Hollestein, L., Weinstock, M., Le Roux, E., & Olsen, C. (2017). More than many: how to manage the most frequent cancer? *Journal of Investigative Dermatology*, *137*(9), 1823-1826. https://doi.org/10.1016/j.jid.2017.06.017

More than many: how to manage the most frequent cancer?

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Abstract: 58 (60)
Word count: 2030 (1000-2000)
References: 19 (10)
Figures: 1

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Bullet points clinical relevance/pullquote (12 words):
Multiple prevention and health care strategies are needed to manage Keratinocyte Cancer.

Abstract:
Leiter et al. report on the increasing incidence of Keratinocyte Cancers (KC) in Germany. The true population burden is even larger then reported, as many of these new patients will develop multiple KC. KC puts a large burden on health care systems worldwide. Prevention and management strategies are needed to maintain high quality of care for all patients.

More than Many

In this issue of the JID, Leiter et al report on Non Melanoma Skin Cancer (NMSC) incidence and mortality trends and projections in two regions in Germany(Leiter *et al.*, 2017). Histological subtype was not routinely gathered by the included cancer registries and therefore it was not possible to distinguish between basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) and other rare types of skin cancer. We prefer to use the term Keratinocyte Cancer (KC) to refer to BCC and SCC. The authors showed continuously increasing incidence rates since 1970 without evidence of any levelling off. Age-standardised incidence rates have increased 10 fold since 1970 and are expected to double up to by the year 2030, with rates above 200 patients per 100,000 person-years. The age-standardized rates were standardized to the 1976 European standard population, but the proportion of elderly in the 1976 European standard population is much smaller than the true proportion of elderly in the German population. This leads to a misinterpretation of the true KC burden, because elderly have the highest incidence rates of KC. Therefore, the authors presented crude rates, but for aforementioned reason the European standard population was updated in 2013 and includes a larger proportion of elderly. The authors report on the number of new patients, while the number of new tumors is much larger, because patients often develop multiple tumors over time. It has been estimated that 50% of all patients with KC will develop at least one KC (Wehner *et al.*, 2015). As in many other cancer registries worldwide, in Germany only the first KC is registered. Thus, these high incidence rates only represent part of the population burden of KC. Each subsequent KC will develop more rapidly after the previous one (Wehner *et al.*, 2015). Although it is not feasible to register all KC due to limited resources of cancer registries, accurate information on KC incidence is imperative in order to inform stakeholders, such as health care policy makers, and to plan for future health care needs. Possibilities of estimating the total burden include the use of administrative health care claims data for KC surgeries, linkages to hospital records or pathology data or register all KC in a subsample of the total population (Chan *et al.*, 2016).

Burden of KC on the health care systems

The diagnosis and treatment of KC imposes a high burden on healthcare systems, and collectively, they are among the most costly cancers (Housman *et al.*, 2003). Furthermore, the increasing use of more costly treatments, such as Mohs surgery and photodynamic therapy is contributing to rising treatment costs. Overuse of these treatments leads to unnecessary high costs. In the context of 'choosing wisely' campaigns the AAD recommended not to treat uncomplicated small KC on the trunk and extremities with Mohs surgery and developed appropriate use criteria. In the Netherlands, reimbursement for PDT was restricted since it was shown that inexpensive treatments such as topical 5-FU and imiquimod are non-inferior or even superior for superficial BCC (Arits *et al.*, 2013). The choosing wisely campaign initiated the discussion on providing health care which is truly necessary, in order to maintain good access to health care in the future with an increasing KC burden, due to aging populations and increases in incidence rates. Evidence-based interventions on primary, secondary and tertiary prevention levels are needed (Figure 1).

Primary Prevention: Ultraviolet (UV) behavior

The authors note that despite skin cancer prevention campaigns behaviors in relation to UV exposure have not yet changed in Germany, nor has the introduction been reflected in decreased incidence rates. Since 1989, the German Society of Dermatology and the Association of Dermatological Prevention initiated primary prevention campaigns in Germany. In 2009, the SunPass-Healthy Skin was initiated in order to promote UV protection of children at daycare centres. Therefore, it is possible that it is too early to determine if the German prevention campaigns have been successful in

reducing incidence of KC. Skin cancer has a long latency time, and the overall effect may not be apparent yet for this population. If there is an effect of public health campaigns, then this would be firstly observed among young people. The authors did not specifically examine the incidence rates by age. An analysis of KC treatment rates in Australia suggest that incidence rates among younger Australians are beginning to decline, possibly as result of public health campaigns that were implemented from the 1970s (Olsen *et al.*, 2014). Results from the Nambour Skin Cancer Prevention Trial showed that regular use of sunscreen use is a cost-effective way of skin cancer control in Australia: During 5 years follow-up among 812 residents, 11 BCCs, 24 SCC and >800 AK were prevented (Gordon *et al.*, 2009). It is estimated that sunscreen use is likely to be cost-effective over a long period of time. Two European trials among young students observed longer durations of sunbathing associated with sunscreen use (Autier *et al.*, 2007). People who use sunscreen during intentional UV-exposure are able to spend longer periods of time in the sun without burning and thus for a subgroup of the population, sunscreen use may not result in reduced UV-exposure. However, most cumulative UV-exposure is probably gained through non-intentional exposure during outdoor activities, such as gardening, cycling or walking. Other trials among children and adults showed no increase of exposure time with sunscreen use (Autier *et al.*, 2007; Bauer *et al.*, 2005; Gallagher *et al.*, 2000; Green *et al.*, 1999). Therefore, public health campaigns should focus on reducing non-intentional exposure by regular sunscreen use and other protection measures, such as avoiding being outdoors when UV levels are highest, seeking shade and wearing sun protective clothing and hats when outside. Although there is no evidence from RCTs that these other sun protection measures prevent KCs, they have been shown to reduce the prevalence of sunburn in the Australian population.

Secondary Prevention: to screen or not to screen?

The authors report that, contrary to incidence rates, mortality rates are decreasing. This decrease in mortality rates suggest that treatment and early detection has been crucial. In 2003 a pilot skin cancer screening program (i.e. the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN)) was conducted. General Practitioners (GPs) and dermatologists were trained and performed screening in a 2-step manner: (1) the first whole body examination was performed by a GP, internal medicine physician or dermatologist and (2), if applicable, suspicious lesions were referred to a dermatologist. Possible positive results on melanoma mortality led to nationwide reimbursement of bi-annual skin cancer examinations by health insurance companies from 2008 onwards.

It's debatable, whether early detection of BCCs is cost-effective. Authors of a recent systematic review reported that size of BCC is one of the major determinants of associated health care costs and therefore they argued for early detection of BCC (Hoorens *et al.*, 2016). However, BCC are slow-growing tumors and large BCC are rare. Therefore there is also a risk of overdiagnosis (i.e. treating a BCC, which would not have progessed during a patient' life). Treating a low-risk BCC among frail older people may cause more harm than benefits.

The authors did not have data on immunosuppressive drug use or solid organ transplantations. Solid organ transplant recipients are up to 80 times more likely to develop a KC. Moreover, these tumors develop more rapidly and are more likely to be aggressive. In this high-risk group, screening for KC is beneficial.

Tertiary prevention: Follow-up and chemoprevention of KC

Reasons for follow up include: detection of metastasis, recurrences or new tumors. There is a subset of KC patients who never develop a second BCC or SCC during their lifetime (Wehner *et al.*, 2015).

Thus, follow-up may not be indicated for all patients. Yet, it is difficult to predict which patients will develop a subsequent KC in the future. A clinical prediction model to predict the absolute risk for a second KC could be used to guide decisions on tailored follow-up. Recently a prediction model to predict the absolute risk on a second BCC has been developed, but this model needs external validation (Verkouteren *et al.*, 2015).
According to the German guidelines, instruction for self-examination and an annual follow-up is recommended for 3 years for each patient with BCC and possibly life-long for high-risk tumors or patients. However, the benefit of early detection of BCC, because they are slow-growing and rarely metastasize, is the subject of considerable debate. Therefore, in other countries, such as Australia, no specific follow-up scheme is recommended for histologically cleared low-risk tumors. In the UK guidelines state that follow-up can also be performed by a specialized trained nurse or primary care physician.
A strategy to prevent the development of new tumors is the use of chemoprevention. Among high risk groups, such as organ transplant recipients and patients with multiple KC it is more likely that the benefits outweigh the potential harms of medication use. A RCT of nicotinamide use among patients with at least 2 KC showed a decrease of 23% in incidence of subsequent KC after 1 year. Another candidate is a single course of 5-FU, which resulted in a decrease in surgery for SCC during 1 year follow-up among patients with at least 2 KC (Weinstock *et al.*).

Role of the GP in the management of KC

The authors also argue that GPs should play a larger role in the management of KC and that they should receive training for this task. The latter is of pivotal importance. This starts with sufficient training in the curriculum of undergraduates in medical school, which should be followed by substantial postgraduate training in the GP training program and sufficient opportunities to assess diagnostics and management skills in clinical practice. Currently, dermatology is not specifically required in the training program of GPs in Germany and other European countries. A high quality of care is a prerequisite for substitution of hospital care by the GP. GPs must be provided sufficient education, time and resources in order to manage KC.
In Australia the GP has a larger role in skin cancer compared to most European countries and the US. In the past two decades has seen the emergence of skin cancer clinics staffed by GPs, particularly in Queensland, the state with the highest incidence of KC and melanoma. General practitioners can specialize in “skin cancer medicine”, and receive extra training and accreditation. GPs play a pivotal role in the early detection, diagnosis and management of many skin cancers, especially in rural areas (Askew *et al.*, 2007).
In the UK, services for the management of low-risk BCCs can be commissioned from accredited GPs with specialist dermatology training who participate in regular histological accuracy audit (Cancer, 2006). UK guidelines on KC also recommend self-examination or follow-up in primary care for primary adequately treated BCCs (Telfer *et al.*, 2008). Patients with chronic immunosuppression, genetic conditions, or incompletely excised BCCs, will be followed up in secondary care. GPs have no primary management role in treating SCCs in the UK, with all suspected lesions referred urgently to secondary care. Currently there remains limited dermatology training for GPs in the UK at both undergraduate and postgraduate levels (Schofield *et al.*, 2009; Yaakub *et al.*, 2016).
Management of KC by GPs may decrease the workload for dermatologists, but also has advantages for patients. Patients may not need to attend hospital clinics but rather be treated by the physician they are familiar with. In addition, if quality of care in primary care is sufficiently high, costs for the health care system and possible out of the pocket costs for patients of the GP are generally lower compared to a medical specialist.

Conclusion

In order to manage KC in the future, prevention on different levels is needed. We argue that the majority of KCs in the general population are detected early enough and therefore secondary prevention strategies (i.e. screening) on a population level for KC may not be cost-effective. Long-term experience and data from Australia suggests that it takes decades to measure the effect of primary prevention campaigns. Incidence rates among young people plateaued around the year 2000, and have declined since that time, while primary prevention campaigns started in the 1970s. As overall incidence rates in Germany and many countries are still increasing, tertiary prevention strategies are needed to manage the current and future KC burden. Strategies include tailored follow-up and chemoprevention. Management of KC in primary care is a possibility, but sufficient education, time and resources are pivotal. Some strategies may be generalizable, while others are country-specific and depend on health care system factors. Yet, the KC epidemic is universal and calls for for empirical evidence of cost-effective management strategies into the future. Cancer registries fulfill an important role to monitor current and future efforts being made.

Figure 1: Three levels of prevention of keratinocyte cancer

Acknowledgements

We thank Dr. Elisabeth Livingstone for her advice on this commentary.

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