# Cohort studies (and skin cancer) never come alone

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## ABSTRACT

A previous keratinocyte carcinoma is probably the strongest predictor of developing new keratinocyte carcinomas, which makes these patients an interesting population for prevention interventions. Investing in large cohort studies and consortia might increase the validity of observational findings and should stimulate scientists to investigate the underlying mechanisms in detail.

It is well known that the risk of a subsequent cutaneous malignancy is increased in patients with a previous keratinocyte carcinoma (KC). A recent meta-analysis showed that 29% of patients with a history of basal cell carcinoma (BCC) developed a subsequent BCC and 4% a subsequent squamous cell carcinoma (SCC), whereas 13% of patients with a history of SCC developed a subsequent SCC and 16% a subsequent BCC (Flohil *et al.,* 2013). The majority of studies on multiple cutaneous malignancies calculated risks of a subsequent or second primary skin cancer but did not calculate risks of additional skin cancers. In this issue, Adèle Green's research group selected a cohort of 1,191 white-skinned Australian residents from their Nambour skin cancer prevention trial, without KC, before or at the start of this trial, to determine the proportion who developed a BCC exclusively, SCC, or both (Keim *et al.,* 2014). The original cohort consisted of 1,621 residents of the subtropical city Nambour, who were selected at random in 1986, and therefore the cohort reflects a general population sample from Australia followed prospectively between 1992 and 2007. Besides the type of skin cancer, the investigators also assessed anatomic site distributions and other clinical features such as pigmentary characteristics and signs of actinic damage. This study demonstrated that about 21% of the study population developed a first KC and 47% of this group developed at least a second KC. The majority of this latter group developed exclusively BCCs (56%), 28% developed both, 16% developed SCCs exclusively, with age as the most important predictor of increasing incidence rates (Keim *et al.,* 2014). Participants who developed SCC exclusively were the most distinct group, because they had significantly higher prevalences of easily sunburned skin, propensity to tan without burning, and freckling of the back than did the BCC only and mixed groups. The skin, eye, and hair color characteristics showed no significant differences among the three groups. In those with BCCs exclusively or both BCC and SCC, the head and neck area were the predominant sites of development, whereas in the SCC only group the limbs were the predominant sites of development. These differences may be the result of differences in UVR exposure or genetic susceptibilities, and they suggest different tumor biologies.

Major strengths of this study are 16 years of follow-up, a clear case definition (i.e., histopathologically confirmed tumors), full-body skin examinations, and detailed information on clinical features. However, the main limitation lies in the small sample of patients with multiple cutaneous malignancies, especially the group who developed SCCs exclusively ($n$ = 28). Small sample sizes result in wide confidence intervals and a possible type II error (i.e., no power calculation shown). Although the cohort was followed for 16 years, the study population was young (mean age 46 years) at enrollment, suggesting that the majority of the patients had not yet reached the age in which the incidence of cutaneous malignancy is highest.

## ACTINIC NEOPLASIA SYNDROME

Martin Weinstock coined the term ''actinic neoplasia syndrome'' to emphasize that cutaneous (pre-)malignancies are not a single event but often reflect a field dysplasia from which patients suffer chronically (Weinstock *et al.,* 2009). After the 1992 landmark study on this subject (Karagas *et al.,* 1992), many observational studies of different populations demonstrated that almost half of patients with cutaneous malignancy will develop at least a second KC, and even more will show other signs of chronic actinic skin damage (e.g., actinic keratosis, solar elastosis) due to the relatively high levels of acute, intermittent, and/or cumulative UVR exposure during their lives. Therefore, a previous cutaneous malignancy is probably the strongest predictor of developing subsequent malignancies, making this an interesting population for studies of prevention intervention. One might argue that the occurrence of multiple malignancies might pose a greater problem to both patients and health-care systems compared with disease progression or recurrence.

The benefits of primary prevention programs should become evident only after decades (Staples *et al.,* 1998). Even though people become more and more aware of the harmful effects of UVR, they do not seem to change their attitude toward it (i.e., knowledge–behavior gap; Ma *et al.,* 2007). For now, it seems that primary prevention is not meeting its expectations, as the incidence of skin cancer continues to increase worldwide, with the possible exception of Australia, which has a highly active public education campaign (Lomas *et al.,* 2012). As primary prevention falls short, secondary prevention offers a good alternative strategy. This prevention method will be most successful when high-risk populations are defined and screening strategies for specific patient groups constructed. Well-calibrated, discriminating, and validated prediction models could provide physicians with a tool to find high-risk patients, such as patients with histories of skin cancer, and give them appropriate right follow-up and tailored instructions. If there indeed exists a type-specific skin cancer susceptibility, as suggested by Keim *et al.* (2014), different prediction models should be developed, combining environmental, phenotypic, and genotypic risk factors. However, there also exists a significant group of patients who develop both BCCs and SCCs, which is not surprising, as they share many risk factors (Figure 1). Although the risk factor profiles of the different cutaneous (pre-)malignancies are well documented, the extent to which these risk factors are applicable to subsequent tumors is not certain. On the basis of Rothman's sufficient- component cause model, it could be argued that the contribution of the conventional risk factors for a first event is not applicable to subsequent events, defined as the index event bias (Dahabreh and Kent, 2011). In recent decades, huge steps have been made in understanding the genetic predisposition (germline and somatic mutations) for BCC and to a lesser extent for SCC and actinic keratosis.

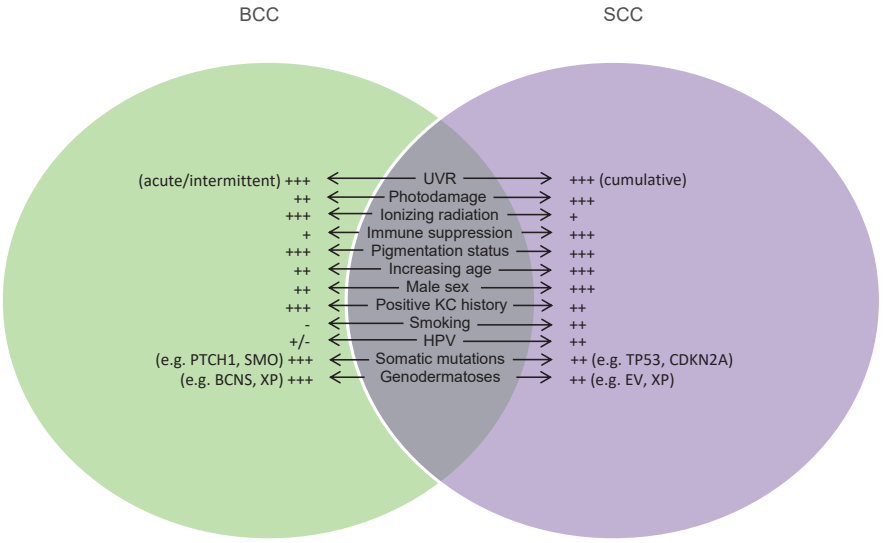


**Figure 1.** Risk factor profiles of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) UVR, ultraviolet radiation; HPV, human papilloma virus; BCNS, basal cell nevus syndrome; EV, epidermodysplasia verruciformis; XP, xeroderma pigmentosum.

However, our genetic understanding of these very common keratinocyte malignancies lags behind melanoma. Except for a few candidate gene studies and a genome-wide association study, no studies have investigated the common or rare genetic variants found in patients with multiple keratinocyte malignancies. There is hope, because an international consortium has been established to explore the genetics of patients with multiple skin cancers and to develop prediction models that include genetic variation.

## PROSPECTIVE FOLLOW-UP STUDIES

As dermato-epidemiologists, we noticed another important element in this study (Keim *et al.,* 2014), which is the enormous return on investment seen in this prospective Nambour skin cancer study. Clinical epidemiology includes experimental and observational research that might aid our understanding of diseases through a quantitative approach of clinical problems. The Nambour skin cancer trial started as an experimental study (a randomized field trial) but extended its follow-up as a prospective cohort study. The advantages of that type of design are the possibility of calculating risk measures (absolute and relative risk) and a relatively low risk of bias compared with other observational designs. The classical argument against cohort studies is that they are too expensive, but large (population-based) prospective cohort studies such as the

Nambour Skin Cancer Study, the Rotterdam Study, Nurses' Health Study, the Health Professionals Follow-up Study, and the PUVA Follow-up Study have a tremendous scientific return on investment in many diseases, including skin cancer (Nan *et al.,* 2011; Stern and Study PF-U, 2012; Hofman *et al.,* 2013; Keim *et al.,* 2014). We are strong advocates of investing in well-designed and large cohort studies (including drug or disease specific registries), but at the same time we encourage investigators to form a consortia to increase sample size and to replicate each other's findings. Collaborative efforts increase the validity of the observational findings and should stimulate laboratory scientists even more strongly to investigate the underlying mechanisms in detail.

In conclusion, good research raises more questions than it answers, and it lifts the bar for scientific progress.

## REFERENCES

Dahabreh IJ, Kent DM (2011) Index event bias as an explanation for the paradoxes of recurrence risk research. JAMA 305:822–3

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

Hofman A, Darwish Murad S, van Duijn CM et al. (2013) The Rotterdam Study: 2014 objectives and design update. Eur J Epidemiol 28: 889–926

Karagas MR, Stukel TA, Greenberg ER et al. (1992) 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 267: 3305–10

Keim U, van der Pols JC, Williams GM et al. (2014) Exclusive development of a single type of keratinocyte skin cancer: evidence from an Australian population-based cohort study. J Invest Dermatol 135:728–33

Lomas A, Leonardi-Bee J, Bath-Hextall F (2012) A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 166:1069–80

Ma F, Collado-Mesa F, Hu S et al. (2007) Skin cancer awareness and sun protection behaviors in white Hispanic and white non-Hispanic high school students in Miami, Florida. Arch Dermatol 143:983–8

Nan H, Xu M, Kraft P et al. (2011) Genome-wide association study identifies novel alleles associated with risk of cutaneous basal cell carcinoma and squamous cell carcinoma. Hum Mol Genet 20:3718–24

Staples M, Marks R, Giles G (1998) Trends in the incidence of non-melanocytic skin cancer (NMSC) treated in Australia 1985-1995: are primary prevention programs starting to have an effect? Int J Cancer 78: 144–8

Stern RS Study PF-U (2012) 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 66:553–62

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