8%, 5.3% and

Table 1. Description of study population and risk factor analysis of first basal cell carcinoma (BCC)

Characteristic	Entire study population (n=10,820)	No. of cases (%) (n=524)	No. of controls (%) (n=10,296)	Crude Odds ratios (95% CI). First BCC (n=524)*	Multivariate Odds ratios (95% CI). First BCC (n=524)**
Total years of follow-up	102 171	6274	95 896		
Mean years of follow-up/patient	9.45	11.97	9.32		
Gender					
female	6481 (59.9)	300 (57.3)	6181 (60.0)	1.00 (ref)	1.00 (ref)
Male	4339 (40.1)	224 (42.7)	4115 (40.0)	1.12 (0.94 - 1.34)	1.04 (0.81 – 1.35)
Age at the entry to study					
Mean. years (range. years)	*69.1 (55-106)*	*68.5 (55-93)*	*69.1 (55-106)*		
< 65	4595 (42.5)	203 (38.7)	4392 (42.7)	1.00 (ref)	1.00 (ref)
65 – 74.99	3252 (30.1)	208 (39.7)	3044 (29.6)	**1.48 (1.21 - 1.80)**	**1.39 (1.11 – 1.75)**
≥ 75	2971 (27.5)	113 (21.6)	2858 (27.8)	0.86 (0.68 - 1.08)	1.01 (0.76 – 1.34)
missing	2	0	2	NA	NA
Hair color					
Brown/black	7435 (68.5)	343 (65.5)	7092 (68.9)	1.00 (ref)	1.00 (ref)
fair/blond	2257 (20.9)	127 (24.2)	2130 (20.7)	**1.23 (1.00 - 1.52)**	1.16 (0.91 – 1.48)
Red	297 (2.7)	26 (5.0)	271 (2.6)	**1.98 (1.31 - 3.01)**	**1.98 (1.24 – 3.14)**
missing	831 (7.7)	28 (5.3)	803 (7.8)	0.72 (0.49 – 1.07)	NA
Eye color					
Brown	2239 (20.7)	99 (18.9)	2140 (20.8)	1.00 (ref)	1.00 (ref)
intermediate	771 (7.1)	39 (7.4)	732 (7.1)	1.15 (0.79 - 1.68)	0.94 (0.62 – 1.43)
Blue	6263 (57.9)	332 (63.4)	5931 (57.6)	1.21 (0.96 - 1.52)	1.10 (0.84 – 1.44)
missing	1547 (14.3)	54 (10.3)	1493 (14.5)	0.79 (0.56 – 1.11)	1.71 (0.88 – 3.33)
Tendency for sunburns					
Low	6634 (61.3)	311 (59.4)	6323 (61.4)	1.00 (ref)	1.00 (ref)
High	3233 (29.9)	183 (34.9)	3050 (29.6)	**1.22 (1.01 - 1.47)**	1.13 (0.91 – 1.40)
missing	953 (8.8)	30 (5.7)	923 (9.0)	0.66 (0.45 – 0.97)	0.40 (0.10 – 1.59)
Outdoor work history (≥25 years)					
No	6086 (56.2)	344 (65.6)	5742 (55.8)	1.00 (ref)	1.00 (ref)
Yes	1194 (11.0)	69 (13.2)	1125 (10.9)	1.02 (0.78 - 1.34)	1.00 (0.75 – 1.34)
missing	3540 (32.7)	111 (21.2)	3429 (33.3)	0.42 (0.25 – 0.70)	NA
History of living in sunny country (>1 year)					
No	8972 (82.9)	452 (86.3)	8520 (82.9)	1.00 (ref)	1.00 (ref)
Yes	1021 (9.4)	44 (8.4)	977 (9.5)	0.85 (0.62 - 1.17)	0.84 (0.59 – 1.20)
missing	827 (7.6)	28 (5.3)	799 (7.8)	0.66 (0.45 – 0.98)	NA
Sun protective behavior ††					
No	4523 (41.8)	228 (43.5)	4295 (41.7)	1.00 (ref)	
Often	2982 (27.6)	148 (28.2)	2834 (27.5)	0.98 (0.80 - 1.22)	
always	2472 (22.8)	118 (22.5)	2354 (22.9)	0.94 (0.75 - 1.19)	
missing	843 (7.8)	30 (5.7)	813 (7.9)	0.70 (0.47 – 1.03)	
Smoking †					
Never smoked	3658 33.8)	185 (35.3)	3473 (33.7)	1.00 (ref)	1.00 (ref)
Former	4546 (42.0)	244 (46.6)	4302 (41.8)	1.07 (0.88 - 1.30)	1.10 (0.86 – 1.42)
Current	2262 (20.9)	89 (17.0)	2173 (21.1)	0.77 (0.59 – 1.00)	0.74 (0.54 – 1.01)
missing	354 (3.3)	6 (1.1)	384 (3.4)	0.32 (0.14 – 0.74)	0.59 (0.19 – 1.82)
Alcohol intake (g/d) †					
No	3577 (33.1)	146 (27.9)	3431 (33.3)	1.00 (ref)	1.00 (ref)

0.01 - 9.99 g	2639 (24.4)	173 (33.0)	2466 (24.0)	1.65 (1.32 - 2.07)	1.21 (0.89 – 1.63)
10 - 19.99 g	919 (8.5)	54 (10.3)	865 (8.4)	1.47 (1.06 - 2.02)	1.10 (0.74 – 1.16)
20 g or more	1170 (10.8)	74 (14.1)	1096 (10.6)	**1.59 (1.19 - 2.12)**	1.17 (0.38 – 1.29)
missing	2515 (23.2)	77 (14.7)	2438 (23.7)	0.73 (0.55 – 0.97)	0.57 (0.38 – 0.86)
Body mass index (BMI, kg/m²) †					
< 25 (under- and normal weight)	3446 (31.8)	182 (34.7)	3264 (31.7)	1.00 (ref)	1.00 (ref)
25-29.99 (overweight)	4439 (41.0)	224 (42.7)	4215 (40.9)	0.95 (0.78 - 1.17)	0.93 (0.74 – 1.16)
30 or more (obese)	1550 (14.3)	75 (14.3)	1475 (14.3)	0.91 (0.69 - 1.20)	1.00 (0.73 – 1.37)
missing	1385 (12.8)	43 (8.2)	1342 (13.0)	0.58 (0.41 – 0.81)	0.67 (0.35 – 1.29)
Educational level					
Low	5218 (48.2)	259 (49.4)	4959 (48.2)	1.00 (ref)	1.00 (ref)
Medium	3208 (29.6)	170 (32.4)	3038 (29.5)	1.07 (0.88 - 1.31)	**1.28 (1.01 – 1.60)**
High	1920 (17.7)	82 (15.6)	1838 (17.9)	0.85 (0.66 - 1.10)	1.06 (0.73 – 1.56)
missing	474 (4.4)	13 (2.5)	461 (4.5)	0.55 (0.31 – 0.96)	0.87 (0.32 – 2.42)

* Univariate Logistic regression analysis

** Multivariate Logistic regression analysis. Variables with p<0.20 and gender included to analysis.

† Assessed at baseline. 1990-91 for the initial cohort and 2000-2001 for the second cohort

†† Defined by questions of wearing sunglasses and/or hat with a rim in sunshine

11.6% of all BCCs, respectively. Among patients with multiple BCC, almost half (48.1%) of those who had a superficial BCC additionally had at least one nodular lesion and 19.5% had also an infiltrating lesion.

BCC incidence

During the first year of follow up, 0.2% of cohort members developed a BCC and cumulative percentages of developing BCC during three, five and ten years of follow up were 0.9%, 1.8%

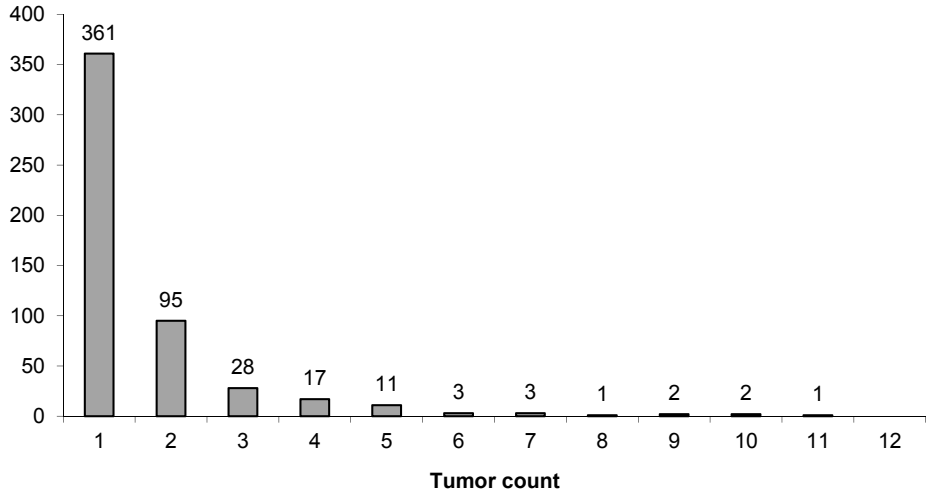


Figure 2. The absolute basal cell carcinoma count in the 10,820 cohort members

and 3.4%, respectively. The incidence rate of first BCC was 513/100 000 person-years. The incidence among women (497/100 000 person-years) was lower than among men (566/100 000 person-years); the risk difference of 87/100 000 was of borderline significance (p=0.058). The incidence for multiple BCCs was 161.5/100 000 person-years and it was significantly lower for women than for men (139 versus 197/100 000 person-years, respectively; risk difference 58/100 000 person-years, p=0.024). Among those with a first BCC, 3, 5 and 10 years

Table 2. The characteristics of the 854 basal cell carcinoma (BCC) in 524 patients

Total tumor count	**Number of cases (%)**
1	361 (68,9)
≥2	163 (31,1)
Tumor count at index date	**Number of cases (%)**
1	456 (87,0)
≥2	68 (13,0)
Tumor site	**Number of tumors (%)**
Head and neck	**561 (65,6)**
Scalp	21 (2,5)
Temporal areas	83 (9,7)
Forehead	84 (9,8)
Retro- and preauricular areas	27 (3,2)
Cheeks	51 (6,0)
Nose / surroundings of the nose	106 (12,4)
nasolabial fold and upper lip	22 (2,6)
lower lip and chin	11 (1,3)
Jaw	13 (1,5)
Ears	36 (4,2)
Eyebrow areas / eye surroundings	46 (5,4)
Head, specific location unknown	15 (1,8)
Neck	46 (5,4)
Trunk	127 (14,9)
Back and shoulders	69 (8,1)
Thorax	39 (4,6)
Abdomen	11 (1,3)
Trunk, specific location unknown	8 (0,9)
Upper extremities	38 (4,4)
Lower extremities	94 (11,0)
Other (pelvic/anogenital area, buttocks)	9 (1,1)
Missing	25 (3,0)
Tumor histology	**Number of tumors (%)**
Nodular	467 (54,7)
Infiltrating	192 (22,5)
Superficial	95 (11,1)
Micronodular	6 (0,7)
Adenoid	4 (0,5)
Other	6 (0,7)
Missing	84 (9,8)

incidence rates per 100 000 person-years for developing multiple BCC were 893, 1,459 and 1,974, respectively.

Risk factors for first BCC

In univariable analyses, an age of 65-75 years at study entry, alcohol use, blond or red hair color, and high tendency for sunburns were significantly associated with an increased risk of developing a first BCC (Table 1). Red hair color had the strongest association (OR 1.98, 95% CI 1.31 – 3.01). Eye color, educational level, outdoor work history, history of living in a sunny country, sun protective behavior and BMI were not significantly associated with a higher risk of BCC. In univariable analysis, current smoking was associated with a decreased risk of being diagnosed with a BCC (OR 0.77; 95% CI 0.59–1.00).

After including gender, age, hair and eye color, tendency for sunburns, history of outdoor work or living in a sunny country, smoking, alcohol consumption, BMI and educational level ($p<0.20$ in the univariable analyses) to a multivariable logistic regression model, older age at study entry (65 - 74 years, adjusted OR 1.39; 95 %CI 1.11 - 1.75 compared to <65 years) and red hair (adjusted OR 1.98; 95% CI 1.24 - 3.14) remained significantly associated with an increased risk of developing a first BCC. In the multivariable model, a high tendency for sunburns was no longer a significant risk factor but medium educational level was positively associated with an increased risk.

Risk factors for multiple BCCs

In the univariable Andersen-Gill multifailure analyses, several demographic factors and tumor characteristics (i.e., male gender, hair color, high tendency for sunburns), as well as higher educational levels were significantly associated with an increased risk of developing multiple BCCs. In contrast, higher age at the time of the first BCC lesion and alcohol use were associated with a decreased risk (Table 3). In the univariable analyses, superficial histological type at first occurrence of BCC and lesions located not in the head and neck region seemed to increase the likelihood of developing subsequent BCCs.

In the multivariable model that adjusted for age at index lesion, gender, hair and eye color, all UV related items, smoking and alcohol intake, lesion histology and location, and aged < 65 years at time of first BCC were associated with a significantly increased risk of developing multiple BCCs (e.g., ≥ 75 years vs. <65 years, adjusted HR 0.58; 95% CI 0.47 - 0.71 and HR 0.65; 95% CI 0.53 - 0.81, respectively; Table 3). Older age (age groups 65-74.99 and ≥ 75) at index lesion is associated with a decreased risk of developing multiple BCCs. For the oldest age group this could be partly explained by the mean follow-up time, which is relatively shorter than the mean follow-up time of the middle and youngest age group (mean follow-up times 6.66, 10.36 and 10.70 years, respectively). However, this does not clarify the decreased risk of developing multiple BCCs in age group 65 - 74.99. Blue eyes and blond hair were not significantly associated with developing multiple BCCs, but people with red hair were about

40% more likely to develop multiple BCCs than those with brown hair (adjusted HR 1.42; 95% CI 1.05 - 1.93). Compared to patients with low educational level, those with a medium and high educational level were about 20% and 40% more likely to develop multiple BCCs, respectively. After adjusting for confounders, the index lesion location on upper extremities was the only BCC characteristic that remained significantly associated with developing multiple BCCs (adjusted HR 1.49; 95% CI 1.02 - 2.15).

Table 3. Distribution and survival analysis of risk factors associated with development of multiple basal cell carcinoma (BCC)

Characteristic	No. of patients with one BCC (%)	No. of patients with multiple BCC (%)	Crude hazard ratios (Anderson-Gill) (95 % CI). multiple BCC (n = 163) ∞	Adjusted hazard ratios (Anderson-Gill) (95 % CI). multiple BCC (n = 163) ∞∞
Total number of patients	361	163		
Years of follow-up	4 160	2 114		
Mean years of follow-up/patient	11.52	12.97		
Gender				
female	215 (59.6)	85 (52.1)	1.00 (ref)	1.00 (ref)
male	146 (40.4)	78 (47.9)	**1.20 (1.05 – 1.37)**	1.11 (0.93 – 1.33)
Age at index lesion				
Mean. years (range. years)	*76.0 (55-98)*	*73.9 (57-95)*		
< 65	41 (11.4)	27 (16.6)	1.00 (ref)	1.00 (ref)
65 – 74.99	115 (31.9)	63 (38.7)	**0.62 (0.52 – 0.75)**	**0.65 (0.53 – 0.81)**
≥ 75	205 (56.8)	73 (44.8)	**0.55 (0.46 – 0.65)**	**0.58 (0.47 – 0.71)**
Hair color				
Brown/black	239 (66.2)	104 (63.8)	1.00 (ref)	1.00 (ref)
fair/blond	92 (25.5)	35 (21.5)	**1.19 (1.02 – 1.38)**	1.13 (0.95 – 1.35)
red	11 (3.0)	15 (9.2)	**1.54 (1.19 – 2.00)**	**1.43 (1.05 – 1.94)**
missing	19 (5.3)	9 (5.5)		
Eye color				
brown	73 (20.2)	26 (16.0)	1.00 (ref)	1.00 (ref)
intermediate	24 (6.6)	15 (9.2)	1.19 (0.90 – 1.58)	**1.41 (1.04 – 1.91)**
blue	224 (62.0)	108 (66.3)	1.15 (0.96 – 1.38)	1.09 (0.88 – 1.35)
missing	40 (11.1)	14 (8.6)		
Tendency for sunburns				
low	229 (63.4)	82 (50.3)	1.00 (ref)	1.00 (ref)
high	111 (30.7)	72 (44.2)	**1.21 (1.06 – 1.39)**	1.13 (0.96 – 1.33)
missing	21 (5.8)	9 (5.5)		
Outdoor work history (≥25 years)				
no	241 (66.8)	103 (63.2)	1.00 (ref)	
yes	40 (11.1)	29 (17.8)	1.06 (0.87 – 1.29)	
missing	80 (22.2)	31 (19.0)		
History of living in sunny country (>1 year)				
no	321 (88.9)	131 (80.4)	1.00 (ref)	
yes	21 (5.8)	23 (14.1)	1.09 (0.87 – 1.36)	
missing	19 (5.3)	9 (5.5)		

Sun protective behavior ††				
no	167 (46.3)	61 (37.4)	1.00 (ref)	1.00 (ref)
often	95 (26.3)	53 (32.5)	**1.22 (1.04-1.43)**	1.12 (0.93 – 1.34)
always	79 (21.9)	39 (23.9)	**1.19 (1.00-1.42)**	1.15 (0.94 – 1.39)
missing	20 (5.5)	10 (6.1)		
Smoking †				
Never smoked	129 (35.7)	56 (34.4)	1.00 (ref)	1.00 (ref)
Former	160 (44.3)	84 (51.5)	1.10 (0.95 – 1.28)	0.95 (0.79 – 1.16)
Current	68 (18.8)	21 (12.9)	0.99 (0.81 – 1.21)	0.88 (0.69 – 1.12)
missing	4 (1.1)	2 (1.2)		
Alcohol intake (g/d) †				
No	104 (28.8)	42 (25.8)	1.00 (ref)	1.00 (ref)
0.01 – 9.99 g	114 (31.6)	59 (36.2)	**0.75 (0.63 – 0.88)**	0.83 (0.69 – 1.01)
10 – 19.99 g	38 (10.5)	16 (9.8)	**0.63 (0.49 – 0.81)**	**0.62 (0.47 – 0.81)**
20 g or more	46 (12.7)	28 (17.2)	**0.80 (0.65 – 0.99)**	0.84 (0.66 – 1.06)
missing	59 (16.3)	18 (11.0)		
Body mass index (BMI. kg/m^2) †				
< 25 (under- and normal weight)	126 (34.9)	56 (34.4)	1.00 (ref)	1.00 (ref)
25-29.99 (overweight)	145 (40.2)	79 (48.5)	1.03 (0.89 – 1.19)	1.08 (0.92 – 1.28)
30 or more (obese)	58 (16.1)	17 (10.4)	0.94 (0.75 – 1.17)	1.01 (0.78 – 1.30)
missing	32 (8.9)	11 (6.7)		
Educational level				
Low	184 (51.0)	75 (46.0)	1.00 (ref)	1.00 (ref)
Medium	111 (30.7)	59 (36.2)	**1.27 (1.09 – 1.48)**	**1.22 (1.02 – 1.45)**
High	59 (16.3)	23 (14.1)	**1.66 (1.37 – 2.01)**	**1.42 (1.12 – 1.81)**
missing	7 (1.9)	6 (3.7)		
Index lesion subtype				
Nodular	206 (57.1)	97 (59.5)	0.84 (0.70 – 1.01)$^{\#}$	0.84 (0.66 – 1.06)$^{\#}$
Infiltrating	93 (25.8)	43 (26.4)	0.86 (0.70 – 1.06)$^{\#}$	0.80 (0.62 – 1.04)$^{\#}$
Superficial	26 (7.2)	28 (17.2)	1.10 (0.87 – 1.39)$^{\#}$	0.92 (0.70 – 1.22)$^{\#}$
Other	8 (2.2)	7 (4.3)	0.89 (0.57 – 1.37)$^{\#}$	0.90 (0.53 – 1.52)$^{\#}$
Missing	28 (7.8)	12 (7.4)		
Index lesion site				
Head/neck	261 (72.3)	114 (69.9)	0.98 (0.79 – 1.21)$^{\#\#}$	1.20 (0.91 – 1.59)$^{\#\#}$
Trunk	46 (12.7)	34 (20.9)	1.17 (0.94 – 1.46)$^{\#\#}$	1.27 (0.98 – 1.65)$^{\#\#}$
Upper extremities	12 (3.3)	11 (6.7)	1.33 (0.96 – 1.85)$^{\#\#}$	**1.49 (1.02 – 2.15)**$^{\#\#}$
Lower extremities	26 (7.2)	26 (16.0)	1.25 (0.96 – 1.61)$^{\#\#}$	1.34 (0.98 – 1.82)$^{\#\#}$
Missing	17 (4.7)	3 (1.8)		

∞ Univariate Anderson-Gill multifailure survival analysis

∞∞ Multivariate adjusted Anderson-Gill multifailure survival analysis. Adjusted for variables shown. Cut of point p for including p<0.20 in univariate analysis

† Assessed at baseline. 1990-91 for the initial cohort and 2000-2001 for the second cohort

†† Defined by questions of wearing sunglasses and/or hat with a rim in sunshine

$^{\#}$ Reference group: all other lesion subtypes combined

$^{\#\#}$ Reference group: all other sites combined

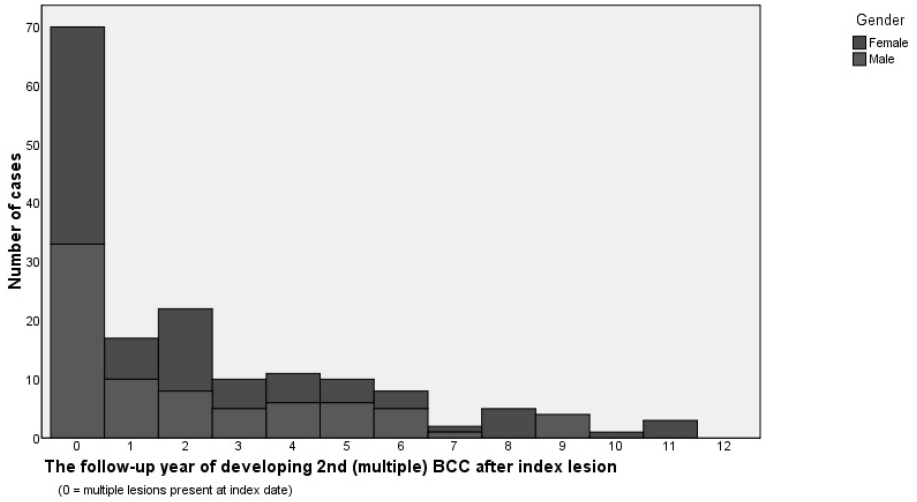


Figure 3. Time to development of subsequent basal cell carcinoma lesions. Zero indicates multiple lesions present at index date

DISCUSSION

In this study, 4.8% of the cohort members had a BCC and approximately one third of them developed multiple BCCs during an average of almost 10 years of follow-up, which is consistent with data from other studies.[12-13, 16] Most risk factors associated with developing a first BCC such as age and hair color are in accordance with other studies, although men were not at an increased risk, which has been observed in some but not all previous studies.[12, 17] As expected, BCC risk increased with age, but people who developed their first BCC before 65 years of age were significantly more likely to develop multiple BCCs. In contrast to developing a first BCC, high educational level was significantly positively associated with developing multiple BCC. This may be explained by the fact that people in higher socioeconomic class have different lifestyles (e.g. more frequently intermittent UV exposure) and in part because they are more likely to develop superficial non-facial BCCs, which are associated with the risk of developing multiple BCCs, or because of the immortal time bias (i.e., people with higher socioeconomic status are more likely to live longer and, thus, may have more time to develop a BCC).[24] However, the mean age at study entry of the participants with a higher education was actually younger (64.77 years vs. 71.32 years) and the mean follow-up period shorter than in the group of participants with only primary education (7.75 years vs. 10.47 years), hereby suggesting that this bias is not affecting our findings. Interestingly, after adjusting for confounding factors, known BCC risk factors such as blue eyes and blond hair were not associated with developing multiple BCC. Red hair seemed to be the most important risk factor for developing subsequent BCCs. No associations were observed between BCC and variables assessing in part cumulative UV exposure during lifetime, i.e. sun protective behavior, outdoor work and history of living in a sunny country.

The observed discrepancy between risk factor profiles of developing one or multiple BCC may suggest that once cumulative environmental-genetic interaction has surpassed a certain threshold and resulted in a BCC, the phenotypic characteristics of patients seem less important. The clinical relevance of this finding is that physicians' risk assessment should differentiate between patients at risk for a first BCC and those who have a history of BCC. Of the people with a prior BCC, those who are relatively young at diagnosis of a first BCC, those who have red hair and a higher socioeconomic status, and/or had a BCC on their upper extremities may require a more stringent follow-up regimen than other BCC patients. However, of the classical phenotypic, UV-exposure and lifestyle risk factors examined in this study, the strength of the risk estimates was modest (adjusted HR<1.5) suggesting that other (genetic) factors may play an important role in the predisposition for developing multiple BCCs. In this sample of the general population, more than 30% of the BCC patients developed a subsequent skin cancer emphasizing the need for (annual) follow-up for several years. This recommendation is often stated in the national BCC guidelines and has major implications in the allocation of dermatological care because of the enormous volume of skin cancer patients in predominantly Caucasian populations (most notably, Australia and USA, but also Europe). Therefore, more observational research is needed to identify people who will benefit most of long term and specialized follow up.

Interestingly, more than half of the additional BCCs among patients with at least one superficial BCC were of the nodular or infiltrating histological type suggesting a common pathogenesis of these clinically and histologically different types of BCC. In clinical practices, this implies that patients with superficial BCC, which are not very aggressive, are at a high risk of developing more aggressive high risk BCCs.[25]. We confirmed that non head and neck location of BCC is a risk factor for developing multiple BCCs[16, 26], especially BCCs located on the upper extremities. Most BCCs were located on the head and neck area, followed by trunk and upper and lower extremities, which is in accordance with previous studies concerning the anatomical distribution.[27]

This is the largest population-based study (including 100 000 person years of follow-up) assessing and comparing risk factor profiles of first and multiple BCCs, based on detailed information of BCC and patient characteristics. In total, four UV related questions were asked (Table 2), but no information was available concerning UV exposure in childhood and adolescence, which seems to be important in the pathogenesis of BCC. Because only histologically confirmed BCCs were included in this study, lesions not biopsied or treated without histopathological confirmation were missed. However, in the study period, the recommended treatment according to the Dutch BCC guidelines[19] was surgical excision and the community hospital that is responsible for most of the health care provided in the study region usually

required pathological confirmation of diagnosis and used relatively few non-invasive skin cancer therapies (cryotherapy, radiotherapy, topical therapies and photodynamic therapy) during the study period (personal communication of chair of dermatology, St Franciscus Hospital, Rotterdam) suggesting that the number of missed BCCs was limited. To minimize multiple counting of a single BCC, a robust and conservative attempt was made to differentiate between biopsied, excised, incident, recurrent and subsequent BCCs.

In conclusion, more than 30% of Dutch BCC patients developed multiple BCC. The risk profiles associated with incident BCC and multiple BCCs differed and require physicians to alter their risk assessment after a first BCC has been diagnosed. More research is needed to identify people who are at risk of developing multiple BCCs because the follow up of this large group of people is putting a strain on limited specialized care.

REFERENCES

1. Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer 2007;121:2105-8.
2. Brewster DH, Bhatti LA, Inglis JH, Nairn ER, Doherty VR. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992-2003. Br J Dermatol 2007;156:1295-300.
3. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. J Invest Dermatol 2004;123:634-8.
4. Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. Arch Dermatol 1999;135:781-6.
5. Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer 1999;81:555-9.
6. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust 2006;184:6-10.
7. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol 1994;30:774-8.
8. Housman TS, Feldman SR, Williford PM, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. J Am Acad Dermatol 2003;48:425-9.
9. Gloster HM, Jr., Neal K. Skin cancer in skin of color. J Am Acad Dermatol 2006;55:741-60; quiz 61-4.
10. Han J, Colditz GA, Hunter DJ. Risk factors for skin cancers: a nested case-control study within the Nurses' Health Study. Int J Epidemiol 2006;35:1514-21.
11. Hoban PR, Ramachandran S, Strange RC. Environment, phenotype and genetics: risk factors associated with BCC of the skin. Expert Rev Anticancer Ther 2002;2:570-9.
12. Karagas MR, Stukel TA, Greenberg ER, Baron JA, Mott LA, Stern RS. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin Cancer Prevention Study Group. Jama 1992;267:3305-10.
13. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524-30.
14. Zanetti R, Rosso S, Martinez C, et al. The multicentre south European study 'Helios'. I: Skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. Br J Cancer 1996;73:1440-6.
15. Pandeya N, Purdie DM, Green A, Williams G. Repeated occurrence of basal cell carcinoma of the skin and multifailure survival analysis: follow-up data from the Nambour Skin Cancer Prevention Trial. Am J Epidemiol 2005;161:748-54.
16. Ramachandran S, Fryer AA, Smith AG, et al. Basal cell carcinoma. Cancer 2000;89:1012-8.
17. Robinson JK. Risk of developing another basal cell carcinoma. A 5-year prospective study. Cancer 1987;60:118-20.
18. Lovatt TJ, Lear JT, Bastrilles J, et al. Associations between ultraviolet radiation, basal cell carcinoma site and histology, host characteristics, and rate of development of further tumors. J Am Acad Dermatol 2005;52:468-73.

19. Dutch guidelines for the management of basal cell carcinoma. Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV), 2003. http://www.cbo.nl/product/richtlijnen/folder20021023121843/basaal2003.pdf accessed at January 22nd 2009.
20. Hauschild A, Breuninger H, Kaufmann R, et al. Short German guidelines: basal cell carcinoma. J Dtsch Dermatol Ges 2008;6 Suppl 1:S2-4.
21. Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. Br J Dermatol 2008;159:35-48.
22. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: 2010 objectives and design update. Eur J Epidemiol 2009;24:553-72.
23. Cleophas TJ, Zwinderman AH, Cleopas TF. Statistics Applied to Clinical Trials.. In: Subgroup analysis using multiple linear regression: confounding, interaction, synergism: Springer Netherlands; 2006:141-50.
24. van Hattem S, Aarts MJ, Louwman WJ, et al. Increase in basal cell carcinoma incidence steepest in individuals with high socioeconomic status: results of a cancer registry study in the Netherlands. Br J Dermatol 2009;161:840-5.
25. Saldanha G, Fletcher A, Slater DN. Basal cell carcinoma: a dermatopathological and molecular biological update. Br J Dermatol 2003;148:195-202.
26. Ramachandran S, Fryer AA, Smith A, et al. Cutaneous basal cell carcinomas: distinct host factors are associated with the development of tumors on the trunk and on the head and neck. Cancer 2001;92:354-8.
27. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 2002;147:41-7.

CHAPTER 9

Prevalence of actinic keratosis, its risk factors and association with skin cancer in an elderly population: the Rotterdam Study

S.C. Flohil

R.J.T. van der Leest

E.A. Dowlatshahi

A. Hofman

E. de Vries

T. Nijsten

Submitted

ABSTRACT

Background

Actinic keratoses (AK) are precursors of cutaneous squamous cell carcinomas (SCC). Limited data is available on the prevalence and risk factors of AK.

Methods

Within the Rotterdam Study, a Dutch population-based cohort study, full body skin examinations were performed among participants aged 45 years or older to estimate the age- and sex standardized prevalence of AK and its associated risk factors. A multinomial logistic regression model calculated adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for associations between risk factors and the presence of 1 – 3, 4 – 9 and ≥ 10 AK. Binary logistic regression compared participants without or with extensive actinic damage (≤ 9 AK versus ≥ 10 AK). By linking the participants to PALGA, the nationwide network and registry of histo- and cytophatology in The Netherlands, participants with a history of cutaneous malignancy were identified.

Results

Of the 2,061 inspected cohort members (mean age 72 years), 21% had 1 to 3, 9% 4 to 9 and 8% ten or more AK. Prevalence of AK in the Rotterdam Study was 49% (95% CI 46%–52%) for men and 28% (26%–31%) for women. Extrapolation suggested that approximately 1.4 of the 16 million Dutch citizens are affected with AK. Male sex, older age, light pigmentation status, severe baldness, skin wrinkling and high tendency for sunburn were significantly associated with number of AKs and extensive actinic damage (≥10 AKs) in the multivariate analyses. Especially bald males were at an increased risk of severe actinic skin damage (adjusted OR= 7.0 [3.8 – 13.1]). The group with no AKs had a lower positive history for SCC than the group with 10 AKs (1.2% and 13.6%, respectively).

Conclusions

The prevalence of AK is very high, especially among elderly bald males, and the presence of severe actinic damage significantly increases a history of SCC. The prevention and management of AK is a true challenge for patients, physicians, and health care policy makers.

INTRODUCTION

Actinic keratoses (AKs) are common keratinocytic intra-epidermal neoplasia (KIN) often occurring on chronically sun-exposed skin of Caucasian people.[1] Although AKs may persist or spontaneously regress. AKs may progress to invasive cutaneous squamous cell carcinoma (SCC) in approximately 0.1 to 20% of the lesions annually.[2-4] Recently, a study suggested AKs may progress to basal cell carcinoma (BCC) as well.[5] AKs are often diagnosed clinically (i.e., rough red scaly patches on chronically sun-exposed skin) without histological confirmation and are, therefore, not recorded in pathology databases and cancer registries.

Population-based studies investigating AK prevalence and its associated risk factors [6-10] conclude that elderly subjects with European ancestry and high cumulative ultraviolet (UV) exposure have the highest risk of developing AKs. However these studies are few and report prevalences of AK varying from 1.4 to 59.2%. These differences in prevalences could be due to the geographic variability in UV radiation levels (Australia > United States of America > Europe) and the differences between the studied populations (e.g. high-risk patients, pigmentation status and age restrictions). Moreover skin examinations and AK count were not conducted uniformly in these studies.[6-11]

Most national guidelines or consensus reports recommend the treatment of AKs, for which a variety of modalities are available, and follow up of these patients because of their invasive potential. Implementing these recommendations puts a further burden on general physicians and the dermatological care that is already strained by the care of cutaneous malignancies.[12-13]

More accurate insight into the prevalence of AK among the general population is pivotal for public health strategies and medical decision makers. For the first time in The Netherlands, the prevalence of AK and its associated risk factors were investigated in a population-based cohort study (i.e. Rotterdam Study) among 2,061 elderly participants.

METHODS

Study population

The Rotterdam Study is an ongoing prospective population-based cohort study that follows inhabitants of the Ommoord district of Rotterdam, The Netherlands since 1990. The study design and objectives of the Rotterdam Study have been described elsewhere.[14] The Rotterdam Study was designed to study frequencies and risk factors associated with diseases of the elderly (e.g. coronary heart disease, Alzheimer disease and osteoporosis). Every 3 to 4 years, participants are interviewed at home and undergo an extensive set of examinations at the Rotterdam Study research facilities.

In January 1990, the first cohort (RS-I) of 7983 participants (78% of invitees) aged 55 years or older was established (figure 1). In 2000, a second cohort (RS-II) was added to the Rotterdam Study, including 3011 participants (67% of invitees) who had turned 55 years of age or had

moved into the study district. The third cohort (RS-III) was established in 2006, in which 3932 participants (65% of invitees) aged 45 to 54 years were added to the cohort. Participants of the present study were all above 50 years of age. The Rotterdam Study is approved by the Medical Ethics Committee of the Erasmus MC University Medical Center and The Netherlands Ministry of Health, Welfare and Sports.

Dermatology in the Rotterdam Study

In August 2010, dermatology was introduced to the Rotterdam Study (figure 1). Since then, full body skin examinations (FBSE; with the exception of the feet and the skin covered by socks and underwear, respectively) are being conducted by four trained physicians focussing on the most common skin diseases such as skin (pre-)malignancies, atopic dermatitis, hand eczema, psoriasis and varicose veins.

Actinic keratoses

An AK was diagnosed clinically and was defined as a rough (keratotic) lesion with adherent scaling and erythema, not fitting another diagnosis.[15] Since AK lesions are often confluent and located on sun- damaged skin, it is difficult to count the total number of individual lesions within a participant.[15]

We counted overall number of AK per participant and subdivided this into the number of AK per localisation using the same categories: no presence of AK, 1 to 3, 4 to 9 or ≥ 10 AK. The subdivision per anatomical localisation consisted of the most important sun-exposed areas including scalp, face (excluding ears), ears, neck, back of hands, forearms, chest or other localisations.

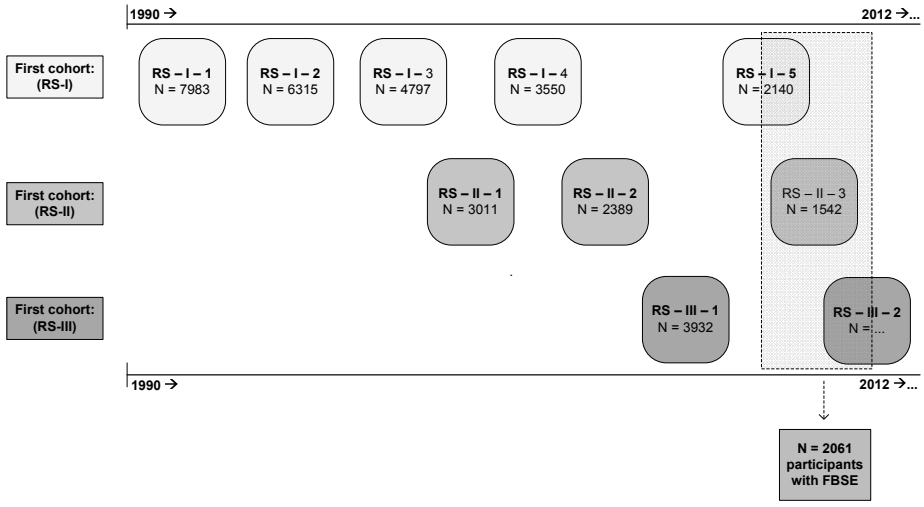


Figure 1. Flowchart of the Rotterdam Study

Abbreviations: AK, actinic keratoses; FBSE, full body skin examination; RS, Rotterdam Study

Risk factors

Sex and age (in years) at date of skin examination were registered. Educational level (classified into 3 categories: low [primary education and primary education with a higher not completed education], medium [lower-level secondary education, lower-level vocational education intermediate-level vocational education], and high [general secondary education, higher-level vocational education and university]), smoking (never versus ever), hair color at young age (red, fair / blond, dark blond / brown and black) and four questions assessing UV exposure were available from interview data. The questions on UV exposure included tendency for sunburns, history of more than 25 years of outdoor work, having lived more than one year in a sunny country and sun-protective behavior (i.e. wearing sunglasses and/or a rimmed hat in the sunshine). The first three UV items had binary responses and the latter was categorized into never / almost never, often / not always and always. Eye color (blue, intermediate, brown) was available from and scored by the ophthalmology department within the Rotterdam study. During FBSE, the following potential phenotypic risk factors for AK were scored; skin color (very white [3.4%], white [79.1%], white to olive [14.5%], light brown [1.7%], brown [1.1%], dark brown / black [0.2%]), Glogau score (type 1 'no wrinkles', type 2 'wrinkles in motion', type 3 'wrinkles at rest' and type 4 'only wrinkles')[16], number of naevi (< 25, 25 – 50, 50 – 100, > 100) and baldness of the scalp based on the Norwood – Hamilton (NH) [17-18] scale for men and the Ludwig scale (LS) [19] for women. In the analyses, baldness of the scalp was divided into none or minimal (NH score A,B,C,I,J and LS score 1), mild (NH score D,E,F,K and LS score 2) and extensive baldness (NH score G,H,L and LS score 3).

Due to significant correlation (phi-test for correlation, $p < 0.001$) between the phenotypic characteristics hair color at young age, eye - and skin color, these three variables were combined into one variable 'pigmentation status' and classified by light, medium or dark pigmentation status.

Skin cancer history

All RS participants were linked to PALGA, the Dutch nationwide network and registry of histo- and cytopathology in The Netherlands, which contains excerpts of all pathology reports with nationwide coverage from 1991 onwards.[20] A linkage between PALGA and our study population was made until September 23th 2011.[21] An excerpt encloses encrypted patient data, a summary of the pathology report and a diagnosis line based upon standard pathology terminology similar to the Systematized Nomenclamenture of Medicine (SNOMED) issues by the College of American Pathologists. Individuals in the database have an encrypted patient identification code which enables linkage with all available pathology data within PALGA. The search in PALGA was based on codes corresponding to all types of BCC (i.e. M80903, M80913, M80923, M80933, M80943, M80963, M80973, M80983), SCC (i.e. M80703, M80713, M80723, M80743, M80753, M80704, M85603, M80711) and melanoma (i.e. M87203, M87213, M87223, M87233, M87263, M87303, M87403, M87423, M87433, M87443, M87453, M87700,

M87703, M87713, M87723, M87743, M87753, M87803). Participants were counted only once per cutaneous malignancy (figure 1).

Statistical analyses

The prevalence of AK within the 2,061 studied participants of the Rotterdam Study was standardized by age (5–year bands) and sex and 95% confidence intervals (95% CI) for proportion were calculated. The sex– and age-specific prevalences were multiplied by the sex- and age-specific population size in The Netherlands (5-year bands). Population size was obtained from Statistics Netherlands and estimated on the first of January 2011.[22] The extrapolated AK prevalence was calculated for the Dutch population aged 50 years or more.

To investigate risk factors associated with the development of AK, uni- and multivariate multinomial logistic regression analyses were performed and odds ratios (OR) with 95% CI were calculated for each of the three outcome groups, 1 to 3, 4 to 9 and ≥ 10 AK.

In addition, considering the ordinal structure of the latter outcome groups, an ordinal logistic regression was used to provide a cumulative OR. A significant cumulative OR corresponds to a statistically significant trend of increase in risk across the AK strata.[23-24] A corresponding p-value for trend (based on the ordinal logistic regression) was calculated (table 4). However, not all variables met the proportional odds assumption for this test and fitted therefore better in the multinomial logistic regression model.

To compare participants with extensive actinic damage (≥ 10 AK) to those with no or less actinic damage (0 to 9 AK), uni- and multivariate binary logistic regression analyses were used to calculate (adjusted) OR with 95% CI. All variables included in the univariate analyses were included in the multivariate analyses as possible confounders for AK risk. No significant interaction terms were observed. All statistical analyses were performed using SPSS for Windows version 17.0 (SPSS inc., Chicago, IL, USA). P-values were two–sided and considered statistically significant if p–value < 0.05.

RESULTS

In total, 2,061 (99.9%) of 2063 participants visiting the Rotterdam Study research facility between August 2010 and April 2012 agreed to undergo a FBSE. Hereof, 208 (10.1%) were from RS-I, 1,542 (74.8%) RS-II and 311 (15.1%) RS-III. The majority of the participants were women (55.0%; Table 1). Mean age at date of FBSE was 71.6 years (standard deviation [SD] 7.1; ranging from 51 to 98 years).

Prevalence of actinic keratoses

Of 2,061 participants, 773 (37.5%) had at least one or more AK of which 56.0% had 1 to 3 AK, followed by 4 to 9 (22.9%) and 10 or more (21.1%). Overall, the prevalence of one AK or more was 49.0% (95% CI 45.8–52.2%) for men and 28.1% (25.5–30.7%) for women (table 2). AK prevalence increased with age in both men and women, but there was a small dip in age

Table 1. Study characteristics of 2061 participants of the Rotterdam Study with a full body skin examination

Characteristics	Total study population (n=2061)	No AK (%) (n=1288)	1 - 3 Aks (%) (n=433)	4 - 9 Aks (%) (n=177)	≥ 10 Aks (%) (n=163)
Sex					
Women	1134 (55.0)	815 (63.3)	220 (50.8)	58 (32.8)	41 (25.2)
Men	927 (45.0)	473 (36.7)	213 (49.2)	119 (67.2)	122 (74.8)
Age at FBSE					
Mean age in years (SD)	71.6 (7.1)	70.2 (7.2)	73.0 (6.4)	74.1 (6.5)	75.6 (6.2)
< 70	874 (42.4)	638 (49.5)	156 (36.0)	50 (28.2)	30 (18.4)
70 - 79.99	947 (45.9)	532 (41.3)	219 (50.6)	98 (55.4)	98 (60.1)
≥ 80	240 (11.6)	118 (9.2)	58 (13.4)	29 (16.4)	35 (21.5)
Pigmentation status (based on eye, hair and skin color)					
Dark	212 (10.3)	164 (12.7)	26 (6.0)	12 (6.8)	10 (6.1)
Medium	1294 (62.8)	813 (63.1)	272 (62.8)	116 (65.5)	93 (57.1)
Light	385 (18.7)	201 (15.6)	92 (21.2)	39 (22.0)	53 (32.5)
Data missing	170 (8.2)	110 (8.5)	43 (9.9)	10 (5.6)	7 (4.3)
Glogau scale					
1 and 2	180 (8.7)	156 (12.1)	17 (3.9)	5 (2.8)	2 (1.2)
3	1684 (81.7)	1026 (79.7)	359 (82.9)	154 (87.0)	145 (89.0)
4	197 (9.6)	106 (8.2)	57 (13.2)	18 (10.2)	16 (9.8)
Naevi					
< 25	1569 (76.1)	985 (76.5)	323 (74.6)	130 (73.4)	131 (80.4)
25 – 50	385 (18.7)	236 (18.3)	90 (20.8)	35 (19.8)	24 (14.7)
50 or more	107 (5.2)	67 (5.2)	20 (4.6)	12 (6.8)	8 (4.9)
Baldness[1]					
No / almost no baldness	1355 (65.7)	940 (73.0)	60 (13.9)	66 (37.3)	83 (50.9)
Mild baldness	389 (18.9)	240 (18.6)	86 (19.9)	35 (19.8)	28 (17.2)
Severe baldness	317 (15.4)	108 (8.4)	287 (66.3)	76 (42.9)	52 (31.9)
Tendency to develop sunburn					
Low	1330 (64.5)	873 (67.8)	275 (63.5)	108 (61.0)	74 (45.4)
High	607 (29.5)	330 (25.6)	129 (29.8)	64 (36.2)	84 (51.5)
Data missing	124 (6.0)	85 (6.6)	29 (6.7)	5 (2.8)	5 (3.1)
Outdoor work history ≥ 25 years					
No	334 (16.2)	220 (17.1)	51 (11.8)	21 (11.9)	42 (25.8)
Yes	151 (7.3)	105 (8.2)	21 (4.8)	14 (7.9)	11 (6.7)
Data missing	1576 (76.5)	963 (74.8)	361 (83.4)	142 (80.2)	110 (67.5)
History of living in sunny country of > 1 year					
No	1730 (83.9)	1064 (82.6)	367 (84.8)	163 (92.1)	136 (83.4)
Yes	213 (10.3)	145 (11.3)	37 (8.5)	9 (5.1)	22 (13.5)
Data missing	118 (5.7)	79 (6.1)	29 (6.7)	5 (2.8)	5 (3.1)
Sun protective behavior[2]					
Never / almost never	672 (32.6)	454 (35.2)	135 (31.2)	49 (27.7)	34 (20.9)
Often / not always	640 (31.1)	358 (27.8)	136 (31.4)	75 (42.4)	71 (43.6)
Always	631 (30.6)	397 (30.8)	133 (30.7)	48 (27.1)	53 (32.5)
Data missing	118 (5.7)	79 (6.1)	29 (6.7)	5 (2.8)	5 (3.1)
Smoking history					
Never	663 (32.2)	434 (33.7)	155 (35.8)	35 (19.8)	39 (23.9)
Ever	1381 (67.0)	846 (65.7)	272 (62.8)	139 (78.5)	124 (76.1)
Data missing	17 (0.8)	8 (0.6)	6 (1.4)	3 (1.7)	0

Characteristics	Total study population (n=2061)	No AK (%) (n=1288)	1 - 3 Aks (%) (n=433)	4 - 9 Aks (%) (n=177)	≥ 10 Aks (%) (n=163)
Education level[3]					
Low	374 (18.1)	235 (18.2)	78 (18.0)	31 (17.5)	30 (18.4)
Medium	1215 (59.0)	751 (58.3)	271 (62.6)	106 (59.9)	87 (53.4)
High	444 (21.5)	285 (22.1)	78 (18.0)	39 (22.0)	42 (25.8)
Data missing	28 (1.4)	17 (1.3)	6 (1.4)	1 (0.06)	4 (2.5)

[1]Based on the Norwood – Hamilton scale for men and Luwdig scale for women.
[2]Wearing sunglasses and/or a rimmed hat in the sunshine.
[3]Low (primary education and primary education with a higher not completed education), medium (lower-level secondary education, lower-level vocational education intermediate-level vocational education), and high (general secondary education, higher-level vocational education and university)
Abbreviations: AK, actinic keratoses; FBSE, full body skin examination; SD, standard deviation; n, number

category 80 – 84 years compared to younger age–groups in men and women (table 2 and figure 2).

Extrapolation to The Netherlands showed that 1,408,641 of the 5,985,164 Dutch citizens aged fifty years or older were affected by AK in 2011, of which 817,823 (58%) were men and 596,487 (42%) were women. This corresponds to an AK prevalence of 23.5% (95% CI 21.7 – 25.3%) in the Dutch population aged 50 years or older; 28.8% (25.9–31.7%) for men and 19.0% (16.7–21.2%) for women.

Location of actinic keratoses

Overall, the face was the location most commonly affected by 1 to 3 (42.5%) and 4 to 9 (33.4%) AK, while ≥ 10 AK were more frequently located on scalp with 36.2% (table 3). Stratification by sex showed that extensive actinic damage (≥ 10 AK) was most often found on scalp (47.5%) in bald men, while this was 0.0% in women. In women, extensive actinic damage was most often located on the face followed by chest, respectively 32.2% and 29.0% (table 3).

Risk factors of actinic keratoses

Male sex, age of 70 years and older, medium and dark pigmentation status, Glogau score 3 and 4, high tendency for sunburn and often / not always use of sun protective measurements were all significantly associated with the three outcome groups in the univariate multinomial logistic regression analysis (appendix table 1). Medium baldness was associated with 4 to 9 (OR 1.8 [95% CI 1.2 – 2.8]) and ≥ 10 AK (OR 2.1 [95% CI 1.3 – 3.4]), whereas severe baldness was associated with all three outcome groups in a linear manner up to an OR 13.9 (9.3 – 20.7) for ≥10 AKs compared to no or minimal hairloss. Naevi and educational level were not significantly associated with AK, whereas ever smoking was associated with 4 to 9 and ≥ 10 AK (OR 2.0 [95% CI 1.4 – 3.0] and OR 1.6 [95% CI 1.1 – 2.4], respectively). All variables remained significantly associated with AKs in the multivariate multinomial model (table 4). After adjusting for the other risk factors, severe baldness remained the strongest risk factor for ≥ 10 AK (adjusted OR 6.3 [95% CI 3.6– 1.0]; p-value for trend < 0.001). After stratification

Table 2. Prevalence of actinic keratoses among 2061 participants of the Rotterdam Study

	Total study population			Men			Women		
Age - groups in years	**Total n = 2061**	**AK (%) n = 773**	**(95% CI)**	**Total n = 927**	**AK (%) n = 454**	**(95% CI)**	**Total n = 1134**	**AK (%) n = 319**	**(95% CI)**
50 - 54	49	0,0	(0.0 - 0.0)	16	0,0	(0.0 - 0.0)	33	0.0	(0.0 - 0.0)
55 - 59	74	6.8	(1.0 - 12.5)	31	12.9	(1.1 - 24.7)	43	2.3	(-2.2 - 6.8)
60 - 64	108	19.4	(12.0 - 26.9)	38	23.7	(10.2 - 37.2)	70	17.1	(8.3 - 25.9)
65 - 69	643	32.7	(29.0 - 36.3)	302	41.1	(35.6 - 46.6)	341	25.2	(20.6 - 29.8)
70 - 74	674	41.1	(37.4 - 44.8)	306	52.9	(47.3 - 58.5)	368	31.3	(26.6 - 36.0)
75 - 79	273	50.5	(44.6 - 56.6)	127	70.9	(63.0 - 78.8)	146	32.9	(25.3 - 40.5)
80 - 84	146	41.1	(33.1 - 49.1)	71	54.9	(43.3 - 66.5)	75	28.0	(17.8 - 38.2)
≥ 85	94	66.0	(56.4 - 75.6)	36	72.2	(57.6 - 86.8)	58	62.1	(49.6 - 74.6)
Overall	2061	37.5	(35.4 - 39.6)	972	49.0	(45.8 - 52.2)	1134	28,1	(25.5 - 30.7)

Abbreviations: AK, actinic keratoses; CI, confidence interval; n, number

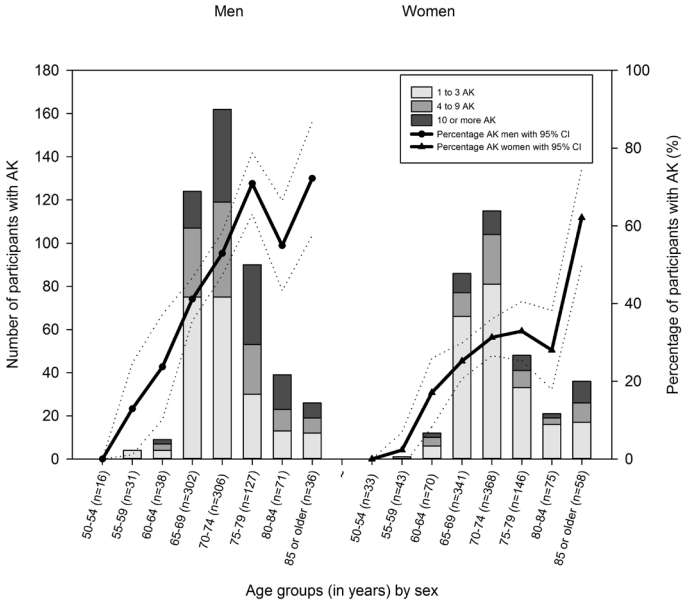


Figure 2. Prevalence of actinic keratoses among 2061 participants of the Rotterdam Study, stratified by sex
Abbreviations: AK, actinic keratoses; BCC, basal cell carcinoma; CI, confidence interval; SCC, squamous cell carcinoma

by sex (data not shown), severe baldness remained significantly associated with ≥10 AK in men (adjusted OR 7.0 [3.8–13.1]), but not in women (no OR could be calculated since only 8 women had severe baldness). Male sex, age of 70 years or older, Glogau 3 and 4 and tendency to develop sunburn remained significantly associated with all three outcome groups. Light pigmentation status was associated with 1 to 3 (OR 2.3 [95% CI 1.3 – 3.8]) and ≥ 10 AK (OR 2.5 [95% CI 1.1 – 5.7]), but not with 4 to 9 AK. Always use of sun protective measurement was associated with ≥ 10 AK (adjusted OR 2.0 [95% CI 1.2 – 3.4]).

Table 3. Anatomical location of actinic keratoses among 774 participants of the Rotterdam Study with actinic keratoses

	Study population			Men			Women		
Number of AK	**1 to 3**	**4 to 9**	**≥ 10**	**1 to 3**	**4 to 9**	**≥ 10**	**1 to 3**	**4 to 9**	**≥ 10**
	n = 891	**n = 290**	**n = 130**	**n = 506**	**n = 205**	**n = 99**	**n = 385**	**n = 85**	**n = 31**
Localisation									
Scalp	117 (13.1)	84 (29.0)	47 (36.2)	109 (21.5)	82 (40.0)	47 (47.5)	8 (2.1)	2 (2.4)	0 (0.0)
Face	379 (42.5)	97 (33.4)	35 (26.9)	182 (36.0)	64 (31.2)	25 (25.3)	197 (51.2)	33 (38.8)	10 (32.3)
Ears	83 (9.3)	11 (3.8)	0 (0.0)	71 (14.0)	10 (4.9)	0 (0.0)	12 (3.1)	1 (1.2)	0 (0.0)
Neck	8 (0.9)	2 (0.7)	1 (0.8)	6 (1.2)	1 (0.5)	0 (0.0)	2 (0.5)	1 (1.2)	1 (3.2)
Back of hands	116 (13.0)	37 (12.8)	9 (6.9)	63 (12.5)	24 (11.7)	6 (6.1)	53 (13.8)	13 (15.3)	3 (9.7)
Forearms	76 (8.5)	30 (10.3)	12 (9.2)	34 (6.7)	12 (5.9)	7 (7.1)	42 (10.9)	18 (21.2)	5 (16.1)
Chest	72 (8.1)	18 (6.2)	14 (10.8)	26 (5.1)	4 (2.0)	5 (5.0)	46 (11.9)	14 (16.5)	9 (29.0)
Elsewhere	40 (4.5)	11 (3.8)	12 (9.2)	15 (3.0)	8 (3.9)	9 (9.1)	25 (6.5)	3 (3.5)	3 (9.7)

Abbreviations: AK, actinic keratoses; n, number

In line with the multinominal model, the multivariate binary logistic regression showed that men, older age (≥ 70 years), Glogau score 3, medium and severe baldness, high tendency to develop sunburn, and often /not always and always use of sun protective measurements were significantly associated with extensive actinic damage (≥10 AKs) (table 5).

Skin cancer history and detection during FBSE

In total, 238 (11.5%) participants had a history of BCC, 51 (2.5%) of SCC and 20 (0.5%) of melanoma. The risk of a history with one of these cutaneous malignancies increased across the AK severity strata (i.e. from none to >10 AKs). For BCC, SCC and melanoma, these risks increased respectively from 7.2 to 26.5%, 1.2 to 13.6% and 0.7 to 1.9% (figure 3). Although these risks increased gradually for BCC and melanoma, a sharper increase was seen for SCC. Participants with >10 AKs (13.6%) had a three fold higher risk for having a SCC history compared to participants with 4 to 9 AKs (4.0%). Of the 2061 participants who received a FBSE during our study period, it was histologically confirmed that 59 (2.9%) had a BCC, 11 (0.5%) had a SCC and 9 (0.4%) a melanoma (including 5 invasive and 4 in situ). Overall, the detection rate of these cutaneous malignancies in our study population was 4.0% (82 out of 2061 participants).

DISCUSSION

In this Dutch population-based study among more than 2,000 people with a mean age of 72 years who were examined by trained physicians, almost 38% had one or more AK and 8% had 10 or more (age- and sex-adjusted 23% and 5%, respectively). This AK prevalence is the highest overall AK prevalence in people aged 50 years or older when compared to previous European population-based studies and comparable or less to studies from the United States of America (USA) and Australia.[7,9]

Table 4. Multivariate multinomial logistic regression: risk factors associated with actinic keratoses among 2061 participants of the Rotterdam Study

Characteristics	1 - 3 AKs adjusted odds ratio (95% CI)	4 - 9 AKs adjusted odds ratio (95% CI)	≥ 10 AKs adjusted odds ratio (95% CI)	P – value[4] (based on ordinal logistic regression)
Sex				
Women	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Men	**2.2 (1.6 -2.9)**	**2.5 (1.5 - 3.9)**	**3.2 (1.8 - 5.6)**	p < 0.001
Age at clinical examination				
< 70	1.0 (ref)	1.0 (ref)	1.0 (ref)	
70 - 79.99	**1.6 (1.2 - 2.1)**	**2.0 (1.4 - 3.0)**	**3.7 (2.3 - 6.0)**	p < 0.001
≥ 80	**1.7 (1.1 - 2.7)**	**2.7 (1.5 - 5.0)**	**6.5 (3.4 - 12.4)**	p < 0.001
Pigmentation status (based on eye, hair and skin color)				
Dark	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Medium	**1.7 (1.1 - 2.8)**	1.5 (0.8 - 3.0)	1.3 (0.6 - 2.7)	p = 0.05
Light	**2.3 (1.3 - 3.8)**	1.9 (0.9 - 4.1)	**2.5 (1.1 - 5.7)**	p < 0.001
Glogau				
1 and 2	1.0 (ref)	1.0 (ref)	1.0 (ref)	
3	**3.7 (1.9 - 7.0)**	**4.1 (1.4 - 11.7)**	**8.0 (1.9 - 34.8)**	p < 0.001
4	**5.5 (2.6 - 11.5)**	**4.9 (1.5 - 16.2)**	**6.0 (1.2 - 29.4)**	p < 0.001
Naevi				
< 25	1.0 (ref)	1.0 (ref)	1.0 (ref)	
25 – 50	**1.4 (1.0 - 1.9)**	1.3 (0.8 - 2.0)	1.0 (0.6 - 1.8)	p = 0.15
50 or more	1.3 (0.7 - 2.2)	1.6 (0.8 - 3.4)	1.3 (0.5 - 3.2)	p = 0.29
Baldness[1]				
No / almost no baldness	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Mild baldness	0.8 (0.6 - 1.1)	1.1 (0.7 - 1.8)	1.2 (0.7 - 2.0)	p = 0.79
Severe baldness	**1.2 (0.8 - 1.8)**	**4.1 (2.5 - 6.8)**	**6.3 (3.6 - 11.0)**	p < 0.001
Tendency to develop sunburn				
Low	1.0 (ref)	1.0 (ref)	1.0 (ref)	
High	**1.4 (1.0 - 1.8)**	**2.0 (1.3 - 2.9)**	**3.3 (2.2 - 5.0)**	p < 0.001
Data missing	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Outdoor work history ≥ 25 years				
No	0.9 (0.5 - 1.7)	1.6 (0.7 - 3.5)	0.6 (0.3 - 1.5)	p = 0.60
Yes	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Data missing	0.8 (0.5 - 1.2)	**0.3 (0.1 - 0.7)**	0.7 (0.4 - 1.3)	p = 0.01
History of living in sunny country of > 1 year				
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Yes	1.3 (0.9 - 1.7)	**1.9 (1.3 - 2.0)**	**2.5 (1.5 - 4.1)**	p < 0.001
Data missing	1.2 (0.9 - 1.6)	1.2 (0.8 - 2.0)	**2.0 (1.2 - 3.4)**	p = 0.02
Sun protective behavior[2]				
Never / almost never				
Often / not always	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Always	**0.7 (0.5 - 0.9)**	1.3 (0.8 - 2.0)	0.9 (0.6 - 1.4)	p = 0.4
Data missing	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Smoking history				
Never	1.1 (0.8 - 1.4)	1,1 (0.7 - 1.8)	0.9 (0.5 - 1.4)	p = 0.84
Ever	0.8 (0.5 - 1.1)	1.0 (0.6 - 1.7)	0.9 (0.5 - 1.6)	p = 0.27

[1] Based on the Norwood – Hamilton scale for men and Luwdig scale for women

[2] Wearing sunglasses and/or a rimmed hat in the sunshine

[3] Low (primary education and primary education with a higher not completed education), medium (lower-level secondary education, lower-level vocational education intermediate-level vocational education), and high (general secondary education, higher-level vocational education and university)
[4] P-value based on multivariate ordinal logistic regression
Abbreviations: AK, actinic keratoses; FBSE, full body skin examination; ref, reference group

Table 5. Risk factors associated with extensive actinic damage (≥ 10 actinic keratoses) among 2061 participants of the Rotterdam Study

Characteristics	0 - 9 AK n =1898	≥ 10 AK n = 163	≥ 10 AK crude odds ratio (95% CI)	≥ 10 AK adjusted odds ratio (95% CI)
Sex				
Women	1093 (42.4)	41 (25.2)	1.0 (ref)	1.0 (ref)
Men	805 (42.4)	122 (74.8)	**4.0 (2.8 – 5.8)**	**2.3 (1.4 - 4.0)**
Age at clinical examination				
< 70	844 (44.5)	30 (18.4)	1.0 (ref)	1.0 (ref)
70 - 79.99	849 (44.7)	98 (60.1)	**3.2 (2.1 – 4.9)**	**2.9 (1.8 - 4.6)**
≥ 80	205 (10.8)	35 (21.5)	**4.8 (2.9 – 8.0)**	**4.7 (2.5 - 8.7)**
Pigmentation status (based on eye, hair and skin color)				
Dark	202 (10.6)	10 (6.1)	1.0 (ref)	1.0 (ref)
Medium	1201 (63.3)	93 (57.1)	1.6 (0.8 – 3.1)	1.0 (0.5 - 2.2)
Light	332 (17.5)	53 (32.5)	**3.2 (1.6 – 6.5)**	1.8 (0.8 - 4.1)
Data missing	163 (8.6)	7 (4.3)		
Glogau				
1 and 2	178 (9.4)	2 (1.2)	1.0 (ref)	1.0 (ref)
3	1539 (81.1)	145 (89.0)	**8.4 (2.1 - 34.1)**	**5.4 (1.3 - 22.9)**
4	181 (9.5)	16 (9.8)	**7.9 (1.8 - 34.7)**	3.4 (0.7 - 16.4)
Naevi				
< 25	1438 (75.8)	131 (80.4)	1.0 (ref)	1.0 (ref)
25 - 50	361 (19.0)	24 (14.7)	0.7 (0.5 – 1.1)	1.1 (0.5 - 2.5)
> 50	99 (5.2)	8 (4.9)	0.9 (0.4 – 1.9)	0.9 (0.5 - 1.5)
Baldness[1]				
No / almost no baldness	1303 (68.7)	83 (50.9)	1.0 (ref)	1.0 (ref)
Mild baldness	361 (19.0)	28 (17.2)	**1.9 (1.2 – 3.1)**	**1.2 (0.7 - 2.1)**
Severe baldness	234 (12.3)	52 (31.9)	**8.9 (6.1 - 12.9)**	**4.5 (2.6 - 7.5)**
Tendency to develop sunburn				
Low	1256 (66.2)	74 (45.4)	1.0 (ref)	1.0 (ref)
High	523 (27.6)	84 (51.5)	**2.7 (2.0 – 3.8)**	**2.7 (1.8 - 4.0)**
Data missing	119 (6.3)	5 (3.1)		
Outdoor work history ≥ 25 years				
No	292 (15.4)	11 (6.7)	1.0 (ref)	1.0 (ref)
Yes	140 (7.4)	42 (25.8)	0.5 (0.3 – 1.1)	0.6 (0.3 - 1.3)
Data missing	1466 (77.2)	110 (67.5)		
History of living in sunny country of > 1 year				
No	1594 (84.0)	136 (83.4)	1.0 (ref)	1.0 (ref)
Yes	191 (10.1)	22 (13.5)	1.4 (0.8 – 2.2)	0.9 (0.5 - 1.6)
Data missing	113 (6.0)	5 (3.1)		
Sun protective behavior[2]				
Never / almost never	638 (33.6)	34 (20.9)	1.0 (ref)	1.0 (ref)

Often / not always	569 (30.0)	71 (43.6)	**2.3 (1.5 – 3.6)**	**2.1 (1.3 - 3.3)**
Always	578 (30.5)	53 (32.5)	**1.7 (1.1 – 2.7)**	**1.9 (1.1 - 3.1)**
Data missing	113 (6.0)	5 (3.1)		
Smoking history				
Never	624 (32.9)	39 (23.9)	1.0 (ref)	1.0 (ref)
Ever	1257 (66.2)	124 (76.1)	**1.6 (1.1 – 2.3)**	0.9 (0.6 - 1.4)
Data missing	17 (0.9)	0 (0.0)		
Education level[3]				
Low	402 (21.2)	30 (18.4)	1.0 (ref)	1.0 (ref)
Medium	1128 (59.4)	87 (53.4)	0.9 (0.6 – 1.4)	0.9 (0.5 - 1.7)
High	402 (21.2)	42 (25.8)	1.2 (0.7 – 2.0)	1.8 (0.4 - 8.5)
Data missing	24 (1.3)	4 (2.5)		

[1] Based on the Norwood – Hamilton scale for men and Luwdig scale for women

[2] Wearing sunglasses and/or a rimmed hat in the sunshine

[3] Low (primary education and primary education with a higher not completed education), medium (lower-level secondary education, lower-level vocational education intermediate-level vocational education), and high (general secondary education, higher-level vocational education and university)

Abbreviations: AK, actinic keratoses; FBSE, full body skin examination

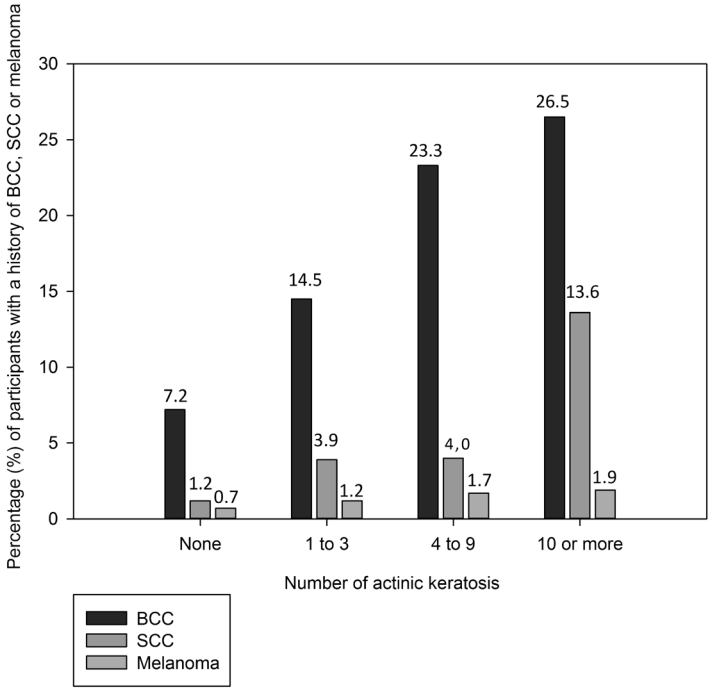


Figure 3. Percentage of participants with and without actinic keratoses who have a history of squamous cell carcinoma (SCC), basal cell carcinoma (BCC) or melanoma

Abbreviations: AK, actinic keratoses; BCC, basal cell carcinoma; SCC, squamous cell carcinoma

In Europe, the South Wales Skin Cancer Study observed an AK prevalence of 23% (95% CI 19.5 – 26.5), unadjusted for age and sex, among 1,034 persons aged 60 years or more. The lower prevalence may be explained by the fact that skin examinations were limited to the head and neck, lower arms (until shoulders), lower legs and feet and performed by research registrars in dermatology. Recently, in the PRAKTIS study a representative sample of 12,483 people of the Italian population aged > 45 years were selected by a stratified random sampling design in which 1.4% was affected by AK.[7] Again, skin examinations were performed by 'interviewers' and limited to the face and upper extremities.[7] In addition, the distribution of phenotypic characteristics of the Dutch (i.e. light skin, hair and eyes) increase the risk for AK development when compared to the the distribution in the Italian population with slightly darker skin, hair and eyes. German studies using claims data estimated an AK prevalences ranging from 2 to 31%, but these data were not population-based and included dermatology patients[25-26], patients without history of skin cancer who were invited to undergo skin examination when visiting their practice-based physician[16] or healthy workers who could undergo a voluntary FBSE at their work.[27] Between 1971-1975, a population-based study across the USA[8], in which 101 dermatologists performed FBSE in more than 8,000 white participants aged between 25 and 74 years, observed a crude AK prevalence of around 17%.[8] More recently, the crude prevalence for AK in the USA was estimated to be 45% in men aged 65 years or older and 35% in women.[28] Two Australian studies from the eighties who screened 2,095 and 1,040 people randomly selected from sample state electoral roll demonstrated that 40-60% of the participants had at least one AK.[6,10]

Risk factors and implications

Multiple risk factors were found to be associated with AK development confirming findings of previous studies assessing AK and SCC risk factors.[29-30] In men, baldness was found to be the strongest risk factor for presence of AK and severe actinic skin damage, probably because it continuously exposes the scalp in a horizontal plane to UV radiation resulting in high cumulative UV doses. In clinical practice, these patients with large cutaneous fields affected by AKs on the scalp are numerous and difficult to manage.

Patients possessing risk factors associated with extensive actinic damage such as severe baldness may require directed public health campaigns, a case-finding approach (i.e., inspection of the bald scalp during physician visits) including providing more information on sun protection and behavior.

In the past decade, pharmaceutical companies have focused on AK treatments resulting in new treatments other than cryotherapy, namely fluorouracil, imiquimod, photodynamic therapy and most recently Ingenol mebutate gel.[31-32] Recently, topical tretinoin failed to act as a chemopreventive agent for AK development [33], whereas sunscreen use is effective in both AK and SCC prevention.[34-35]

Although it remains controversial whether or not to actively treat AKs (as not all will progress to SCC), people with multiple lesions (in this study defined as ≥10) are most likely to benefit from treatment and require a closer follow-up over time to prevent or detect the early development of SCC. Even this conservative approach is a health care challenge because it involves 5% of the Dutch 50-plus citizens (approximately 300,000 people) and this proportion is likely to increase over time. This is confirmed by a quick review of the claims data demonstrating that dermatologist reported twice as many AK related visits and treatment between 2007 and 2011 (from 42,115 to 76,395) emphasizing the strain cutaneous (pre-) malignancies put on the health care system.[36]

Strengths and limitations

The fact that FBSE were performed by a few trained physicians in more than 2,000 participants from a population-based study makes the Dutch point prevalence highly accurate. In general, AK have a typical presentation and are therefore clinically diagnosed by dermatologists and general practitioners. However AK can resemble keratinocyte carcinoma (including BCC and SCC), possibly leading to misclassification and an under or overestimation of AK in this study.[5] Nevertheless, this possible non – differential misclassification is considered small as trained physicians performed FBSE and previous studies observed a positive predictive value for AK diagnosis ranging from 74 to 94%.[37-38] In this study, AK prevalence was determined cross-sectionally and it was unknown whether participants were previously treated for AK which also could have resulted in an underestimation of the Dutch AK prevalence. Unfortunately, the design of the study does not allow a longitudinal follow up of individual AK to study its natural course. The individual number of AK lesions within a participant was not counted; instead AK presence was divided into three categories (i.e., 1 to 3, 4 to 9, ≥ 10). Although categorical data is less precise than continuous, previous studies showed that the inter-observer variation between dermatologists was large when counting the individual number of AK lesions within a participant and using categorised data greatly reduced this variation.[15] The population of the Rotterdam Study is 45 years and older and almost exclusive Caucasian possibly limiting the generalizibility of the findings. However, none of the participants aged below 55 years (n = 50) had AK and AKs are rare in people with darker skin suggesting that the extent of this limitation is rather small. At time of FBSE, only feet and areas covered by underwear were not examined because of practical and psychological reasons. It is unlikely that this restriction resulted in an underestimation of the AK prevalence because these areas are not chronically UV exposed.

CONCLUSIONS

More than a quarter of people are affected by AK and 8% by 10 or more lesions emphasizing that cutaneous (pre)malignancies are an enormous burden for health care providers.

Preventive measures including promoting sun protective behavior, and raising awareness on cutaneous keratinocyte carcinoma and persistent AKs, should focus in particular on elderly, bald men and those with photodamaged facial skin to reduce the number of SCC.

ACKNOWLEDGEMENTS

The authors thank the participants of the Rotterdam Study for their participation and the research physicians and assistants for the data collection. We would like to thank Loes Hollestein for the statistical assistance and Robert Stern for critically reviewing the manuscript.

REFERENCES

1. LeBoit PE, Burg G, Weedon D, Sarasin A. Actinic keratoses. World Health Organization Classification of Tumors: Pathology and Genetics of Skin Tumors 2006:30-3.
2. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988;1:795-7.
3. Callen JP, Bickers DR, Moy RL. Actinic keratoses. J Am Acad Dermatol 1997;36:650-3.
4. Quaedvlieg PJ, Tirsi E, Thissen MR, Krekels GA. Actinic keratosis: how to differentiate the good from the bad ones? Eur J Dermatol 2006;16:335-9.
5. Criscione VD, Weinstock MA, Naylor MF, et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 2009;115:2523-30.
6. Green A, Beardmore G, Hart V, Leslie D, Marks R, Staines D. Skin cancer in a Queensland population. J Am Acad Dermatol 1988;19:1045-52.
7. Naldi L, Chatenoud L, Piccitto R, et al. Prevalence of actinic keratoses and associated factors in a representative sample of the Italian adult population: Results from the Prevalence of Actinic Keratoses Italian Study, 2003-2004. Arch Dermatol 2006;142:722-6.
8. He W, Zhu F, Ma X, et al. Actinic skin damage and mortality--the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. PLoS One 2011;6:e19907.
9. Harvey I, Frankel S, Marks R, Shalom D, Nolan-Farrell M. Non-melanoma skin cancer and solar keratoses II analytical results of the South Wales Skin Cancer Study. Br J Cancer 1996;74:1308-12.
10. Marks R, Foley P, Goodman G, Hage BH, Selwood TS. Spontaneous remission of solar keratoses: the case for conservative management. Br J Dermatol 1986;115:649-55.
11. Harvey I, Frankel S, Marks R, Shalom D, Nolan-Farrell M. Non-melanoma skin cancer and solar keratoses. I. Methods and descriptive results of the South Wales Skin Cancer Study. Br J Cancer 1996;74:1302-7.
12. Holterhues C, Vries E, Louwman MW, Koljenovic S, Nijsten T. Incidence and trends of cutaneous malignancies in The Netherlands, 1989-2005. J Invest Dermatol 2010;130:1807-12.
13. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in The Netherlands: Increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer 2012;48:2046-53.
14. Hofman A, van Duijn CM, Franco OH, et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 2011;26:657-86.
15. Weinstock MA, Bingham SF, Cole GW, et al. Reliability of counting actinic keratoses before and after brief consensus discussion: the VA topical tretinoin chemoprevention (VATTC) trial. Arch Dermatol 2001;137:1055-8.
16. Glogau RG. Aesthetic and anatomic analysis of the aging skin. Semin Cutan Med Surg 1996;15:134-8.
17. Norwood OT. Male pattern baldness: classification and incidence. South Med J 1975;68:1359-65.
18. Taylor R, Matassa J, Leavy JE, Fritschi L. Validity of self reported male balding patterns in epidemiological studies. BMC Public Health 2004;4:60.
19. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. Br J Dermatol 1977;97:247-54.
20. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29:19-24.

21. Flohil SC, Koljenovic S, de Haas ER, Overbeek LI, de Vries E, Nijsten T. Cumulative risks and rates of subsequent basal cell carcinomas in The Netherlands. Br J Dermatol 2011;165:874-81.
22. Wisgerhof HC, Edelbroek JR, de Fijter JW, et al. Subsequent squamous- and basal-cell carcinomas in kidney-transplant recipients after the first skin cancer: cumulative incidence and risk factors. Transplantation 2010;89:1231-8.
23. Wei-Passanese EX, Han J, Lin W, Li T, Laden F, Qureshi AA. Geographical variation in residence and risk of multiple nonmelanoma skin cancers in US women and men. Photochem Photobiol 2012;88:483-9.
24. Qureshi AA, Wei-Passanese EX, Li T, Han J. Host risk factors for the development of multiple non-melanoma skin cancers. J Eur Acad Dermatol Venereol. 2012 doi: 10.1111/j.1468-3083.2012.04483.x. [Epub ahead of print]
25. Guther S, Ramrath K, Dyall-Smith D, Landthaler M, Stolz W. Development of a targeted risk-group model for skin cancer screening based on more than 100 000 total skin examinations. J Eur Acad Dermatol Venereol 2012;26:86-94.
26. Breitbart EW, Waldmann A, Nolte S, et al. Systematic skin cancer screening in Northern Germany. J Am Acad Dermatol 2012;66:201-11.
27. Augustin M, Herberger K, Hintzen S, Heigel H, Franzke N, Schafer I. Prevalence of skin lesions and need for treatment in a cohort of 90 880 workers. Br J Dermatol 2011;165:865-73.
28. Almeida MQ, Stratakis CA. Carney complex and other conditions associated with micronodular adrenal hyperplasias. Best Pract Res Clin Endocrinol Metab 2010;24:907-14.
29. Marks R, Rennie G, Selwood T. The relationship of basal cell carcinomas and squamous cell carcinomas to solar keratoses. Arch Dermatol 1988;124:1039-42.
30. Green A, Battistutta D. Incidence and determinants of skin cancer in a high-risk Australian population. Int J Cancer 1990;46:356-61.
31. Flohil SC, Proby CM, Forrest AD, et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. Br J Dermatol 2012;167:22-9.
32. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med 2012;366:1010-9.
33. Weinstock MA, Bingham SF, Digiovanna JJ, et al. Tretinoin and the prevention of keratinocyte carcinoma (Basal and squamous cell carcinoma of the skin): a veterans affairs randomized chemoprevention trial. J Invest Dermatol 2012;132:1583-90.
34. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 1993;329:1147-51.
35. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet 1999;354:723-9.
36. Nan H, Qureshi AA, Prescott J, De Vivo I, Han J. Genetic variants in telomere-maintaining genes and skin cancer risk. Hum Genet 2011;129:247-53.
37. Venna SS, Lee D, Stadecker MJ, Rogers GS. Clinical recognition of actinic keratoses in a high-risk population: how good are we? Arch Dermatol 2005;141:507-9.
38. Ponsford MW, Goodman G, Marks R. The prevalence and accuracy of diagnosis of non-melanotic skin cancer in Victoria. Australas J Dermatol 1983;24:79-82.

Appendix Table 1. Univariate multinomial logistic regression: risk factors associated with actinic keratoses among 2061 participants of the Rotterdam Study

Characteristics	1 - 3 AKs crude odds ratio (95% CI)	4 - 9 AKs crude odds ratio (95% CI)	≥ 10 AKs crude odds ratio (95% CI)
Sex			
Women	1.0 (ref)	1.0 (ref)	1.0 (ref)
Men	**1.7 (1.3 - 2.1)**	**3.5 (2.5 - 4.9)**	**5.1 (3.5 - 7.4)**
Age at clinical examination			
< 70	1.0 (ref)	1.0 (ref)	1.0 (ref)
70 - 79.99	**1.7 (1.3 - 2.1)**	**2.4 (1.6 - 3.4)**	**3.9 (2.6 - 6.0)**
≥ 80	**2.0 (1.4 - 2.9)**	**3.1 (1.9 - 5.2)**	**6.3 (3.7 - 10.7)**
Pigmentation status (based on eye, hair and skin color)			
Dark	1.0 (ref)	1.0 (ref)	1.0 (ref)
Medium	**2.1 (1.4 - 3.3)**	**2.0 (1.1 - 3.6)**	**1.9 (1.0 - 3.7)**
Light	**2.9 (1.8 - 4.7)**	**2.7 (1.3 - 5.2)**	**4.3 (2.1 - 8.8)**
Glogau			
1 and 2	1.0 (ref)	1.0 (ref)	1.0 (ref)
3	**3.2 (1.9 - 5.4)**	**4.7 (1.9 - 11.6)**	**11.0 (2.7 - 45.0)**
4	**4.9 (2.7 - 8.9)**	**5.3 (1.9 - 14.7)**	**11.8 (2.7 - 52.3)**
Naevi			
< 25	1.0 (ref)	1.0 (ref)	1.0 (ref)
25 - 50	1.2 (0.9 - 1.5)	1.1 (0.8 - 1.7)	0.8 (0.5 - 1.2)
50 or more	0.9 (0.5 - 1.5)	1.4 (0.7 - 2.6)	0.9 (0.4 - 1.9)
Baldness[1]			
No / almost no baldness	1.0 (ref)	1.0 (ref)	1.0 (ref)
Mild baldness	1.2 (0.9 - 1.6)	**1.8 (1.2 - 2.8)**	**2.1 (1.3 - 3.4)**
Severe baldness	**1.8 (1.3 - 2.6)**	**7.6 (5.2 - 11.1)**	**13.9 (9.3 - 20.7)**
Tendency to develop sunburn			
Low	1.0 (ref)	1.0 (ref)	1.0 (ref)
High	**1.2 (1.0 - 1.6)**	**1.6 (1.1 - 2.2)**	**3.0 (2.1 - 4.2)**
Outdoor work history ≥ 25 years			
No	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.9 (0.5 - 1.5)	1.4 (0.7 - 2.9)	0.5 (0.3 - 1.1)
History of living in sunny country of > 1 year			
No	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.7 (0.5 - 1.1)	**0.4 (0.2 - 0.8)**	1.2 (0.7 - 1.9)
Sun protective behavior[2]			
Never / almost never	1.0 (ref)	1.0 (ref)	1.0 (ref)
Often / not always	**1.3 (1.0 - 1.7)**	**1.9 (1.3 - 2.9)**	**2.6 (1.7 - 4.1)**
Always	1.1 (0.9 - 1.5)	1.1 (0.7 - 1.7)	**1.8 (1.1 - 2.8)**
Smoking history			
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever	0.9 (0.7 - 1.1)	**2.0 (1.4 - 3.0)**	**1.6 (1.1 - 2.4)**
Education level[3]			
Low	1.0 (ref)	1.0 (ref)	1.0 (ref)
Medium	1.1 (0.8 - 1.5)	1.1 (0.7 - 1.6)	0.9 (0.6 - 1.4)
High	0.8 (0.6 - 1.2)	1.0 (0.6 - 1.7)	1.2 (0.7 - 1.9)

[1] Based on the Norwood – Hamilton scale for men and Luwdig scale for women

[2] Wearing sunglasses and/or a rimmed hat in the sunshine

[3] Low (primary education and primary education with a higher not completed education), medium (lower-level secondary education, lower-level vocational education intermediate-level vocational education), and high (general secondary education, higher-level vocational education and university)
Abbreviations: AK, actinic keratoses; FBSE, full body skin examination; Ref, reference group

CHAPTER 10

General discussion and interpretation of the results

General discussion and interpretation of the results

The studies presented in this thesis provide insight into the occurrence of basal cell carcinoma (BCC) in The Netherlands. Knowledge on the occurrence of BCC is warranted as the burden of BCC increases with population ageing. In this chapter, I will first provide a short summary of the results related to the research questions posed in the introduction of this thesis. Then, the limitations of the studies will be presented and finally, I will discuss possible implications and recommendations for future perspectives.

What are the incidence, prevalence and (future) trends of primary basal cell carcinoma in The Netherlands?

Incidence rates of BCC (age-standardised to the European Standard Population, ESR) are increasing in The Netherlands. This is based on data on first, histologically confirmed primary BCC per patient from Eindhoven Cancer Registry (ECR).[1] Between 1973 and 2009, BCC rates quadrupled from 40 to 165 per 100 000 person-years for men and quintupled from 34 to 157 for women. Until 2002, these rates annually increased with 2 to 4%, but then the rate of increase doubled to 6 to 8% per year in both men and women. Future predictions up to 2020 showed a continuous rise in rates for all age-categories, indicating no signs of plateauing or decreasing incidence. The overall 19-years prevalence of BCC (between 1990 and 2008) was 1.4%, but was three folds higher in the oldest age-category (65 years or more). Finally, the lifetime risk of developing a BCC in The Netherlands in 2009 was estimated 1 in 5 for men and 1 in 6 for women.

What are the cumulative risks and rates of developing a subsequent basal cell carcinoma?

First, this question was answered with data from PALGA, the nationwide network and registry of histo- and cytopathology in The Netherlands.[2] Then, these observations were put in a broader perspective when compared to other studies in a systematic review and meta-analysis. Data from PALGA showed that the 5-year cumulative risk of developing a subsequent histologically confirmed BCC was almost 30%. Incidence rates for a subsequent BCC were especially high in the first 6 months after first BCC diagnosis (25 318 per 100 000 person-years), but with increasing time since first BCC diagnosis these rates decreased rapidly, to 6 953 per 100 000 person-years after 5 years of follow-up. Based on these data, follow-up visits for (early) detection of subsequent BCC(s) were recommended. Early BCC detection may reduce patient morbidity by preventing growth in vital structures and mutilating local tissue destruction. When the tumor is relatively small, more (less invasive) treatment options (e.g. nonsurgical therapies such as photodynamic therapy and 5-fluorouracil cream) are available, often resulting in a better aesthetic outcome. When surgical excision is the treatment of choice, less cosmetic disfigurement is induced and less time for reconstruction is needed when excising a smaller compared with a larger tumor, and concurrently, costs will be reduced.

The 5-year cumulative risk of developing multiple BCCs (27.7%; based on PALGA) was in accordance with the estimated pooled proportion (29.2%) based on the 19 studies included in the meta-analysis described in this thesis. After stratifying by continent in the meta-analysis, the effect size of the estimated pooled proportion for BCC after BCC was as expected the highest in Australia (57.9%), followed by North America (32.5%; primarily including studies from the United States of America) and Europe with 27.3%.

How often are clinically suspected basal cell carcinomas diagnosed without histological confirmation?

Although I attempted to get a grip on the frequency of clinically diagnosed BCCs without histological confirmation, it remains difficult to draw any firm conclusions based on my study, as the results are not easy to generalize to the whole of The Netherlands. To answer this research question two population-based databases were linked, ECR (cancer registry) and PALGA (pathology), to identify patients of four dermatology departments in the southeast Netherlands who had their first, histologically confirmed BCC in 2004. Their patient records were reviewed for subsequent BCCs without histological confirmation. During a mean follow-up period of 6 years, approximately 7% of the subsequent BCCs in patients with a prior histologically confirmed BCC were clinically diagnosed without histological confirmation.
This Dutch study was compared to studies from other European regions such as Malta, Finland and Scotland. The frequencies of diagnosing a clinically suspected BCC without histological confirmation differed widely between the four regions ranging from 0.7 to 24.1%. This is probably to a large extent explained by the methodological differences between the studies (e.g. study design and size), but also in part by the different reimbursement criteria used in the European regions.

What are the risk factors associated with the development of single or multiple basal cell carcinoma(s)?

This and the following research question are answered with data from the Rotterdam Study, which is a large population-based cohort study (including three sub-cohorts) among inhabitants of 45 years and older living in the Ommoord district in Rotterdam, The Netherlands.[3] Currently, 14 926 inhabitants participate within this unique Dutch study.
A linkage was made between the first two followed cohorts of the Rotterdam Study and PALGA, surrounding hospitals and general practices. Participants with a history of BCC before study entry were excluded. Of the eligible 10,820 cohort members included in our study, 524 (4.8%) had a BCC of whom 361 had one and 163 patients had multiple BCCs (31.1%). Multivariate analyses showed that age (between 65 and 75 years at study entry versus < 65 years), red hair and medium educational level were significant risk factors for a *first* BCC, whereas people who developed a first BCC after 65 years of age were significantly less likely to develop *multiple* histologically confirmed BCCs. Red hair was also a risk factor for multiple

BCC development together with medium and high educational level and a first BCC located on the upper extremities. In conclusion, of the people with prior BCC, those who are relatively young at diagnosis of a first lesion, those who have red hair and higher socioeconomic status, and/or those who had a lesion on their upper extremities may require a more stringent follow-up regimen than other patients with BCC.

What is the prevalence of and what are risk factors for actinic keratosis in The Netherlands?

Full body skin examinations among 2061 unselected Rotterdam Study participants were performed to get a more accurate insight in AK prevalence among the Dutch population. It unraveled that almost 37.5% (95% CI 35.4 - 39.6) of the participants had at least one and 8% had ten or more AKs. Extrapolated to the whole Dutch population aged 50 years or older, this would translate into an AK prevalence of 23.5% (95% CI 21.7 – 25.3%); 28.8% (25.9–31.7%) for men and 19.0% (16.7–21.2%) for women. This suggests that approximately 1.4 of the 16 million Dutch citizens are currently affected with AK. This prevalence is the highest overall AK prevalence in people aged 50 years or older when compared to previous European population-based studies and comparable or less to studies from the United States of America (USA) and Australia.[4-7] Preventative measures should especially focus on elderly, bald males, those with light pigmentation status or with photo-damaged facial skin, and persons who have a high tendency to develop a sunburn, as these were significantly associated with increased likelihood of AK development in the multivariate analyses.

Increase in BCC rates

From 1973 until 2002, there was a steady annual increase in BCC rates over time.
Public awareness may have contributed to this, but the main causes of the increase are probably ageing and lifestyle changes such as altered patterns of UV-exposure, including more outdoor leisure activities and sports, travelling and the expanding use of sun beds. In the second half of the twentieth century, a reduction in the number of working hours was established by the society together with a guaranteed number of holidays.[8] In the following years air travel became less expensive and more accessible to the general Dutch population which encouraged people to travel to sunny destinations.[9]
Although rates continue to increase in elderly, BCCs are now more commonly diagnosed in younger persons, probably in part attributed to UV-exposure patterns including sun bed use.[10] Sunbed use has increased dramatically and evidence for a dose-response relationship between its use and the risk of BCC has been established.[10-11] In The Netherlands, the popularity of sunbed use started around 1975, but regulatory changes have only been introduced recently.
In 2002, the speed of increase accelerated not only for BCC rates in The Netherlands but also for SCC rates, although not in trends of melanoma incidence.[12] Besides a genuine increase in BCC rates, the most probable explanation for this relatively steep acceleration in the first

primary BCC incidence rate and number of cases is changes in medical practice, i.e. increased (early) detection and more KC being diagnosed histologically. The increase may be driven by changing skin surveillance by patients and physicians as skin cancer awareness increased and more full body skin examinations are performed. The fact that the most marked increase in incidence is on the trunk is also consistent with increased surveillance.[13] Further, it is possible that improved processes within the registry have resulted in a greater proportion of lesions being captured, but this seems an unlikely explanation for the size of the increase observed. Also, the most common used treatment modality for BCC by dermatologists has changed over time. In the 1980's radiotherapy was often used in the treatment of BCC, while in the 1990's cryotherapy became more popular. Nowadays, surgical excision is most often used instead of radiotherapy, cryotherapy, curettage, electro-dissection or a wait-and-see policy in elderly with multiple co-morbidities.[14] This may have resulted in more histologically confirmed BCCs. Also, Mohs micrographic surgery (MMS) is becoming more common in the treatment of BCC. However, according to the Dutch guideline of BCC, MMS is only advised for primary BCCs with unfavourable prognostic factors, such as aggressive subtype and/or H-zone location, and for recurrent BCCs located in the face. Currently, in The Netherlands the total number of BCCs per year is estimated to be around 40,000. Rough calculations estimate that around 3,000 of these BCC are being treated with MMS and this number is likely to increase in the future. MMS is only performed in a limited number of Dutch dermatology centers and therefore not all BCCs, even those fulfilling the indication criteria for this procedure as stated in the guideline, are treated with this technique. In the coming years, we will probably witness a rise in the number of Dutch centers offering MMS, not only due to the increase in BCC incidence, but also because the benefits of this technique will be acknowledged and MMS will be considered a part of good medical care. However, the Dutch Society of Dermatology and Venereology should keep the indication criteria for MMS within boundaries in order to avoid United States practices where approximately 25% the BCCs are treated with this expensive technique.

Although the rise in melanoma incidence can partly be explained by over diagnosis through improvement of histological diagnostic criteria, this is probably not the case for BCC because the criteria remained stable over time.[15] Another possibility is the change in the distribution of phenotypic characteristics of the population, particularly given the expansion of the ECR registry area, but evidence suggests that this is unlikely since the proportion of people with dark skin has increased, suggesting an inverse effect on BCC incidence.

Limitations of the studies within this thesis

The studies presented in chapters 2 and 3 are based on population-based data of ECR. ECR represents the population living in the southeast Netherlands, therefore, to estimate patient-based data of BCC occurrence in The Netherlands these data had to be extrapolated. Off course, BCC incidence rates may differ across the country due to demographic variability such as socio-economic status, work-related UV-exposure and ethnicity. However, this bias is

assumed to be very small as nationwide melanoma incidence rates only differed slightly from the rates observed in the ECR region.[16] In addition, there is a delay of up to 3 years between BCC recording by registry clerks of ECR and publishing incidence numbers. Considering the rising trends in BCC incidence rates, the incidence rates in 2012 are most likely higher than the most recently reported incidence rates of 2009 (chapter 3).

Both ECR and PALGA only contain data on histologically confirmed BCCs and also within the Rotterdam Study only histologically confirmed BCCs were included. Therefore, the true incidence and risk of subsequent BCCs may have been underestimated in studies using these databases as some patients may have been diagnosed and/or treated on clinical diagnosis alone. However, establishment of the diagnosis with certainty is only on the basis of histological confirmation. Therefore, BCC data from cancer registries or pathology databases are reliably as they limit the risk on false-negative and false-positive BCC diagnoses of clinically suspected BCC lesions without histological confirmation. In addition, a study from the United States observed that the positive predictive value of the clinical diagnosis of BCC is only 80% and that is when the dermatologist is reasonable confident about the diagnosis.[17] This is in line with a French medical cost analysis study which found that a clinically suspicious BCC case was only histologically confirmed in 85% of the cases.[18] Strengths of the included studies using ECR and PALGA as a data source are its population-based design instead of specialized hospital-based data, the latter often represent a selected population inflating observed BCC incidence rates. With these population-based data it was possible to reliably estimate the BCC occurrence in The Netherlands, not only for the first but also for multiple BCCs per patient.

In addition, the population of the Rotterdam Study is aged 45 years and older (chapters 8 and 9) and almost exclusive Caucasian possibly limiting the generalizability of the results to only the elderly, white part of the Dutch population.[3] However, AK and BCC are considered skin diseases of the elderly and rarely develop in people with darker skin suggesting that the extent of this bias is limited. Although one of the strengths of the Rotterdam Study is its prospective population-based study design (i.e. unselected population) with long follow-up duration, AK prevalence was determined cross-sectionally and it was unknown whether participants were previously treated for AK which also could have resulted in an underestimation of the Dutch AK prevalence.

Implications and future perspectives

In 1991, Coebergh *et al.* already observed that incidence rates of BCC in The Netherlands were increasing, emphasizing the need for adequate intervention by health care providers to stop this growing group of patients.[1] Twenty years later, the data presented in this thesis observe that these rates are still increasing, and even show acceleration in the speed of increase since 2002 for both sexes. Although future predictions showed no signs of plateauing or decrease in these rates, earlier predictions made for 2005 were underestimated with 21% compared to the observed number of BCC cases for 2005. This suggests that the incidence rates increased

faster than was estimated based on data from 1989–2000. In addition, observed incidence rates of 2009 (chapter 3: based on data from 2000 - 2008) were already higher than those predicted for 2010 (chapter 2). Although this shows the limitations of prediction modelling, it also underlines that future perspectives on BCC numbers are even worse than assumed.
The group of patients with SCC and melanoma has also been increasing in The Netherlands. However, as BCC reflects more than 70% of all skin cancer cases, it represents the largest bulk of patients that currently strain dermatological care in terms of diagnosis, treatment and follow-up.[12, 19] Besides cutaneous malignancies, there are also a large number of people with cutaneous pre-malignancies such as AK. As it remains impossible for physicians to indicate which AK will become invasive, it is still controversial whether or not to actively treat AK and if follow-up of all AK patients is necessary. The current Dutch guideline recommends follow-up twice a year of patients with more than three AKs (and a history of KC and / or high risk sun behavior and / or immune-compromised patients) followed by annual follow-up visits for three years.[20] Based on our data, it is most likely that participants with ten or more lesions will certainly benefit from treatment and may require a closer follow-up over time to prevent or detect early SCC development. From a practical point of view, it seems also impossible for physicians to treat all 1.4 million Dutch inhabitants with AK (based on extrapolated data).

The rates and trends of BCC incidence observed in The Netherlands fit into a pattern observed in other parts of Europe.[21] Incidence of BCC is strongly dependant by geographic location. It is the highest in subtropical locations such as Australia and parts of North America, which are primarily inhabited by Caucasians with light pigmentation traits who in the far past migrated to these continents.[21-24]
In neighboring countries the number of people with BCC is also increasing; however there are often no cancer registry data available to really determine the incidence. As BCC related death is extremely rare, the necessity of BCC registration is not given high priority, despite the high workload and related costs.[21, 25-30] In The Netherlands we are fortunate to have ECR, which is located in the southeast Netherlands and part of the Dutch Comprehensive Cancer Centres.[1] It is the only population-based cancer registry in The Netherlands that routinely reports the first primary histologically confirmed BCC per patient. This patient-based BCC information is collected by ECR from early 1970's using PALGA as the main signalling source. Most cancer registries only register the first, histologically confirmed BCC per patient due to the large number of tumors involved, coding difficulties, associated time and costs. In absence of tumor-based rates, these patient-based rates underscore the importance of addressing the needs of this BCC population, but also provide insight into the frequency of BCC occurrence in The Netherlands and the heavy strain it puts on current health care. Also, the scientific skin cancer reports based on ECR data are considered to be among the most robust studies available. Since 1999, ECR collects information on more than one BCC per patient according to certain registration rules (see introduction); however these data are

not assumed completely reliable because of several methodological and practical issues.[31] It is the question whether this attempt of ECR to register tumor-based BCC data is necessary as data from the PALGA database gave clear insight in tumor-based BCC information and the number of people affected with multiple BCCs. In addition, PALGA provides information on BCC subtypes (and more detailed information on location) while this is not registered by ECR. However, as already mentioned above, limitations of cancer registry and pathology databases are exclusion of BCCs that are diagnosed without histological confirmation. However, this degree of underestimation is considered relatively small as observed in chapter 6. In the future, it may be interesting for cancer registries to include skin cancer treatments to monitor the effectiveness of newly introduced therapies of BCC, SCC and melanoma in daily practice.

Primary and secondary prevention

Prior primary prevention strategies seem to have failed and knowledge on risk factors for BCC development has not translated in significant behavioral changes. Although it is known that UV-exposure is a common risk factor for cutaneous malignancies, people enjoy being in the sun and a browned skin is still considered a sign of health and beauty. Also, prevention of skin cancer development by avoiding UV-damage is a long term benefit, whereas on short term sun avoidance has no clear benefits for the general population.

Even in Australia where there have been enormous efforts to change UV-related behavior as its incidence of cutaneous malignancies is higher than anywhere else in the world, evidence showed that young people have poor sun protective behavior.[32] However, data from Australian population surveys have also shown an increase in the use of sunscreen, together with more frequent use of protecting clothing during summer when outdoors. [33-35] Recent studies in Australia report trends of plateauing in keratinocyte carcinomas (KC, including BCC and SCC) and more recently in melanoma rates. This may provide some indirect evidence of the impact of long-running primary prevention campaigns such as *Slip! Slop! Slap!* (i.e. an internationally recognized sun protection campaign prominently introduced in Australia during the 1980's).[32,36]

In Europe, the most commonly used form of primary prevention is sunscreen use, however this probably not the best method of protection as it increases the time spent in the sun without getting a sunburn.[37] Besides topical sunscreen, many therapies such as tretinoin, retinaldehyde, anti-inflammatory drugs (i.e. NSAIDs), and statins have been tested as chemopreventive agents for KC. So far, only two agents, sunscreen and systemic retinoids, have shown to be effectively prevent SCC development but not BCC. [38-40]

In the past, the focus of most Dutch health care campaigns was on melanoma as it is one of the most deadly types of skin cancer and therefore best known among the general population. An unpublished survey on the internet (with easy access) showed that around 60% of the participants did not know what a BCC or SCC was, while this was only 19% for melanoma (personal communication drs. Kreukels). One of the successes of these campaigns is that

more melanomas are being diagnosed in an earlier stage and more people present themselves to their physicians with a suspicious mole.[41-42] Because of this, the mortality of melanoma is not increasing as steadily as the incidence.[43] Although these (melanoma) campaigns focused on the general population, special attention was being paid to parents with young children as prevention of sunburn on young age was a central theme. Although KC are not as lethal as melanoma, it is important to also focus on KC as they include the largest group of skin cancer patients, although increased melanoma awareness is also of importance. The amount of attention of current prevention programs (with main focus on melanoma) is in contrast with the incidence of these cancers in The Netherlands, as melanoma is the least (only 11% of the cases) and KC the most common skin cancer (more than 80% of the cases).[12] Besides continuing already existing campaigns (with focus on prevention of UV-damage on young age), more attention should be paid to the elderly to increase KC awareness and its associated risk factors.

In addition to primary prevention, secondary prevention is also important as almost one third of the BCC patients develops a subsequent BCC. Prevention is probably more effective when focused on a smaller group of patients that have the highest risk of developing multiple lesions. Patients at high risk of developing multiple BCCs should be identified to assist physicians in the adequate selection of individuals (from the large number of patients with BCC), who should be followed up more closely over time. Although this was investigated in chapter 8, the study design only allowed identification of phenotypic and behavioral risk factors, genetic information was not included. Recently, genome-wide association studies detected multiple polymorphisms associated with the development of a first BCC.[44-46] No genetic research investigated the association between these polymorphisms and multiple BCC development. Future research in this area could help building an adequate prediction model (including phenotypic, genetic and environmental information) to predict which patients are at high risk of developing multiple BCCs. Such a prediction model could consequently lead to more insight into BCC aetiology and open doors to new therapies.

Conclusion

The frequency of occurrence of BCC in The Netherlands is and remains a large burden for current health care and will only increase in the future. This thesis presents studies on different aspects and contributes to the current knowledge on the occurrence of BCC and AK in The Netherlands and its associated risk factors. More research is needed into aetiology, genetics, treatment, primary, secondary and tertiary prevention to manage BCC patients optimally. A more comprehensive management is needed to reduce the strain on current dermatological care in terms of diagnosis, treatment and follow-up.

REFERENCES

1. Coebergh JW, Neumann HA, Vrints LW, van der Heijden L, Meijer WJ, Verhagen-Teulings MT. Trends in the incidence of non-melanoma skin cancer in the SE Netherlands 1975-1988: a registry-based study. Br J Dermatol 1991;125:353-9.
2. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29:19-24.
3. Hofman A, van Duijn CM, Franco OH, et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 2011;26:657-86.
4. Harvey I, Frankel S, Marks R, Shalom D, Nolan-Farrell M. Non-melanoma skin cancer and solar keratoses II analytical results of the South Wales Skin Cancer Study. Br J Cancer 1996;74:1308-12.
5. Naldi L, Chatenoud L, Piccitto R, Colombo P, Placchesi EB, La Vecchia C. Prevalence of actinic keratoses and associated factors in a representative sample of the Italian adult population: Results from the Prevalence of Actinic Keratoses Italian Study, 2003-2004. Arch Dermatol 2006;142:722-6.
6. The Burden of Skin Diseases 2004 by the Lewin Group, inc http://www.sidnet.org/pdfs/burden%20of%20diseases%202004.pdf accessed at June 14th 2012.
7. Green A, Beardmore G, Hart V, Leslie D, Marks R, Staines D. Skin cancer in a Queensland population. J Am Acad Dermatol 1988;19:1045-52.
8. Randle HW. Suntanning: differences in perceptions throughout history. Mayo Clin Proc 1997;72:461-6.
9. Statistics Netherlands http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=03770&D1=2&D2=a&VW=T accessed at July 2nd 2012.
10. Zhang M, Qureshi AA, Geller AC, Frazier L, Hunter DJ, Han J. Use of tanning beds and incidence of skin cancer. J Clin Oncol 2012;30:1588-93.
11. Levine JA, Sorace M, Spencer J, Siegel DM. The indoor UV tanning industry: a review of skin cancer risk, health benefit claims, and regulation. J Am Acad Dermatol 2005;53:1038-44.
12. Holterhues C, Vries E, Louwman MW, Koljenovic S, Nijsten T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989-2005. J Invest Dermatol 2010;130:1807-12.
13. Valery PC, Neale R, Williams G, Pandeya N, Siller G, Green A. The effect of skin examination surveys on the incidence of basal cell carcinoma in a Queensland community sample: a 10-year longitudinal study. J Investig Dermatol Symp Proc 2004;9:148-51.
14. Dutch Society for Dermatology and Venereology. Evidence-based guideline Treatment of the basal cell carcinoma. http://www.huidarts.info/documents/?v=2&id=69 accessed at August 2nd 2010
15. Weyers W. The 'epidemic' of melanoma between under- and overdiagnosis. J Cutan Pathol 2012;39:9-16.
16. Integraal Kankercentrum Nederland http://cijfersoverkanker.nl/ accessed at June 14th 2012.
17. Schwartzberg JB, Elgart GW, Romanelli P, Fangchao M, Federman DG, Kirsner RS. Accuracy and predictors of basal cell carcinoma diagnosis. Dermatol Surg 2005;31:534-7.
18. Bernard P, Dupuy A, Brun P, et al. [Therapeutic modalities and economic assessment in the treatment of superficial basal cell carcinomas and multiple actinic keratoses by French dermatologists]. Ann Dermatol Venereol 2007;134:527-33.
19. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: Increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer 2012;48:2046-53.

20. Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV). Guideline actinic keratosis 2010. www.nvdv.nl accessed at August 2nd 2012.
21. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012;166:1069-80.
22. Richmond-Sinclair NM, Pandeya N, Ware RS, et al. Incidence of basal cell carcinoma multiplicity and detailed anatomic distribution: longitudinal study of an Australian population. J Invest Dermatol 2009;129:323-8.
23. Jung GW, Metelitsa AI, Dover DC, Salopek TG. Trends in incidence of nonmelanoma skin cancers in Alberta, Canada, 1988-2007. Br J Dermatol 2010;163:146-54.
24. Harris RB, Griffith K, Moon TE. Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona, 1985-1996. J Am Acad Dermatol 2001;45:528-36.
25. Katalinic A, Kunze U, Schafer T. Epidemiology of cutaneous melanoma and non-melanoma skin cancer in Schleswig-Holstein, Germany: incidence, clinical subtypes, tumor stages and localization (epidemiology of skin cancer). Br J Dermatol 2003;149:1200-6.
26. Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer 2007;121:2105-8.
27. Brewster DH, Bhatti LA, Inglis JH, Nairn ER, Doherty VR. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992-2003. Br J Dermatol 2007;156:1295-300.
28. Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. Arch Dermatol 1999;135:781-6.
29. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. Int J Cancer 2010;127:2190-8.
30. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med 2005;353:2262-9.
31. van der Geer S, Siemerink M, Reijers HA, et al. The burden of skin cancer in dermatology. 2012 *(submitted)*.
32. Montague M, Borland R, Sinclair C. Slip! Slop! Slap! and SunSmart, 1980-2000: Skin cancer control and 20 years of population-based campaigning. Health Educ Behav 2001;28:290-305.
33. Youl PH, Janda M, Aitken JF, Del Mar CB, Whiteman DC, Baade PD. Body-site distribution of skin cancer, pre-malignant and common benign pigmented lesions excised in general practice. Br J Dermatol 2011;165:35-43.
34. Dobbinson S, Wakefield M, Hill D, et al. Prevalence and determinants of Australian adolescents' and adults' weekend sun protection and sunburn, summer 2003-2004. J Am Acad Dermatol 2008;59:602-14.
35. Dixon HG, Lagerlund M, Spittal MJ, Hill DJ, Dobbinson SJ, Wakefield MA. Use of sun-protective clothing at outdoor leisure settings from 1992 to 2002: serial cross-sectional observation survey. Cancer Epidemiol Biomarkers Prev 2008;17:428-34.
36. Youl PH, Youlden DR, Baade PD. Changes in the site distribution of common melanoma sub-types in Queensland, Australia over time: implications for public health campaigns. Br J Dermatol 2012.
37. Devos SA, Van der Endt JD, Broeckx W, et al. Sunscreen use and skin protection behaviour on the Belgian beach: a comparison 9 years later. Eur J Cancer Prev 2012;21:474-7.
38. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet 1999;354:723-9.

39. Wu PA, Stern RS. Topical tretinoin, another failure in the pursuit of practical chemoprevention for non-melanoma skin cancer. J Invest Dermatol 2012;132:1532-5.
40. Darlington S, Williams G, Neale R, Frost C, Green A. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. Arch Dermatol 2003;139:451-5.
41. Baade P, Meng X, Youlden D, Aitken J, Youl P. Time trends and latitudinal differences in melanoma thickness distribution in Australia, 1990-2006. Int J Cancer 2012;130:170-8.
42. Frangos JE, Duncan LM, Piris A, et al. Increased diagnosis of thin superficial spreading melanomas: A 20-year study. J Am Acad Dermatol 2012;67:387-94.
43. Hollestein LM, van den Akker SA, Nijsten T, Karim-Kos HE, Coebergh JW, de Vries E. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. Ann Oncol 2012;23:524-30.
44. Stacey SN, Gudbjartsson DF, Sulem P, et al. Common variants on 1p36 and 1q42 are associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits. Nat Genet 2008;40:1313-8.
45. Stacey SN, Sulem P, Masson G, et al. New common variants affecting susceptibility to basal cell carcinoma. Nat Genet 2009;41:909-14.
46. Nan H, Xu M, Kraft P, et al. Genome-wide association study identifies novel alleles associated with risk of cutaneous basal cell carcinoma and squamous cell carcinoma. Hum Mol Genet 2011;20:3718-24.

CHAPTER 11

Summary / Samenvatting

SUMMARY

In **chapter 1** a general introduction to this thesis is given. A BCC is the most common skin cancer among Caucasians and its incidence rates are increasing worldwide. However, these rates are often based on cancer registries who often only register the first, histologically confirmed BCC per patient. Therefore, there is limited data available on the number of patients developing multiple BCCs (two or more), and those patients that have clinically diagnosed BCCs without histological confirmation. In this thesis, different aspects of the epidemiology of BCC in The Netherlands is described in order to provide insight to the size of BCC occurrence to all clinicians and policy makers involved in management of these patients.

In **chapter 2** we describe the occurrence of BCC in The Netherlands in terms of incidence and prevalence. This study is based on data on first primary carcinomas between 1973 and 2008 and retrieved from the Eindhoven Cancer Registry (Comprehensive Cancer Center South). After extrapolation of these data to the Dutch population, a total of 444 131 histologically confirmed cases were observed during these last 36 years. The age-standardised incidence rates (European Standard Population [ESR]) increased approximately threefold from 40 to 148 per 100 000 person-years in men and from 34 to 141 in women. The prevalence of BCC in The Netherlands between 1990 and 2008 was estimated on 1.4%. This prevalence was with 5.4% the highest among patients aged 65 years or more. In 2008, the lifetime risk of developing a BCC before the age of 85 years was 1 in 5 for men and 1 in 6 for women. The observed predictions of future trends in incidence for the years 2010, 2015 and 2020 showed no signs of plateauing for all ages and sex.
In conclusion, the absolute number of patients with a first histologically confirmed BCC in The Netherlands increased in the last 36 years with almost a sevenfold in both men and women. This chapter emphasizes that BCCs are a large public health problem. These estimates should urge Dutch policymakers to provide solutions for the growing group of patients with BCC.

In **chapter 3** we estimate trends in BCC incidence in the Southeast Netherlands by sex, age-groups and tumor sites. We gained all first, histologically confirmed BCCs between 1973 and 2009 from Eindhoven Cancer Registry. Joinpoint regression analyses were applied and observed a significant increase in rates since 1973 in both sexes. From 2002 – 2003 until 2009, this increase in rates accelerated, represented by an estimated annual percentage change (EAPC) of 6.8% for men and 7.9% for women. Young women (aged below forty years) had a constant linear increase of 6.3% over the whole study period. In 2009, the head and neck region was most often affected in both men and women with 58.4% of the total number of BCCs diagnosed (n = 4511) within the ECR catchment area. However, in the last 5 – 7 years, the steepest increases in trends were seen on the trunk with an EAPC of 12.8% for men and 14.8% for women. These results show an alarming acceleration in the speed of increase in BCC rates in The Netherlands, especially from 2002 onwards.

In **chapter 4** we present the cumulative risks and incidence rates associated with the development of multiple BCCs per patient in The Netherlands. This retrospective cohort study was performed with data from PALGA, the nationwide network and registry of histopathology and cytopathology in The Netherlands. Pathology reports of the first 2 483 patients with a first, histologically confirmed BCC in the year 2004 were selected. The selected patients were retrospectively followed for 5 years within the PALGA database for subsequent BCC pathology reports. In total, 2 483 patients developed 3 793 BCCs. The five-year cumulative risk of developing multiple BCCs was 29.2%. The incidence rate for the development of two or more BCCs was 25 318 per 100 000 person-years in the first half year after first BCC diagnosis, decreasing to 6 953 per 100 000 person-years after 5 years of follow-up. These data emphasise that at date of first BCC diagnosis, a full body skin examination should be performed and repeated annually for at least three years.

In **chapter 5** a systematic review and meta-analysis is performed to investigate the risk of a subsequent BCC, squamous cell carcinoma (SCC) or melanoma in patients with a previous keratinocyte carcinoma (KC; including BCC and SCC). We included 45 articles. In BCC patients, the pooled proportion for a subsequent BCC, SCC or melanoma was respectively, 29.2%, 4.3% and 0.5%. The pooled proportion for a subsequent SCC, BCC or melanoma in SCC patients was respectively 13.3%, 15.9% and 0.5%. The pooled standardised incidence ratios (SIR) for a subsequent BCC, SCC or melanoma were respectively 17.4, 3.2 and 2.4 in BCC patients and 4.2, 15.0 and 2.7 in SCC patients. In subgroup analyses (i.e. stratified by study quality, study design and continent), the effect sizes of the pooled proportion and SIR remained similar although not identical.
A history of a prior KC is a very strong predictor for developing a subsequent BCC and SCC and to a lesser extent melanoma. Secondary prevention (early detection of subsequent episodes of the disease) is pivotal in patients with a prior KC. Patients should be well informed about future risk and require adequate follow up by physicians.

In **chapter 6** we investigate the number of subsequent non-histologically diagnosed BCCs in patients (n = 1 290) from four hospitals located in the serving area of the Eindhoven Cancer Registry who had a first histologically diagnosed BCC in 2004. A linkage was made with PALGA to obtain pathology reports of subsequent histologically diagnosed BCCs up to November 1st 2010. Patient records were extracted from the participating dermatology departments and reviewed up to November 1st 2010 to identify non-histologically diagnosed BCCs. In total, 1 089 were followed, contributing to 6 253 person-years. More than one third (33.2%) of them developed subsequent histologically and/or non-histologically diagnosed BCCs. All in all, 1974 BCCs were observed of which 1833 (92.9%) were histologically and 141

(7.1%) were non-histologically diagnosed BCCs. Sixty-six patients (6.1%) had subsequent non-histologically diagnosed BCCs, of which 42 had one (63.6%) and 24 two or more (36.4%).

In **chapter 7** we compare the proportion of non-histologically confirmed BCCs observed in chapter 6 to data from other European regions; Malta, Scotland and Finland. Also, it describes the treatment methods of histologically and non-histologically confirmed BCCs and how these differ between the regions. After (manually) reviewing the (electronic) patient records and checking the (hospital) pathology databases to find evidence of histologically diagnosed BCCs, it was observed that the frequency of BCCs diagnosed without histological confirmation differed widely between the four European regions from 0.7% until 24.1%. The highest percentage was found in Scotland; however this study had the smallest study population which may have inflated the proportion. The lowest was observed in Malta, where it is custom to verify all clinically suspicious BCCs histologically by biopsy and/or surgical excision.
In The Netherlands and Finland, clinically diagnosed BCCs without histological confirmation were most often treated with cryotherapy, whereas in Scotland 5% Imiquimod cream was the preferred treatment modality. Although there were methodological differences between the four sub-studies and the percentage of non-histologically diagnosed BCC differed, these findings do confirm that the burden of BCC is underestimated when based solely on data from pathology databases and/ or cancer registries.

In **chapter 8** risk factors associated with single and multiple BCC(s) development is reported. This research was embedded within the Rotterdam Study, which is a prospective population-based cohort study started in 1990 in the Ommoord district of Rotterdam, The Netherlands. In this chapter two cohorts of 10 994 Dutch people of 55 years or older were studied from 1990 to 2007. Participants with histological confirmed BCCs were identified from PALGA, hospitals and general practices. Of the eligible 10 820 cohort members, 524 (4.8%) developed a BCC, of whom 361 had one and 163 (31.1%) had multiple BCC(s). Age between 65 - 75 years and red hair were significant risk factors for a first BCC in a multivariate logistic regression model. Patients who were relatively young at their first BCC diagnosis, those with red hair, those with higher socioeconomic status, and/or those with a BCC lesion on their upper extremities had a higher risk of developing multiple lesions. This latter group probably requires a closer follow-up over time for (early) detection of subsequent BCCs.

In **chapter 9** we investigate the prevalence of actinic keratosis (AK), its risk factors and association with skin cancer in an elderly population. Within the Rotterdam Study, full body skin examinations were performed among 2061 participants aged 45 years or older. Of these cohort members (mean age 72 years), 21% had 1 to 3, 9% 4 to 9 and 8% ten or more AK. Prevalence of AK in the Rotterdam Study was estimated 49% (95% CI 46%–52%) for men

and 28% (26%–31%) for women. Extrapolation suggested that approximately 1.4 of the 16 million Dutch citizens are affected with AK. Male sex, older age, light pigmentation status, severe baldness, skin wrinkling and high tendency for sunburn were significantly associated with number of AKs and extensive actinic damage (≥10 AKs) in the multivariate analyses. Especially bald males were at an increased risk of severe actinic skin damage (adjusted OR= 7.0 [3.8 – 13.). The group with no AKs had a lower positive history for skin cancer (including BCC, SCC and melanoma) than the group with 10 or more AKs. The prevalence of AK is very high, especially among elderly bald males, and the presence of severe actinic damage significantly increases a history of skin cancer. The prevention and management of AK is a true challenge for patients, physicians, and health care policy makers.

In **chapter 10** the main findings of the studies presented in this thesis are discussed and placed into perspective. In addition, study limitations are described and recommendations for future research are given.

SAMENVATTING

In **hoofstuk 1** geef ik een algemene inleiding op dit proefschrift. Het basaalcelcarcinoom (BCC) is de meest voorkomende vorm van huidkanker onder de Kaukasische bevolking en de incidentiecijfers zijn wereldwijd aan het stijgen. Echter, deze incidentiecijfers zijn vaak gebaseerd op kanker registratie data, die in de meeste gevallen alleen de eerste, histologisch bevestigde BCC per patiënt registeren. Hierdoor is er weinig bekend over het aantal patiënten wat twee of meerdere BCCs krijgt, en over het voorkomen van klinisch gediagnosticeerde BCCs zonder histologische bevestiging. In dit proefschrift onderzoek ik verschillende epidemiologische aspecten van het BCC in Nederland. Op deze manier wil ik inzichtelijk maken hoe vaak deze vorm van huidkanker in Nederland voorkomt - nu, en in de toekomst - en wie er risico loopt om een BCC te krijgen. Daarnaast beschrijf ik de prevalentie van aktinische keratoses (AKs) in Nederland. AKs zijn een van de meest gevoelige markers voor huidveroudering en kunnen mogelijk een indicatie geven over het risico op huidkanker ontwikkeling.

In **hoofdstuk 2** wordt de incidentie en prevalentie van het BCC in Nederland beschreven. Het onderzoek werd uitgevoerd met data van het Integraal Kankercentrum Zuid (IKZ). Alle inwoners van de IKZ regio met een eerste histologisch bevestigde BCC, gedurende de periode 1973 tot en met 2008, werden geselecteerd. Extrapolatie van deze gegevens toonde aan dat er gedurende dit tijdvak in heel Nederland 444 131 mensen waren met een eerste histologisch bevestigde BCC. Tijdens de 36-jarige studieperiode verdriedubbelde de voor leeftijd gestandaardiseerde incidentie (Europese Standaard Populatie [ESP]) voor mannen van 40 naar 148 en voor vrouwen van 34 naar 141 per 100 000 persoonsjaren. Gedurende 1990 en 2008, kreeg 1.4% van alle Nederlanders de diagnose 'BCC' te horen. Deze prevalentie was met 5.4 procent het hoogst bij personen van 65 jaar en ouder. Verder werd berekend dat in 2008 naar verwachting 1 op 5 mannen en 1 op 6 vrouwen een BCC zal ontwikkelen vóór het 85e levensjaar. Voorspellingen voor 2010, 2015 en 2020 lieten een continue stijging van incidentie zien voor alle leeftijdsgroepen en geslacht. Concluderend kan er worden gezegd dat het absolute aantal patiënten met een eerste, histologisch bevestigde BCC in Nederland in de afgelopen 36 jaar met ongeveer een zevenvoud is toegenomen bij zowel mannen als vrouwen. Dit onderzoekt onderstreept dat BCCs een groot gezondheidsprobleem vormen. Er zal ingegrepen moeten worden om de groeiende patiënten stroom in juiste banen te leiden.

In **hoofdstuk 3** worden tijd trends in BCC incidentie berekend voor geslacht, verschillende leeftijdsgroepen en anatomische tumor locatie, op basis van alle personen met een eerste, histologisch bevestigde BCC gedurende de periode 1973 tot en met 2009. Ook deze data werd verkregen via het IKZ. Met behulp van de 'jointpoint'-regressie analyse werd gekeken in welk jaar een significante verandering (een zogenaamd 'knikpunt') in de incidentie zichtbaar was. Vanaf 1973 werd een significante toename in BCC incidentie gezien bij zowel mannen als vrouwen. In de jaren 2002 – 2003 tot en met 2009 versnelde deze incidentie, resulterend

in een 'estimated annual percentage change' (EAPC; de geschatte jaarlijkse procentuele verandering van het incidentiecijfer berekend op basis van jaarlijkse incidentiecijfers in de desbetreffende periode) van 6.8% bij mannen en 7.9% bij vrouwen. Bij jonge vrouwen (< 40 jaar) werd een constante lineaire stijging van 6.3% gedurende de gehele studie periode gezien. In 2009 waren de meeste BCCs, zowel bij de mannen als de vrouwen, gelokaliseerd in het hoofd hals gebied (58.4% van het totale aantal BCCs [n = 4511] gediagnosticeerd binnen de IKZ regio). Echter, de sterkste toename in BCC incidentie werd gezien gedurende 2005 – 2009 op de romp met een EAPC van 12.8% bij mannen en 14.8% bij vrouwen. Er kan worden geconcludeerd dat er in de laatste 5 tot 7 jaar een alarmerende toename in leeftijd en locatie specifieke BCC incidentie wordt gezien in de regio zuidoost Nederland.

In **hoofdstuk 4** onderzoeken wij het cumulatieve risico en het incidentiecijfer voor het ontwikkelen van multipele BCCs (twee of meer) per persoon in Nederland. Dit onderzoek werd verricht met gegevens van het Pathologisch Anatomisch Landelijk Geautomatiseerd Archief (PALGA). Pathologie rapporten van 2 483 patiënten met een eerste histologisch bevestigde BCC in het jaar 2004 werden geselecteerd. Deze groep werd vervolgens gedurende 5 jaar retrospectief binnen de PALGA database gevolgd. In totaal ontwikkelden de 2 483 patiënten 3 793 BCCs. Het 5-jaars cumulatieve risico op het ontwikkelen van een of meer nieuwe BCCs bedroeg 29.2%. Het incidentiecijfer voor multipele BCCs was 25 318 per 100 000 persoonjaren gedurende de eerste zes maanden na de eerste BCC diagnose. Dit daalde naar 6 953 per 100 000 persoonsjaren na 5 jaar follow-up. Op basis van deze resultaten wordt er geadviseerd patiënten met een BCC een volledig huidonderzoek te laten ondergaan ten tijde van de eerste BCC diagnose en bij vervolgbezoeken, voor minstens drie jaar.

In **hoofdstuk 5** beschrijven we een systematische review met meta-analyse waarin het risico op het krijgen van een BCC, plaveiselcelcarcinoom (PCC) of melanoom wordt beschreven bij patiënten die eerder werden gediagnosticeerd met een BCC of PCC. In totaal werden 45 artikelen geïncludeerd. Voor BCC patiënten was de 'gepoolde' proportie voor het krijgen van een nieuwe BCC, PCC of melanoom, respectievelijk 29.2%, 4.3% en 0.5%. De 'gepoolde' proportie voor het krijgen van een PCC, BCC of melanoom bij patiënten met een PCC in de voorgeschiedenis was achtereenvolgend 13.3%, 15.9% and 0.5%. De 'gepoolde' gestandardiseerde incidentie ratio (SIR) voor het krijgen van een BCC, PCC of melanoom was 17.4, 3.2 en 2.4 voor patiënten die eerder een BCC hadden en 4.2, 15.0 en 2.7 voor patiënten die eerder een PCC hadden. Effect groottes in de subgroep analyses (stratificatie voor studie kwaliteit, design en continent) waren van dezelfde orde hoewel niet identiek. Concluderend, een voorgeschiedenis met een BCC of PCC geeft een hoog risico op het ontwikkelen van een opvolgende BCC of PCC, en in mindere mate op melanoom. Secundaire preventie lijkt dus van groot belang te zijn bij deze patiënten groep. Zij dienen goed geïnformeerd te worden over hun toekomstig risico op meerdere huidtumoren.

In **hoofdstuk 6** wordt het aantal niet-histologisch bevestigde BCCs (= 'op het blote oog gediagnosticeerd') onderzocht op vier afdelingen dermatologie, gelokaliseerd binnen de IKZ regio. Dit onderzoek werd verricht bij 1 290 patiënten die in 2004 hun eerste histologisch bevestigde BCC hadden. Er werd een link gemaakt met PALGA om zo de pathologie rapporten te verkrijgen van alle histologisch bevestigde BCCs van deze patiëntengroep tot 1 november 2010. Op de afdelingen dermatologie werden de patiënten statussen nagekeken om zo niet-histologisch bevestigde BCCs op te sporen. Van de 1089 gevolgde BCC patienten kreeg 33.2% meerdere BCCs (inclusief histologisch en niet-histologisch bevestigde BCCs). In totaal werden er 1 974 BCCs vastgesteld, waarvan 1 833 (92.9%) histologisch bevestigd en 141 (7.1%) niet-histologisch bevestigd. Zesenzestig patiënten (6.1%) hadden alleen opvolgende niet-histologisch bevestigde BCCs, waarvan er 42 (63.6%) één en 24 (36.4%) twee of meer.

In **hoofdstuk 7** wordt er wederom gekeken naar het voorkomen van niet-histologisch bevestigde BCCs. Waar dit in hoofdstuk 6 alleen in de regio zuidoost Nederland werd onderzocht, maakt men in dit hoofdstuk een vergelijking met soortgelijke studies uit andere Europese regio's zoals Malta, Finland en Schotland. Daarnaast wordt er in dit hoofdstuk gekeken naar de behandeling van histologisch en niet-histologisch bevestigde BCCs en hoe dit verschilt binnen Europa. In Nederland, Malta, Finland en Schotland werden in verschillende ziekenhuizen handmatig de (elektronische) patiënten dossiers en (ziekenhuis) pathologie databases doorgekeken. Hier werd op zoek gegaan naar histologische en niet-histologisch bevestigde BCCs. Op basis van deze substudies werd geconcludeerd dat het voorkomen van niet-histologisch bevestigde BCCs sterk varieert tussen de vier regio's wisselend van 0.7% tot 24.1%. Het hoogste percentage werd gevonden in Schotland. Dit was tegelijkertijd ook de kleinste studie, wat mogelijk heeft gezorgd voor inflatie van het percentage. Het laagste cijfer werd gezien in Malta, alwaar het standaard is om alle voor BCC verdachte laesies histologisch te bevestigen. In Nederland en Finland werden de klinisch gediagnosticeerde BCCs meestal behandeld met cryotherapie, terwijl in Schotland 5% imiquimod crème de eerste keus was. Hoewel er methodologische verschillen waren tussen de vier substudies en het percentage niet-histologisch bevestigde BCCs uiteenliep, toont dit hoofdstuk duidelijk aan dat de ziektelast van BCCs in Europa wordt onderschat wanneer dit alleen wordt gebaseerd op gegevens uit pathologie databases en/of kanker registratie studies.

In **hoofdstuk 8** rapporteren wij de risicofactoren geassocieerd met het krijgen van één en multipele BCC(s). Dit werd onderzocht binnen de Rotterdam Study (c.q. ERGO studie). Dit is een prospectieve populatiegebonden cohort studie gestart in 1990 in de wijk Ommoord in Rotterdam in Nederland. In dit hoofdstuk werden twee cohorten van 10 994 inwoners van 55 jaar en ouder onderzocht van 1990 tot en met 2007. Deelnemers met histologisch bevestigde BCCs werden geïdentificeerd via PALGA, omringende ziekenhuizen en huisartsen. Van de 10 820 geselecteerde deelnemers hadden er 524 (4.8%) een BCC, waarvan 361 deelnemers er

één en 164 (31.1%) multipele hadden. Uitkomsten van de multivariate logische regressie analyse toonde aan dat de leeftijd 65 - 75 jaar en het hebben van rood haar significante risicofactoren waren voor het krijgen van één BCC. Deelnemers die relatief jong waren bij diagnose van hun eerste BCC, deelnemers uit een hogere sociaaleconomische klasse en diegene die hun eerste BCC op hun armen hadden, bleken een significant verhoogd risico op multipele BCCs te hebben. Deze laatste groep patiënten zal daarom mogelijk strenger in de tijd gevolgd moeten worden om opvolgende BCCs (vroeg) te detecteren.

In **hoofdstuk 9** onderzoeken wij binnen een oudere populatie de prevalentie van AKs, de hiermee geassocieerde risicofactoren en de associatie met huidkanker. Bij 2061 deelnemers van 45 jaar en ouder (gemiddelde leeftijd 72 jaar) van de Rotterdam Study werd een volledig huid onderzoek uitgevoerd. Hiervan bleek 21% 1 tot en met 3 AKs te hebben, 9% 4 tot en met 9 en 8% tien of meer. De AK prevalentie binnen de Rotterdam Study was 49% (95% BI 46%–52%) voor mannen en 28% (26%–31%) voor vrouwen. Extrapolatie van deze data toonde aan dat bijna 1.4 van de 16 miljoen Nederlanders AKs heeft. Mannen, oudere leeftijd, lichte pigmentatie status, kaalheid, rimpels in het gezicht en gevoeligheid voor zonnebrand waren allen significant geassocieerd met ernstige aktinische schade ($\geq$10 AKs) in de multivariate analyses. Vooral kale mannen hadden een verhoogd risico op ernstige aktinische schade (aangepaste odds ratio = 7.0 [3.8 – 13.1]). De groep deelnemers zonder AKs hadden minder vaak een voorgeschiedenis met een BCC, PCC of melanoom vergeleken met de groep deelnemers met tien of meer AKs. Concluderend kan er gezegd worden dat de prevalentie van AKs erg hoog is, vooral bij oudere kale mannen, en dat de aanwezigheid van ernstige aktinische schade het risico op een huidkanker voorgeschiedenis verhoogd. De preventie en management van AKs is en zal een uitdaging worden voor patiënten, artsen en gezondheidszorg medewerkers.

In **hoofdstuk 10** worden de belangrijkste bevindingen van dit proefschrift besproken en in perspectief geplaatst. Daarnaast worden studie limitaties beschreven en suggesties voor toekomstig onderzoek gegeven.

CHAPTER 12

List of co-authors

List of publications

Curriculum Vitae

Phd Portfolio

Dankwoord

LIST OF CO-AUTHORS

Affiliations at the time at which the research was conducted:

Tiina Ahti
Department of Dermatology and Allergology, Helsinki University Central Hospital, Helsinki, Finland

Lidia R. Arends
Department of Biostatistics, Erasmus MC University Center, Rotterdam, The Netherlands
Pedagogical and Educational Sciences, Erasmus University, Rotterdam, The Netherlands
Institute of Psychology, Erasmus University Rotterdam, Rotterdam, The Netherlands

Jan-Willem W. Coebergh
Department of Public Health, Erasmus MC University Center, Rotterdam, The Netherlands
Comprehensive Cancer Center South, Eindhoven, The Netherlands

Emmilia A. Dowlatshahi
Department of Dermatology, Erasmus MC University Center, Rotterdam, The Netherlands

Alisdair D. Forrest
Department of Dermatology, Ninewells Hospital and Medical School, University of Dundee, United Kingdom

Ellen R.M. de Haas
Department of Dermatology, Erasmus MC University Center, Rotterdam, The Netherlands

Albert Hofman
Department of Epidemiology, Erasmus MC University Center, Rotterdam, The Netherlands

Gitty Jaanen - van der Sanden
Comprehensive Cancer Center South, Eindhoven, The Netherlands

Ville Kiiski
Department of Dermatology, Erasmus MC University Center, Rotterdam, The Netherlands

Senada Koljenović
Department of Pathology, Erasmus MC University Center, Rotterdam, The Netherlands

Robert J.T. van der Leest
Department of Dermatology, Erasmus MC University Center, Rotterdam, The Netherlands
Rita Micallef
Malta National Cancer Registry, Department of Health Information and Research, Guardamangia, Malta

H.A. Martino Neumann
Department of Dermatology, Erasmus MC University Center, Rotterdam, The Netherlands

Tamar E.C. Nijsten
Department of Dermatology, Erasmus MC University Center, Rotterdam, The Netherlands

Lucy I.H. Overbeek
PALGA, the nationwide network and registry of histopathology and cytopathology, Utrecht, The Netherlands

Sari Pitkänen
Department of Dermatology and Allergology, Helsinki University Central Hospital, Helsinki, Finland

Charlotte M. Proby
Department of Dermatology, Ninewells Hospital and Medical School, University of Dundee, United Kingdom

Michelle M. van Rossum
Department of Dermatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Olli Saksela
Department of Dermatology and Allergology, Helsinki University Central Hospital, Helsinki, Finland

Inge Seubring
Department of Dermatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Sofie van Tiel
Department of Dermatology, Erasmus MC University Center, Rotterdam, The Netherlands

1. Esther de Vries
2. Department of Dermatology, Erasmus MC University Center, Rotterdam, The Netherlands
3. Department of Public Health, Erasmus MC University Center, Rotterdam, The Netherlands
4. Comprehensive Cancer Center South, Eindhoven, The Netherlands

LIST OF PUBLICATIONS

Flohil SC, Bolling MC, Kooi KA, Lemmink HH, Jonkman MF. A new pathogenic keratin 5 mutation in a Hindustan family with localized epidermolysis bullosa simplex. *Eur J Dermatol. 2010;20:27-9.*

Kiiski V, de Vries E, **Flohil SC**, Bijl MJ, Hofman A, Stricker BHCh, Nijsten T. Risk factors for single and multiple basal cell carcinomas. *Arch Dermatol. 2010;146 :848-55.*

Flohil SC, de Vries E, van Meurs JBJ, Fang Y, Stricker BHCh, Uitterlinden AG, Nijsten T. Polymorphisms of vitamin D-binding protein are not associated with development of (multiple) basal cell carcinomas. *Exp Dermatol. 2010;19:1103-5.*

Flohil SC, de Vries E, Neumann HAM, Coebergh JW, Nijsten T Incidence, prevalence and future trends of primary basal cell carcinoma in The Netherlands. *Acta Derm Venereol. 2011;91:24-30.*

Flohil SC, Koljenović S, de Haas ERM, Overbeek LIH, de Vries E, Nijsten T. Cumulative risks and rates of subsequent basal cell carcinomas in The Netherlands. *Br J Dermatol. 2011;165:874-81.*

Flohil SC, Koljenović S, de Haas ERM, Overbeek LIH, de Vries E, Nijsten T. Het blijft vaak niet bij één basaalcelcarcinoom. *Ned Tijdschr Geneeskd. 2011;155:A4110.*

Flohil SC, de Vries E, Nijsten T. Epidemiologie van het basaalcelcarcinoom in Nederland. *Ned Tijdschr Derm Venereol. 2012;2:96-100.*

Flohil SC, van Tiel S, Koljenović S, Jaanen-van der Sanden G, Overbeek LIH, de Vries E, Nijsten T. Frequency of non-histologically diagnosed basal cell carcinomas in daily Dutch practice. *J Eur Acad Dermatol Venereol. 2012 doi: 10.1111/j.1468-3083.2011.04407.x. [Epub ahead of print].*

de Vries E, Micallef R, Brewster DH, Gibbs JH, **Flohil SC**, Saksela O, Sankila R, Trakatelli M, Coebergh JW, Proby CM on behalf of the EPIDERM group. Population-based estimates of the occurrence of multiple versus first primary basal cell carcinomas in 4 European regions. *Arch Dermatol. 2012;148:347-54.*

Flohil SC, Proby CM, Forrest AD, van Tiel S, Saksela O, Pitkänen S, Ahti T, Micallef R, de Vries E on behalf of the EPIDERM group. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. *Br J Dermatol. 2012;167:22-29.*

Trakatelli M, Siskou S, Proby CM, Tiplica GS, Hinrichs B, Altsitsiadis E, Kitsou A, Ferrandiz L, Aquilina S, Apap C, Ulrich M, Fiorentini C, Magnoni C, de Vries E, **Flohil SC**, Kalokasidis K, Moreno-Ramirez D, Ruiz-de-Casas A, Majewski S, Ranki A, Pitkänen S, Saksella O, Sotiriadis D, Stockfleth E on behalf of the EPIDERM group. The patient journey: a report of skin cancer care across Europe. *Br J Dermatol. 2012;167:43-52.*

Flohil SC, van Dorst AM, Nijsten T, Neumann HAM, Munte K. Mohs micrographic surgery for basal cell carcinomas: appropriateness of 'Rotterdam' criteria and predictive factors for three or more stages. *J Eur Acad Dermatol 2012 (accepted for publication).*

Flohil SC, Seubring I, van Rossum MM, Coebergh JWW, de Vries E, Nijsten T. Trends in basal cell carcinoma incidence rates: a 37-year Dutch observational study. J Invest Dermatol 2012 *(accepted for publication)*.

CURRICULUM VITAE

Sophie Christien Flohil is op 10 april 1985 geboren te Geldrop. In 2003 behaalde zij haar gymnasium diploma aan het Pleincollege Sint Joris te Eindhoven. Hetzelfde jaar werd zij door middel van decentrale selectie geplaatst voor de studie geneeskunde aan de Erasmus Universiteit van Rotterdam en ging zij in Rotterdam wonen. Na haar reguliere co-schappen in het Sint Elisabeth ziekenhuis te Tilburg, begon zij in 2009 aan haar afstudeeronderzoek op de afdeling Dermatologie van het Erasmus Medisch Centrum te Rotterdam. Later dat jaar liep zij ook haar oudste co-schap op deze afdeling. Eind 2009 behaalde zij cum laude haar arts-examen en op 1 januari 2010 werd zij toegelaten tot de opleiding tot dermatoloog bij professor H.A.M. Neumann in het Erasmus Medisch Centrum. In de periode 2010 tot en met juli 2012 hield zij zich hoofdzakelijk bezig met haar huidige proefschrift onder begeleiding van dr. E. de Vries, prof.dr. T. Nijsten en prof.dr. H.A.M. Neumann. Per juli 2012 is zij gestart met haar klinische stages. Tijdens haar studie geneeskunde leerde zij haar partner Niels Hoevenaars kennen. Zij wonen samen in Rotterdam.

PhD PORTFOLIO

Summary of PhD training and teaching activities:

Name PhD student:	Sophie Christien Flohil
PhD period:	January 2010 – December 2012
Erasmus University Medical Center:	Department of Dermatology
Promotores:	Prof.dr. T.E.C. Nijsten and Prof.dr. H.A.M. Neumann
Supervisor:	Dr. E. de Vries

	Year	Workload (Hours/ECTS)
1. PhD training		
General academic skills		
- Academic writing and presentation course	2009	20 hours
Research skills		
- Essentials of descriptive cancer epidemiology Karolinska Institute, Sweden	2010	32 hours
- NIHES course: SPSS	2009	8 hours
- NIHES course: Conceptual foundation of epidemiologic study design	2010	15 hours
- NIHES course: Principles of genetic epidemiology	2010	25 hours
- NIHES course: Biostatistics for clinicians	2011	25 hours
- NIHES course: Survival analysis	2011	35 hours
- DOO course: Evidence based medicine	2010	20 hours
- DOO course: Samenwerking	2011	8 hours
- Basic course: Regelgeving en organisatie (BROK)	2010	22 hours
Presentations		
Oral		
- Vitamine D-bindende proteïnes zijn niet geassocieerd met basaalcelcarcinomen. 11de Wetenschappelijke vergadering van de Nederlandse Vereniging voor Experimentele Dermatologie, Lunteren, Nederland	2010	1 ECTS
- Mohs micrographic surgery in The Netherlands: indication criteria and predictive factors. 20th EADV congress, Lisbon, Portugal	2011	1 ECTS
- Cumulative risks and rates of subsequent basal cell carcinomas. 20th EADV congress, Lisbon, Portugal	2011	1 ECTS
- Mohs micrographische chirurgie in The Netherlands: indication criteria and predictive factors. Skintermezzo, Gerlos, Oostenrijk	2012	1 ECTS
- Epidemiologie van het basaalcelcarcinoom in Nederland, Wetenschappelijke jaarvergadering Nederlandse Vereniging van Dermatologie en Venereologie, Rotterdam, Nederland	2012	1 ECTS
- Multipele basaalcelcarcinomen in Nederland, SPA II, Spa, België	2012	1 ECTS

-	Epidemiologie van aktinische keratose, DIS symposium, Amsterdam, Nederland	2012	1 ECTS
-	Prevalence of actinic keratosis, its risk factors and association with skin cancer in an elderly population: the Rotterdam Study, Malmö, Sweden	2012	1 ECTS
-	Actuele ontwikkelingen AK en BCC in Nederland, Rotterdam, Nederland	2012	1 ECTS
Poster			
-	Vitamin D-binding proteins are not associated with (multiple) basal cell carcinoma development, 6th EADO congress, Athens, Greece	2010	1 ECTS
-	Basal cell carcinoma in The Netherlands: how often do they occur? 6th EADO congress, Athens, Greece	2010	1 ECTS
-	De incidentie van multipele basaalcelcarcinomen in Nederland, 12de Wetenschappelijke vergadering van de Nederlandse Vereniging voor Experimentele Dermatologie, Lunteren, Nederland	2011	1 ECTS
International conferences			
-	6th EADO congress, Greece, Athens	2010	1 ECTS
-	SPA I: Oncologie in de parel van de Ardennen, Spa, Belgium	2010	1 ECTS
-	20th EADV congress, Lisbon, Portugal	2011	1 ECTS
-	SPA II: Oncologie in de parel van de Ardennen, Spa, Belgium	2012	1 ECTS
-	6th IDEA congress, Malmö, Sweden	2012	1 ECTS
National conferences			
-	11de Wetenschappelijke vergadering van de Nederlandse Vereniging voor Experimentele Dermatologie, Lunteren, Nederland	2010	1 ECTS
-	Dermatologen dagen, Papendal, Nederland	2011	1 ECTS
-	DIS symposium, Amsterdam, Nederland	2012	1 ECTS
Other			
-	PhD day, Rotterdam, Nederland	2010	8 hours
-	NIHES masterclass: improving forensic analysis with human genomics	2010	2 hours
-	NIHES masterclass: from 'data analysis' to 'model fitting'	2011	2 hours
-	NIHES masterclass: epidemiologic methods are useless	2011	2 hours
-	Dermatoscopie Boerhaave cursus, Leiden, Nederland	2010	8 hours
-	Dermatoscopie specialistische basis cursus met e-learning, Leiden, Nederland	2011	8 hours
-	Dermatoscopie cursus, Rotterdam, Nederland	2012	4 hours
Supervising master's theses:			
-	Sofie van Tiel	2011	
-	Joris Verkouteren	2011	

Occasional reviewer for:

- British Journal of Dermatology
- Journal of Investigative Dermatology
- Acta Dermato-Venereologica
- Cancer Epidemiology, Biomarkers and Prevention
- Photochemistry and Photobiology
- Journal of the American Academy of Dermatology
- Journal of the European Academy of Dermatology

DANKWOORD

Het is klaar! Consummatum est!
Dit promotieonderzoek was nooit zo ver gekomen zonder de hulp van een heel aantal mensen. Dit laatste hoofdstuk is voor hen.

Allereerst zou ik graag mijn twee promotoren willen bedanken: prof. dr. T. Nijsten en prof. dr. H.A.M. Neumann. Tamar, zonder jou was mijn onderzoek nooit zo voortvarend verlopen. Ondanks je eigen drukke programma had je een antwoord op al mijn vragen, keek je met veel geduld mijn werk na en had je zelfs in het zoveelste overleg nog energie voor discussie – ik ben ontzettend trots dat ik jou als begeleider had tijdens mijn onderzoek!
Professor Neumann, hartelijk dank voor de mogelijkheid om onderzoek te doen op uw afdeling en niet te vergeten voor het feit dat ik nu in opleiding tot dermatoloog ben. Ik hoop nog heel veel van u te leren.
Daarnaast heb ik ook veel gehad aan de begeleiding van mijn co-promoter; dr. E. de Vries. Esther, eindelijk mag ik gebruik maken van superlatieven ;-). Heel erg bedankt voor je fantastische begeleiding, je aanmoediging en je rotsvaste vertrouwen – het was een constante motivatie.

Mijn hartelijke dank gaat verder uit naar de leescommissie, prof. dr. R.J. Baatenburg de Jong, prof. dr. J.W.W. Coebergh en dr. N.W.J. Kelleners-Smeets, voor het beoordelen van mijn proefschrift op korte termijn. Ook wil ik graag prof. dr. I. Mathijssen en dr. M.J.P. Gerritsen bedanken voor hun bereidheid om deel uit te maken van de grote commissie. Prof. dr. R. Kaufmann, thank you for wanting to be a member of the doctoral examination board.

Graag zou ik ook alle medewerkers van de Eindhoven Kanker Registratie, en in het bijzonder prof. dr. J.W.W. Coebergh en Gitty Jaanen willen bedanken voor het aan mij toe vertrouwen van de data en de fijne samenwerking.

Daarnaast heb ik tijdens mijn onderzoek dankbaar gebruik gemaakt van gegevens van het Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief – hiervoor ben ik vooral Dr. L.I.H. Overbeek veel dank verschuldigd.

Graag zou ik ook alle medewerkers van het ERGO centrum willen bedanken. Jullie hebben het dermatologie-ERGO-team met open armen ontvangen en nooit was iets te veel gevraagd. Dit maakte de werkdagen op het ERGO-centrum heel plezierig. Prof. dr. A. Hofman, bedankt voor het opzetten van dit bijzondere onderzoek.

Alle co-auteurs die hebben meegewerkt aan de artikelen die in dit proefschrift staan wil ik bedanken voor hun zwoegwerk, schrijfwerk, verbeterwerk en enthousiasme.

Wat was mijn promotietijd een bijzondere periode – naast ontzettend veel te hebben geleerd heb ik gelachen en genoten! Dit is voor een groot deel te danken aan mijn paranimfen: Robert en Emmilia. Robert, ik geloof dat wij voorlopig nog niet van elkaar af zijn en wat mij betreft is dat alleen maar een heel geruststellend vooruitzicht. Naast onze samenwerking bij een aantal 'heftige' artikelen waarbij we soms door de bomen het bos niet meer zagen, kunnen wij elkaar er altijd doorheen slepen door het grappige ervan in te zien – hiervoor mijn oprechte dank. Emmilia, samen met jou heb ik het allereerste dermatologie-ERGO-team gevormd en dat ging super! Ook naast het werk ben je er altijd voor een gezellig praatje, opbeurende woorden en lachwekkende momenten. Dank dat jullie mijn paranimfen willen zijn en naast me willen staan op de grote dag – het einde is ook voor jullie in zicht!

Loes, bedankt voor je hulp en geduld bij al mijn statistische vragen – je bent een enorme slimmerik. Satu, Enes, Leonie, Joris en Merel, jullie hebben het onderzoek doen in alle fases leuker en makkelijker gemaakt, vooral dankzij onze bijzondere 'whatsapp' sessies – bedankt daarvoor. Cynthia, dank voor al je (promotie) wijsheden die je me hebt bijgebracht, ik had ze nodig.

Daarnaast is een bedankje voor al mijn collega's van de afdeling Dermatologie op zijn plek. De eerste paar maanden van mijn opleiding waren nogal intens, vooral gezien de eindfase van dit boekje. Dank voor jullie geduld, hulp bij vragen en adviezen en het algemene thuisgevoel op de afdeling. Er volgen waarschijnlijk nog vele leuke opleidingsjaren!

Lieve schoonfamilie en aanhang, mijn grote dank voor jullie steun en begrip in deze volle tijden. Altijd geïnteresseerd en bereid om te helpen. Ik vind het heel fijn om in jullie familie opgenomen te zijn.

Tenslotte mijn lieve familie, ik zou mezelf niet zijn zonder jullie. Op elk moment in mijn leven hebben jullie me gesteund en in me geloofd, hebben jullie me verdedigd en aangemoedigd, mijn moeilijke en mooie momenten gedeeld. Dat ik vandaag niet alleen een dokter maar ook een doctor ben heb ik mede te danken aan jullie. Ook al vinden jullie het niet nodig om hiervoor bedankt te worden, het is bijzonder om zo'n sterke en fijne familie te hebben. Mijn dank voor alles dat jullie gegeven hebben.

Tot slot, aan Niels, die me elke dag meemaakt – saaie en spannende dagen, mooie en grappige momenten, vervelende en speciale ochtenden en avonden – dank dat je bent wie je bent. Ik hoop samen met jou oud te mogen worden.