General discussion

The research presented in this thesis provides insight into the epidemiology of basal cell carcinoma (BCC), in particular into the epidemiology of patients with metachronous BCC (mBCC). An update of the knowledge on the occurrence of mBCC is warranted as the burden of BCC is still increasing (**chapter 2**). In this chapter I will first shortly answer the five research questions posed in the introduction of this thesis. Then I will show the limitations of the included studies. Finally, I will discuss potential implications and future perspectives of my research.

RESEARCH QUESTIONS

1. What is already known about the epidemiology of BCC and where are the gaps?
These questions were answered in **chapter 2** and **3** in a broad non-systemic review of the literature on BCC. Numerous studies on BCC incidence in white-skinned individuals worldwide all point out the high and still increasing incidence. In addition, approximately one third of all individuals with a first BCC will develop at least a second BCC and are at risk of other ultraviolet radiation (UVR) related skin cancers,[1] which is in line with the concept of field cancerization.[2] Nevertheless, the majority of BCC research has been done in patients with one BCC, or without differentiating between single or mBCC or different keratinocyte carcinomas (KC, i.e., BCC and squamous cell carcinoma (SCC)), which is the reason little is known about the true burden of disease (i.e., disability-adjusted life year and health care costs) and both the non-genetic and genetic risk factors (i.e., predictors) of patient with mBCC. The latter makes targeted secondary prevention and tailored follow-up difficult, and screening programs less likely to be cost effective, since it is not known who the high-risk patients exactly are. Thus there is a need for skin cancer consortia and large prospective population-based cohort studies with a long follow-up up in which prediction models for mBCC patients can be developed and validated/replicated.

2. What are the non-genetic and genetic predictors of a superficial first BCC?
These questions were addressed in **chapter 4** using histopathologically confirmed skin cancer data gathered through a linkage between the prospective population-based cohort study named the Rotterdam Study[3] and the Dutch nationwide network and registry of histopathology and cytopathology (PALGA).[4] Based on several previous observational studies eleven non-genetic predictors were included in the binary logistic regression analyses of which three were significantly associated with a superficial first BCC. We found that patients with a superficial first BCC were significantly younger (odds ratio (OR) 0.95, 95% confidence interval (CI) 0.93-0.98), almost two times more often female (OR 1.88, 95% CI 1.16-3.03) and 12-18 times more likely to have their

BCC on the trunk or extremities (truncal OR 12.20, 95% CI 7.08-21.03; extremities OR 17.57, 95% CI 10.06-30.70) than patients with a non-superficial first BCC. We did not find a significant association between a superficial first BCC and having more than 1 BCC at initial diagnosis or having at least another mBCC (*last statement is based on unpublished data*). Based on several previous genome-wide association studies (GWAS) of loci that confer risk of BCC or non-melanoma skin cancer twenty single nucleotide polymorphisms (SNPs) were included in the binary logistic regression analyses of which one SNP (rs12203592), mapped to IRF4, looked promising (OR 1.83, 95% CI 1.13-2.97), but after adjustment for multiple testing, no significant differences in genetic make-up between superficial first BCC and non-superficial first BCC patients were found. Overall, superficial first BCCs could have a different etiology than the other subtypes. Although we did not find a significant association between SNPs previously associated with BCC and risk for superficial first BCC, we cannot rule out that there is no genetic susceptibility for a superficial first BCC, since our cohort of patients was small. Larger genetic studies will be needed to investigate whether this is indeed the case.

3. How to deal with the competing risk of death when analyzing metachronous BCCs?
This question was answered in **chapter 5** with histopathologically confirmed skin cancer data gathered through a linkage between the Rotterdam Study and PALGA. We first pointed out that the competing risk problem could be a real problem in survival analysis of metachronous KC data and then we compared two different methods of estimating the survival probability, namely the Kaplan Meier (KM) curve and the cumulative incidence curve (CIC). After ten years of follow-up the probability of a subsequent KC was 40% using the KM method and only 34% using the CIC method. The KM method gave an overestimation of the real probability by not taking the competing risk of death into account. Twenty years after diagnosis, the difference was even larger (74% for KM vs 52% for CIC) because the problem of competing risk due to death of included patients became larger. Thus, the competing risks problem can occur for all end points other than overall mortality when using the KM method and could be avoided using the CIC method. In chapter 6 and 7 we used this knowledge and showed that the Fine and Gray semiparametric proportional hazards model could be used to deal with competing risk of death and generate valid hazard ratios (HR) for the included predictors.

4. What are the non-genetic predictors, absolute risks and cumulative incidences of metachronous BCCs?
These questions were addressed in **chapter 6** and **7** using histopathologically confirmed skin cancer data gathered through a linkage between the Rotterdam Study and PALGA.

Based on a scarce amount of literature on non-genetic predictors of mBCC several phenotypic, lifestyle, and tumor-specific characteristics were included in the initial prediction models. In **chapter 6** the follow-up was stopped after the second new BCC (i.e., first mBCC) whereas in **chapter 7** the follow-up was extended up to the fifth new BCC (i.e., fourth mBCC).

In **chapter 6** we showed that of the thirteen non-genetic predictors included in our prediction model, only five remained in the multivariable Fine and Gray semiparametric proportional hazards model. These were: age at first BCC, sex, coffee consumption, superficial subtype of the first BCC and more than one BCC at first date of diagnosis. The latter being the strongest predictor of a second BCC (HR 2.5, 95% CI 1.9-3.3). The apparent concordance index (i.e., discriminative ability) of the multivariable model was reasonable, ranging between 0.63-0.65 from 1-5 years after the first BCC diagnosis. A score chart was developed, which makes it easier for a physician to calculate the absolute risk of a second BCC. For example: a 65-year-old (two points) man (one point) who drinks no coffee (two points) presenting with one (zero points) superficial (one point) BCC has a total score of 6, which corresponds to a 3-year risk of 21% of a second BCC. This patient could be regarded as a high-risk patient, however this is a grey area in which dermatologists should come together and define new guidelines on follow-up/ screening.

In **chapter 7** we showed that of the fourteen included non-genetic predictors nine remained in the multivariable Fine and Gray semiparametric proportional hazards model, namely age at BCC diagnosis, sex, pigment status, easily sunburned, coffee consumption, more than one BCC at diagnosis, superficial subtype of BCC, localization of BCC and the number of previous BCC diagnosis dates (newly added variable compared to the other prediction model). The strongest predictors were more than one BCC at diagnosis (HR 1.9, 95% CI 1.5-2.4) and the number of previous BCC diagnosis dates (increasing HR with increasing number of previous diagnosis dates; HR 3 previous dates 3.9, 95% 2.5-6.2), which could be proxies of field cancerization. In contrast to the prognostic model for a second BCC, pigment status, easily sunburned and location of BCC at diagnosis now did remain in the model, but the univariable HRs and 95% CIs were small and quite similar. The discriminative ability of the multivariable model was reasonable, ranging between 0.67-0.70 from 1-5 years after any BCC diagnosis. Again a score chart was developed showing that for example a 65-year-old (five points) man (one point) with a light pigment status (two points) who burns easily (one point), drinks no coffee (four points), presenting with one (zero points) superficial (one point) truncal (one point) BCC on his fourth BCC diagnosis date (nine points) has a total score of 24, which corresponds to a 3-year risk of approximately 34% of a fifth BCC. The cumulative incidence of a mBCC at 3 years was 15%, and 34%, 45% and 67% for the second, third, fourth and fifth BCC, respectively.

In conclusion, a combination of readily available clinical characteristics, especially more than one BCC at diagnosis and number of previous BCC diagnosis dates, can reasonably identify patients at high risk of mBCC. Risk of a mBCC was highest in the first 2-3 years after diagnosis.

5. What are the genetic predictors of multiple/metachronous BCCs?

This question was first answered in **chapter 8** performing a candidate gene approach (CGA) and a pilot GWAS of multiple BCC using data gathered through a linkage between the Rotterdam Study and PALGA. We used the word "multiple" instead of "metachronous" because a small part of the included patients only had multiple BCCs on their first diagnosis date and no further BCCs in time. The CGA comparing single BCC to multiple BCC included nineteen candidate SNPs from GWAS and CGA of BCC or KC and yielded no significant associations between these BCC-related SNPs and the risk of multiple BCC. In addition, the pilot GWAS identified genome-wide suggestive associations in chromosomes 2, 3, 18, and 22 (P-values $<5x10^{-6}$) of which the most significant SNP was rs78857623 (P-value 1.2×10^{-7}) mapped to an intron in the tumor suppressor gene *FHIT*.

In **chapter 9** we presented the results of a combined effort between our dermatology department and two research groups in the USA to identify gene variants for multiple KCs. A CGA and GWAS of multiple KC was performed combining our data with data from three large USA prospective cohort studies, namely the Nurses' Health Study (NHSI and II), Health Professionals Follow-up Study[5] and the Framingham Heart Study.[6] The GWAS on multiple KC identified eight independent SNPs with suggestive associations (p-value $<5.5x10^{-6}$) of which the most significant SNP was located at chromosome 9 (rs7468390; p-value 3.92x10-7). However, in stage two none of these SNPs were replicated in an independent sample of 574 multiple KCs from the Rotterdam Study and only two of them were associated with multiple KCs in the same direction in the combined meta-analysis. The nineteen previously reported candidate BCC SNPs were included in a CGA and we found that rs1805007 (*MC1R* locus) was significantly associated with risk of multiple KCs (p-value$2.80x10^{-4}$).

Overall, it remains likely that there are genetic differences between patients with multiple BCC and single BCC, but we could not confirm this in our genetic analyses. The latter could be explained by our relatively small sample sizes.

LIMITATIONS OF THE STUDIES

The articles on which **chapters 2** and **3** are based, compiled previous literature on BCC epidemiology, which led to some inherent limitations. **Chapter 2** consisted of a

scholarly review, which means that a non-systematic search of the scientific literature took place before the article was written. However, since the purpose of the article was to give a broad epidemiologic overview of BCC, it was practically impossible and not the scope to perform one systematic search. This may have biased the information presented and therefore affected the generalizability of our conclusions. However, we included as many different studies and outcomes as possible (>200 scientific articles). In **chapter 3** we gave our opinion on the scarcity of large population-based cohort studies on mBCC by writing a commentary on an original mBCC article. This means that due to the scope of this commentary only several articles could be included, which therefore could have affected the generalizability of our conclusions.

Chapters 4-9 are all based on data obtained from a linkage between the Rotterdam Study and PALGA. The use of a pathology registry (i.e., PALGA) coupled with a large long ongoing prospective cohort study (i.e., Rotterdam Study) gave us the opportunity to include multiple detailed predictors and distinguish between (metachronous) BCC and SCC, which helped us to discover predictors specific to either KC. This is important because there exist differences in risk factor profiles between BCC and SCC patients (e.g., smoking, UVR exposure patterns). Even though the Rotterdam Study data we used consisted of 14,926 participants, of whom approximately 10% developed at least one BCC, these are still small numbers when performing GWAS, because SNPs often have relatively low allele frequencies and small effect sizes. Therefore we collaborated with three different prospective USA cohort studies (**chapter 9**) to increase the sample size and power for our genetic studies, but it was no longer possible to differentiate between BCC and SCC, since the USA cohorts did not have the same phenotypes available. Likewise we could not (yet) replicate and validate our prediction models (**chapter 6** and **7**) because we could not find external cohorts which had the same detailed data as we had.

Other potential limitations of our studies were:

1) a limited generalizability (i.e., external validity) because the Rotterdam Study population is aged 45 years or older and mainly exists of white-skinned people, whereas current BCC incidence trends show an increasing incidence in young women.[7-9] However, these young women seem to represent a special group and overall BCC is still considered to be a skin disease of the older white-skinned population, suggesting this bias played only a minor role.
2) underestimation of the absolute number of BCCs and potential non-differential misclassification because
   a. we only included histopathologically confirmed BCCs. However, a recent observational study showed that only a small percentage (ca. 7%) of patients with mBCC had subsequent non-histologically confirmed BCCs.[10] In addition,

the evidence based guideline regarding BCC from the Dutch Society for Dermatology and Venereology (NVDV) states that all biopsied/excised BCCs should be sent for a histopathological diagnosis.[11] Besides, including non-histopathological BCCs could have led to a significant misclassification bias because a clinical BCC diagnosis, even made by a dermatologist, has a relatively low diagnostic accuracy.[12,13]

b. of incomplete PALGA coverage. The Rotterdam Study cohort members could have developed BCCs before PALGA had complete nationwide coverage in 1991. However, between 1971 and 1991 partial coverage was achieved and the mean age of the included participants in 1991 was 61 years, which is seven years younger compared with the mean BCC age of diagnosis,[14] suggesting that the impact of this bias is small.

IMPLICATIONS AND FUTURE PERSPECTIVES

In 1973 Epstein already observed that a relatively large part of patients who were previously treated for a BCC developed mBCC.[15] An observation that is in line with the concept of field cancerization[2] and with regard to the skin has been called actinic neoplasia syndrome to emphasize that patients with a first UVR-related cutaneous (pre)malignancy frequently develop other cutaneous (pre)malignancies, in part due to the field dysplasia from which they chronically suffer.[16] These observations were corroborated in a recent meta-analysis, which showed that approximately one third of the BCC patients will at least develop a second BCC and are at risk of SCC (4,3%) and melanoma (0,5%) as well.[1] The risks of developing other UVR-related skin cancers after a first BCC are increased, however, the majority of patients who develop a first BCC will develop BCCs only, something which could be a consequence of particular genetic susceptibilities.[17,18]

Since Epstein's observation no prediction models for mBCC have been developed (until now) and relatively few studies have been conducted to identify patients at risk of mBCC, but plenty of observational studies have pointed out the risk factors of a BCC, and the growing incidence numbers, burden of disease and health care costs.[19-21] It is clear that there is an increased risk of mBCC on a population level, but on an individual level it is still unclear who these patients at risk are. Looking at the increasing incidence and burden it is time we find the missing pieces and translate this into a clinical relevant prediction model for mBCC to help physicians in their therapeutic approach, something which has been done in multiple other research areas as well. A good example is the cardiovascular risk table for Dutch general practitioners which gives a 10-year risk of cardiovascular disease or mortality using age, sex, blood pressure,

smoking and cholesterol, and helps these physicians in determining their treatment plan (e.g., nothing, diet and/or medication).[22] The data presented in this thesis fill some of these knowledge gaps and support the aforementioned findings concerning risks of mBCC and field cancerization. We noticed that approximately 30% of the analyzed Rotterdam Study participants developed mBCC, which is similar to risks found in previous studies. The results presented in **chapters 2-3** and **6-7** demonstrate that proxies of field cancerization, namely more than one BCC at diagnosis and number of previous BCC diagnoses, were the strongest predictors of mBCC (HR varying from 1.9-3.9). However, BCC is a complex disease and the discriminative ability of our models was only reasonable, which most likely could be explained by residual confounding and the fact that we could not include all possible other predictors (because of the sample size) that could add to the total explained variability of mBCC.

In the last decades numerous observational studies (e.g., cohort, case-control, cross-sectional) have been conducted to find BCC risk factors. This has led to the discovery of multiple universally accepted predictors, but also to a lot of questionable (i.e., probably false) risk factors, often with small effect sizes and sometimes opposite effect directions. One could wonder if we should keep looking for (m)BCC predictors or should focus on the strongest and/or most easy to determine risk factors only. I think we should keep looking, as it seems that a significant part of the mBCC risk variation cannot be explained by known predictors, which also shows that risk factors for a first event are not automatically relevant for a second event (pigment status, UVR-related characteristics), and the finding of new predictors (even with small effect sizes) could lead to more focused prevention strategies and new therapeutic options. In the search for mBCC risk factors we should be non-conventional and look into new research areas like the (skin) microbiome as well.[23] In the interest of improving research quality it would be better if we would perform these studies (in particular genetic) in large (inter) national research consortia in order to the increase the validity of study findings and find new risk predictors with small effects sizes and low frequencies as well[24] and stimulate laboratory scientists to study underlying mechanisms in detail. The classical paradigm that most of the explained cancer variability is due to non-genetic/environmental factors (or as more recently stated due to bad luck)[25] seems erroneous and the attributable risk of genetic factors should not be overlooked.[26] Fortunately a paradigm shift took place and the last decade several studies were performed that looked into the genetic epidemiology of BCC. Most of these studies were CGAs or GWASs and the significant genetic predictors found in there usually had small effect sizes (OR <1,5) and only explain a small fraction of the total BCC heritability. Unfortunately, our CGAs and GWASs yielded no relevant significant predictors of multiple BCCs, most likely due to our small sample sizes (**chapter 8-9**). Based on our results one might argue that it is unlikely that there exist common variants (i.e., SNPs) with strong effects contributing

to the susceptibility for multiple BCC. Nevertheless, significant SNPs with weak effects and rare variants might be clinically irrelevant, but could lead to new pathways and therefore new treatment options. The missing heritability could be hidden in SNPs with small effect sizes and low frequencies that were not picked up in the current sample sizes, but another likely explanation is that we should look into for example gene-environment interactions, exome sequencing and epigenetics.[27] Recently, a GWAS found a potential gene-caffeine interaction which could be involved in caffeine-mediated BCC inhibition.[28]

The question remains if we should aim for a perfectly discriminating prediction model, as adding dozens of significant predictors (with small effect sizes) will decrease the applicability of such a model in clinical practice. Even if we would have the ideal (i.e., flawless discrimination, perfectly calibrated and externally validated) prediction model for mBCC, physicians should still be encouraged to think about their follow-up schemes because we, as physicians, would like to give personalized care and pursue shared decision making. However, a recently published cross-sectional study in USA elderly skin cancer patients showed that there were no differences in given treatments (61% surgical) between BCC patients with limited life expectancy and normal life expectancy.[29] A one-size-fits-all approach is not the answer to the growing skin cancer problem in our BCC patients, of whom the majority is over 65 years of age.

Another question concerns the duration and frequency of follow-up once we identified the patients at risk of mBCC. Previous observational studies have shown that most mBCC occur within approximately 3 years after a diagnosis, but that risks remain elevated over time.[30-32] This was in line with our results (**chapter 6-7**) in which we noticed that the median follow-up time until the second BCC was 3.0 years and seemed to shorten until it reached 1.8 years after the fourth BCC. Fortunately, BCCs are rarely lethal[33] and increase slowly in size, with a median growth of approximately 3 millimeters per year as pointed out in a recently published systematic review.[34] This review, which was based on the WHO criteria for screening, also showed that small changes in size can affect treatment options, their effectiveness and associated costs, especially in the H-zone and that current data supports early detection of BCCs on the face. In contrast to this systematic review, the U.S. Preventive Services Task Force concluded in 2016 that "the current evidence is insufficient to assess the balance of benefit and harms of screening for skin cancer in adults with a clinical visual skin examination".[35] Important data in this field comes from the first nationwide skin cancer screening program in Germany,[36] however seven years after the introduction of this program no discernible beneficial effect was found.[37] In addition, an Australian cost-effectiveness analysis of an educational intervention encouraging self-skin examinations for early detection of skin cancers showed that the overall costs and effects outweighed the positive health gains.[38] A way to increase the cost-effectiveness

is to restrict screening to high-risk patients, but the downside of this targeted screening is the so-called 'prevention paradox' in which you do not address the overwhelming majority of low-risk BCC patients that develop mBCC.[39] In the international dermatology society there is currently no consensus on the follow-up scheme of BCC patients, but they almost all promote self-monitoring (Table 1). The national dermatology guidelines differ in the advice on the length and frequency of follow-up, which could depend on a countries' BCC incidence and population composition, and lack prediction models that could define high-risk groups. The Dutch BCC guideline advices not to do regular follow-up (except in well-known high risk groups like immunosuppressed), whereas the German guideline advices, in a population that is similar to that of the Netherlands, half-yearly visits the first 3 years after which lifelong yearly follow-up. The Australian guideline advices lifelong follow-up every 6-12 months, which was expected because they have the highest UVR-related skin cancer incidences rates in the world. Based on these findings I would suggest to follow Dutch BCC patients at risk for a mBCC once per year at least 3-5 years after every new BCC, without forgetting the patients' health status and wishes. Since skin cancer patients already determine a significant amount of the workload of dermatologists, we should consider translocating less complex skin cancer care to general practitioners. Recent studies show that general practitioners are willing to do this but currently often lack the diagnostic capabilities and tools.[40] However, education sessions can improve diagnostic accuracy and surgery skills and diminish unnecessary referrals.[41-43]

The prediction models we created to identify mBCC patients were as far as we know the first prediction models reported for this outcome. However, recently an Australian group developed another prediction model based on prospective population-based cohort data to estimate the future risks of metachronous KC in patients with and without prior KCs.[44] Although this study did not differentiate between BCC and SCC, it did show that the strongest predictors were signs of field cancerization, namely number of prior skin cancers excised and number of skin lesions destroyed. Both our models and the Australian model have room for improvement when looking at the discriminative capacities and have not been externally validated yet. This points to the fact that there are still too few large prospective cohort studies and skin cancer consortia with the same data, which can be used to replicate and validate findings from other BCC studies.

CONCLUSION

The diagnosis, treatment and follow-up of BCC (and other UVR-related cutaneous (pre) malignancies) currently consumes a relatively large part of the dermatological care (in the Netherlands/Western countries) and it is unlikely that this will change in the near

Table 1. Follow-up schemes for BCC patients according to different guidelines

Country	Date	Conclusion[1]	Reference
Netherlands (NVDV)	2015	Primary BCC: no routine follow-up, advice on self-monitoring; except for high-risk patients (like nevoid basal cell carcinoma syndrome, prolonged immunosuppressed and severe actinic damage), whom get at least yearly follow-up	http://www.nvdv.nl/wp-content/uploads/2014/08/20160725-eindversie-richtlijn-BCC-2015.pdf
Germany (ADO, DK, DDG)	2012	Primary BCC: advice on self-monitoring, follow-up every 6 months first 3 years, after which lifelong yearly follow-up (more often when e.g., immunosuppressed, genetic predisposition, history of multiple BCC)	http://www.awmf.org/uploads/tx_szleitlinien/032-021l_S2k_Basalzellkarzinom_2013-verlaengert.pdf
Great Britain (BAD)	2008	Primary BCC: advice on self-monitoring or follow-up in primary care. Patients with history of multiple BCCs: follow-up ≥ 3 years	http://www.bad.org.uk/shared/get-file.ashx?id=45&itemtype=document
France (FSD)	2004	Primary BCC: at least yearly follow-up for 5 years, preferably lifelong	http://www.sfdermato.org/media/pdf/recommandation/cbc-2004-recommandations-96f90a29d135dac081b7053db84cdb57.pdf
European (EDF)	2012	Primary BCC: advice on self-monitoring and ideally a lifelong yearly follow-up. However if unfeasible then follow-up of high-risk patients (i.e., high risk of recurrence, already treated for a recurrence, history of multiple BCCs) every 6-12 months for 3-5 years	http://www.euroderm.org/edf/index.php/edf-guidelines/category/5-guidelines-miscellaneous?download=24:guideline-basal-cell-carcinoma-update-2012
Australia (ACD)	2008	Primary BCC: advice on self-monitoring and lifelong follow-up every 6-12 months	https://www.dermcoll.edu.au/atoz/basal-cell-carcinoma-bcc/
USA (AAD)	2017 (draft version)	Primary BCC: advice on self-monitoring and at least yearly follow-up	https://www.aad.org/File%20Library/Main%20navigation/Practice%20Center/Quality/Quality%20measures/AAD-BCC-Guidelines-FOR-MEMBER-COMMENT.pdf

[1] Conclusion is a summarized version of the guideline's follow-up conclusions/recommendations, focusing on multiple BCCs

Abbreviations: NVDV, Dutch Society of Dermatology and Venereology; ADO, Arbeitsgemeinschaft Dermatologische Onkologie; DK, Deutschen Krebsgesellschaft; DDG, Deutschen Dermatologischen Gesellschaft; BAD, British Association of Dermatologists; FSD, French Society of Dermatology; EDF, European Dermatology Forum; ACD, Australasian College of Dermatologists; AAD, American Academy of Dermatologists.

future, as BCC incidence is still increasing. Identifying and focusing on BCC patients at high risk of developing mBCC will optimize BCC care and reduce the strain on dermatological care. This thesis can assist dermatologists and general practitioners to accomplish this as it presents research on non-genetic and genetic epidemiology of mBCC patients, including prediction models to identify these patients. However, replication and external validation of these models and larger genetic studies on mBCC are needed.

REFERENCES

1 Flohil SC, van der Leest RJ, Arends LR *et al.* Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. *Eur J Cancer* 2013; **49**: 2365-75.

2 Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer* 1953; **6**: 963-8.

3 Hofman A, Brusselle GG, Darwish Murad S *et al.* The Rotterdam Study: 2016 objectives and design update. *Eur J Epidemiol* 2015; **30**: 661-708.

4 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.

5 Zhang M, Song F, Liang L *et al.* Genome-wide association studies identify several new loci associated with pigmentation traits and skin cancer risk in European Americans. *Hum Mol Genet* 2013; **22**: 2948-59.

6 Splansky GL, Corey D, Yang Q *et al.* The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol* 2007; **165**: 1328-35.

7 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.

8 Birch-Johansen F, Jensen A, Mortensen L *et al.* 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.

9 Flohil SC, Seubring I, van Rossum MM *et al.* Trends in Basal cell carcinoma incidence rates: a 37-year Dutch observational study. *J Invest Dermatol* 2013; **133**: 913-8.

10 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* 2013; **27**: 907-11.

11 NVDV. Evidence-based Richtlijn Basaalcelcarcinoom. In: NVDV. 2015.

12 Green A, Leslie D, Weedon D. Diagnosis of skin cancer in the general population: clinical accuracy in the Nambour survey. *Med J Aust* 1988; **148**: 447-50.

13 Heal CF, Raasch BA, Buettner PG *et al.* Accuracy of clinical diagnosis of skin lesions. *Br J Dermatol* 2008; **159**: 661-8.

14 Arits AH, Schlangen MH, Nelemans PJ *et al.* Trends in the incidence of basal cell carcinoma by histopathological subtype. *J Eur Acad Dermatol Venereol* 2011; **25**: 565-9.

15 Epstein E. Value of follow-up after treatment of basal cell carcinoma. *Arch Dermatol* 1973; **108**: 798-800.

16 Weinstock MA, Lee KC, Chren MM *et al.* Quality of life in the actinic neoplasia syndrome: The VA Topical Tretinoin Chemoprevention (VATTC) Trial. *J Am Acad Dermatol* 2009; **61**: 207-15.

17 Keim U, van der Pols JC, Williams GM *et al.* Exclusive development of a single type of keratinocyte skin cancer: evidence from an Australian population-based cohort study. *J Invest Dermatol* 2015; **135**: 728-33.

18 Heagerty AH, Fitzgerald D, Smith A *et al.* Glutathione S-transferase GSTM1 phenotypes and protection against cutaneous tumours. *Lancet* 1994; **343**: 266-8.

19 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.

20 Hollestein LM, de Vries E, Aarts MJ *et al.* Burden of disease caused by keratinocyte cancer has increased in The Netherlands since 1989. *J Am Acad Dermatol* 2014; **71**: 896-903.

21 Guy GP, Jr., Machlin SR, Ekwueme DU *et al.* Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. *Am J Prev Med* 2015; **48**: 183-7.

22 NHG. Cardiovasculair risicomanagement. In: NHG. 2012.

23 Nakatsuji T, Chen TH, Butcher AM *et al.* A commensal strain of Staphylococcus epidermidis protects against skin neoplasia. *Sci Adv* 2018; **4**: eaao4502.

24 Ioannidis JP. How to make more published research true. *PLoS Med* 2014; **11**: e1001747.

25 Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* 2015; **347**: 78-81.

26 Begg CB. The search for cancer risk factors: when can we stop looking? *Am J Public Health* 2001; **91**: 360-4.

27 Trerotola M, Relli V, Simeone P *et al.* Epigenetic inheritance and the missing heritability. *Hum Genomics* 2015; **9**: 17.

28 Li X, Cornelis MC, Liang L *et al.* A genome-wide analysis of gene-caffeine consumption interaction on basal cell carcinoma. *Carcinogenesis* 2016; **37**: 1138-43.

29 Linos E, Chren MM, Stijacic Cenzer I *et al.* Skin Cancer in U.S. Elderly Adults: Does Life Expectancy Play a Role in Treatment Decisions? *J Am Geriatr Soc* 2016; **64**: 1610-5.

30 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.

31 Flohil SC, Koljenovic S, de Haas ER *et al.* Cumulative risks and rates of subsequent basal cell carcinomas in the Netherlands. *Br J Dermatol* 2011; **165**: 874-81.

32 Wehner MR, Linos E, Parvataneni R *et al.* Timing of subsequent new tumors in patients who present with basal cell carcinoma or cutaneous squamous cell carcinoma. *JAMA Dermatol* 2015; **151**: 382-8.

33 Lo JS, Snow SN, Reizner GT *et al.* Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. *J Am Acad Dermatol* 1991; **24**: 715-9.

34 Hoorens I, Vossaert K, Ongenae K *et al.* Is early detection of basal cell carcinoma worthwhile? Systematic review based on the WHO criteria for screening. *Br J Dermatol* 2016; **174**: 1258-65.

35 Force USPST, Bibbins-Domingo K, Grossman DC *et al.* Screening for Skin Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016; **316**: 429-35.

36 Choudhury K, Volkmer B, Greinert R *et al.* Effectiveness of skin cancer screening programmes. *Br J Dermatol* 2012; **167 Suppl 2**: 94-8.

37 Stang A, Jockel KH, Heidinger O. Skin cancer rates in North Rhine-Westphalia, Germany before and after the introduction of the nationwide skin cancer screening program (2000-2015). *Eur J Epidemiol* 2018; **33**: 303-12.

38 Gordon LG, Brynes J, Baade PD *et al.* Cost-Effectiveness Analysis of a Skin Awareness Intervention for Early Detection of Skin Cancer Targeting Men Older Than 50 Years. *Value Health* 2017; **20**: 593-601.

39 Rose G. Strategy of prevention: lessons from cardiovascular disease. *Br Med J (Clin Res Ed)* 1981; **282**: 1847-51.

40 van Rijsingen MC, van Bon B, van der Wilt GJ *et al.* The current and future role of general practitioners in skin cancer care: an assessment of 268 general practitioners. *Br J Dermatol* 2014; **170**: 1366-8.

41 Beecher SM, Keogh C, Healy C. Dedicated general practitioner education sessions can improve diagnostic capabilities and may have a positive effect on referral patterns for common skin lesions. *Ir J Med Sci* 2018.

42 Ahmadi K, Prickaerts E, Smeets JGE *et al*. Current approach of skin lesions suspected of malignancy in general practice in the Netherlands: a quantitative overview. *J Eur Acad Dermatol Venereol* 2018; **32**: 236-41.

43 van Rijsingen MC, Vossen R, van Huystee BE *et al*. Skin tumour surgery in primary care: do general practitioners need to improve their surgical skills? *Dermatology* 2015; **230**: 318-23.

44 Whiteman DC, Thompson BS, Thrift AP *et al*. A Model to Predict the Risk of Keratinocyte Carcinomas. *J Invest Dermatol* 2016; **136**: 1247-54.