Keratinocyte carcinoma in Iceland

Epidemiology and risk in association with medication

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Thesis for the degree of Philosophiae Doctor

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Keratinocyte krabbamein á Íslandi

Faraldsfræði og lyfjanotkun

Jónas A. Aðalsteinsson

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Ágrip

Vitað er að mikil aukning hefur verið á grunnfrumu og flöguþekjumeinum í húð síðustu ár í vestrænum löndum en ekki er alveg skýrt hvers vegna svo er. Helstu áhættuþættir þessara meina eru ljós húð og útfjólublá geislun, og einnig hafa sum lyf verið bendluð við aukina áhættu með því að valda ónæmisbælingu eða auknu næmi fyrir útfjólublárri geislun í húð. Ekki er mikið til af rannsóknum sem skoða faraldsfræði og áhættuþætti þessara húðmeina, og það er óljóst hvort sum þessara lyfja sem auka þessa áhættu myndu gera það á Íslandi þar sem er lítil útfjólublá geislun miðað við flest önnur lönd. Helstu markmið þessarar rannsóknarar var að athuga sérstaklega tíðni þessara meina á Íslandi og einnig skoða hvaða áhrif ákveðin lyf gætu verið að hafa á áhættu íslendinga að fá þessi mein. Við skoðuðum sérstaklega hydrochlorothiazide (HCTZ), TNF-alpha hindra og statín, sem hafa í sumum rannsóknum verið bendluð við aukna áhættu á húðmeinum. Einnig þá skoðuðum við hugsanleg tengsl metformin við húðmein, en metformin hefur sýnt að lækki áhættu á krabbameinum í sumum rannsóknum. Gagnagrunnur hjá krabbameinsskrá var notaður til þess að reikna tíðnitölur, og var lyfjagrunnur landlæknisembættis notaður til þess að skoða tengsl við lyf. Niðurstöður okkar sýndu að þrátt fyrir það að útfjólublá geislun á Íslandi sé lág hefur tíðni grunn- og flöguþekjumeina aukist til muna, og Ísland er eina landið þar sem að tíðni grunnfrumumeins og grunns flöguþekjumeins er hærra í konum heldur en körlum. Þetta kann að skýrast af því konur virðast vera líklegri til þess að nota ljósabekki og stunda sólböð þegar þær eru erlendis heldur en karlmenn. Karlmenn vinna oftar úti heldur en konur en erlendis þá eru þeir því í hárri áhættu að fá húðkrabbamein vegna mikillrar geislunar. Á Íslandi er þessi geislun heldur minni. Einnig sáum við að þessi aukning á húðmeinum er mest á búk og fótleggjum kvenna, sem bendir enn frekar til ljósabekkja eða sólarlandafera sem orsök. Varðandi lyf, þá var HCTZ tengt við aukna áhættu á bæði grunn- og flöguþekjuæxlum. HCTZ eykur næmi fyrir útfjólubláum geislum og því var ekki endilega viðbúist að lyfið auki áhættu í landi með svo litla bakgrunns geislun. TNF-alpha hindrar og statín voru bæði tengt við aukna áhættu á flöguþekjumeinum, en ekki grunnfrumukrabbameini. Læknar sem skrifa út þessi lyf þurfa að vera meðvitaðir um þessa tengingu. Metformín var tengt við lægri áhættu á grunnfrumukrabbameini en ekki flöguþekjukrabbameini, en þörf er á frekari rannsóknum til þess að staðfesta þessa tengingu.

Lykilorð:

Flöguþekjukrabbamein, grunnfrumukrabbamein, faraldsfræði, lyf, áhættuþættir

Abstract

An epidemic of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) has led to a significant healthcare burden in white populations. The incidence of both cancers is on the rise, the reasons for which are unclear. While the principal risk factors for these cancers are fair skin and ultraviolet radiation (UVR) exposure, certain medications have also been implicated in increased skin cancer risk through immunosuppression, immunomodulation, or UVR sensitization. Whole population studies assessing the epidemiology of and risk factors for BCC and SCC are lacking, and it is unclear whether medications significantly increase the risk of BCC and SCC development in the low UV radiation environment that Iceland provides. The primary objective of this study was to establish incidence rates and tumor burden in an unselected, geographically isolated population that is exposed to low levels of UVR. The secondary objective was to delineate the relationship between SCC/BCC and hydrochlorothiazide (HCTZ), TNF-alpha inhibitors (TNFi), and statins. These medications have, in some studies, been associated with increased risk of BCC and SCC development through UV sensitization, immunosuppression, and immunomodulation, respectively. Lastly, the relationship between metformin, which has been shown in some studies to decrease cancer risk, and BCC and SCC development was investigated.

To accomplish our goals, we undertook a whole-population study based on the Icelandic cancer registry. We assessed incidence according to age, residence, and multiplicity and assessed trends using joinpoint analysis. Age-standardized (World) and age-specific incidence rates were calculated along with cumulative and lifetime risks. To assess the relationship between medication and skin cancer, we used a population-based case-control study design. The group of cases consisted of all individuals diagnosed for the first time with SCCis, invasive SCC, and BCC of the skin. For each case, ten unaffected population controls, matched by year of birth and sex, were randomly selected from the National Register of Iceland. We employed conditional logistic regression analysis to calculate multivariate odds ratios (ORs).

During the study period, the incidence for all subtypes of KC increased, despite Iceland's low background UVR. This increase was most prominent in women on sites not generally exposed to UV radiation in Iceland: the trunk and

legs. Joinpoint analysis showed the fastest increase in SCCis incidence to be in women. Women with SCCis also had a higher likelihood of developing new lesions than men, with a multiplicity of 1.71. Men are more likely than women to develop invasive SCCs, which occur almost exclusively in the head and neck. Lip SCCs were much more likely to be invasive than in situ. HCTZ was associated with all subtypes of KC. TNFis and statins were associated with SCC but not BCC.

Cutaneous KC is becoming a significant public health problem worldwide. Iceland is the only reported population, to our knowledge, in which the incidence of BCC and SCCis is significantly higher in women than in men. While in most countries, men have a higher incidence of BCC and SCC, Iceland's low UV radiation environment might protect men, as women may be more likely to engage in high-risk tanning behaviors. Despite the low background UV radiation in Iceland, high cumulative exposure to the UV sensitizing medication HCTZ was associated with the development of BCC, SCCis, and invasive SCC, suggesting that sun-protective behaviors alone may not eliminate the carcinogenic potential of HCTZ in high UV countries. TNFis and statins increased individual risk for SCC, but not BCC, a phenomenon also seen in organ transplant recipients and patients on immunosuppressive medications such as cyclosporine. These associations require further study. Public health efforts (focusing on the potentially harmful effects of UVR) and physician education will be essential to counteract the increasing skin cancer incidence in Iceland as its population ages. Since metformin use was associated with decreased BCC development, it is possible that metformin might be a reasonable option for patients at high risk for developing BCC, or used to slow the rate of BCC development in patients with multiple skin cancers. This requires further study using prospective design models.

Keywords:

Squamous cell carcinoma, basal cell carcinoma, epidemiology, medication, risk factors

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Contents

List of abbreviations

BCC: Basal cell carcinoma

SCC: Squamous cell carcinoma

KC: Keratinocyte carcinoma

ICR: Icelandic Cancer Registry

NMSC: Non-melanoma skin cancer

SMO: Smoothened

UVR: Ultraviolet radiation

SCCis: Squamous cell carcinoma in-situ

ICR: Icelandic cancer registry

APC: Antigen-presenting cell

PUVA: Psoralen UVA

nbUVB: Narrow-band UVB

HTCZ: Hydrochlorothiazide

CNI: Calcineurin inhibitor

CsA: Cyclosporine

TNFi: TNF α inhibitor

NSAID: Non-steroidal anti-inflammatory drugs

ASR: Age-standardized rates

APC: Annual percentage change

DDU: Daily dose units

IQR: Interquartile range

OR: Odds ratio

CI: Confidence interval

UPF: Ultraviolet protection factor

SPF: Sun protection factor

FDA: Food and drug administration

Shh: Sonic hedgehog

List of figures

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List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-VI):

I. Adalsteinsson, J.A., Ratner, D., Olafsdottir, E., Grant-Kels, J., Ungar, J., Silverberg, J.I., Kristjansson, A.K., Jonasson J.G., Tryggvadottir, L. Basal cell carcinoma: an emerging epidemic in women in Iceland. Br J Dermatology. February 2020. DOI: 10.111/bjd.18937.

II. Adalsteinsson, J.A., Olafsdottir, E., Ratner, D., Feng, H., J., Ungar, J., Silverberg, J.I., Kristjansson, A.K., Jonasson J.G., Tryggvadottir, L. Invasive and in situ squamous cell carcinoma of the skin: a nationwide study in Iceland. Br J Dermatology. February 2021. DOI: 10.1111/bjd.19879.

III. Adalsteinsson, J.A., Muzumdar S., Waldman, R., Hu, C., Wu, R., Ratner, D., Ungar, J., Silverberg, J.I., Olafsdottir, G., Kristjansson, A.K., Tryggvadottir, L., Jonasson J.G. Association between hydrochlorothiazide and the Risk of In-Situ and Invasive Squamous Cell Skin Carcinoma and Basal Cell Carcinoma: A Population-Based Case-Control Study. Journal of the American Association of Dermatology. March 2021. DOI: 10.1016/j.jaad.2020.08.025.

IV. Adalsteinsson, J.A., Muzumdar S., Waldman, R., Hu, C., Wu, R., Ratner, D., Feng, H., Ungar, J., Silverberg, J.I., Olafsdottir, G., Kristjansson, A.K., Tryggvadottir, L., Jonasson J.G. Statins are associated with increased risk of squamous cell carcinoma of the skin: a whole-population study from Iceland. Arch Dermatol Res. March 2021. DOI: 10.1007/s00403-021-02227-w

V. Adalsteinsson, J.A., Muzumdar S., Waldman, R., Hu, C., Wu, R., Ratner, D., Ungar, J., Silverberg, J.I., Olafsdottir, G., Kristjansson, A.K., Tryggvadottir, L., Jonasson J.G. Anti-Tumor Necrosis Factor Therapy is Associated with Increased In-Situ Squamous Cell Carcinoma of the Skin: A Population-Based Case-Control Study. Journal of the American Association of Dermatology. June 2021. DOI: 10.1016/j.jaad.2020.11.029.

VI. Adalsteinsson, J.A., Muzumdar S., Waldman, R., Hu, C., Wu, R., Ratner, D., Feng, H., Ungar, J., Silverberg, J.I., Olafsdottir, G., Kristjansson, A.K., Tryggvadottir, L., Jonasson J.G. Metformin is associated with decreased risk of basal cell carcinoma: A whole-population case-control study from Iceland. Journal of the American Association of Dermatology. February 2021. DOI: 10.1016/j.jaad.2021.02.042.

Declaration of contribution

- The doctoral student, Jónas Aðalsteinsson (JA), planned the structure and design for all studies in co-operation with Jón Gunnlaugur Jónasson (JGJ), Laufey Tryggvadóttir (LT), and Desirée Ratner. JA prepared and submitted all necessary study approvals with assistance from JGJ and LT. JA planned the statistical analysis for studies I and II with assistance from LT and Elínborg Ólafsdóttir. JA planned the statistical analysis for studies III-V with assistance from LT, Guðríður Ólafsdóttir, Chaoran Hu and Rong Wu. JA analyzed the data from all studies, drafted the papers and conclusions, submitted the papers for review and acted as the corresponding author for all papers. JA completed critical revisions for all papers alongside the doctoral committee and other co-authors. Finally, JA wrote the thesis under guidance from his doctoral committee.

1 Introduction

Keratinocytes comprise the majority of the cells in the top layer of the skin or the epidermis. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin are both cancers of keratinocytes. They together form a category of tumors known as keratinocyte carcinoma (KC) (M. R. Albert & Weinstock, 2003). These are more often referred to as non-melanoma skin cancer (NMSC), although this term is not as accurate, as NMSC can also refer to other skin cancers such as Merkel cell carcinoma or adnexal tumors (Eisemann, 2016). KC is the most common cancer in Caucasian populations, whose associated healthcare costs have increased significantly in recent years (Michael R Albert & Weinstock, 2003; Cameron et al., 2018; Joseph et al., 2001). The major risk factors for KC are fair skin and ultraviolet radiation (UVR) exposure (Didona, 2018). However, certain medications have also been implicated in increased skin cancer risk through immunosuppression (Dreyer et al., 2013), immunomodulation (Yang et al., 2017a), or UVR sensitization (Shin et al., 2019).

Iceland provides a unique environment in which to study KC epidemiology and risk factors as its population is homogeneous (Helgason et al., 2003; Vidarsdottir et al., 2008), and Reykjavik, Iceland's capital, is the northernmost capital in the world with low levels of daily ambient UVR; (Hery et al., 2010). Many national cancer registries have limitations when it comes to KC registration. First, BCCs are often not documented, and squamous cell carcinoma in situ (SCCis) is in most cases lumped together with invasive SCC (Lomas, 2012a). This is not the case in the Icelandic Cancer Registry (ICR), which provides histologic verification of all KCs diagnosed in Iceland since 1981 with separate classifications for BCC, SCCis, and invasive SCC (Sigurdardottir et al., 2012). The ICR can be linked to The Icelandic Prescription Medicine Register, a population-based registry that records all outpatient prescriptions (*The Icelandic Directorate of Health Web Site, Https://Www.Landlaeknir.Is/English*, 2020).

The incidence of KC in Caucasian populations is on the rise worldwide. However, there are apparent epidemiologic differences between BCC and SCC that can be detected when analyzed separately. Many studies lump these tumors together in their analysis, which is suboptimal, considering the differences in their pathogenesis and biological behaviors (Lomas, 2012a).

1.1 KC pathogenesis, genetics, and mortality

1.1.1 BCC

BCC pathogenesis is thought to start with UVA and UVB radiation exposure, whose effects are most prominent in Fitzpatrick types I and II skin, combined with certain genetic predispositions. UV exposure generates cyclobutane pyrimidine dimers, which in turn inhibit the function of the tumor suppressor gene *TP53* within keratinocytes (Montagna & Lopes, 2017). Sporadic mutations in the PTCH receptor within the Hedgehog (Hh) pathway are also important to BCC pathogenesis. Mutations in this receptor lead to dysregulation of smoothened (SMO) with subsequently increased transcription of GLI genes, leading to cellular growth (Gailani et al., 1996). Of note, an autosomal dominant mutation in PTCH leads to Gorlin syndrome, which is characterized by multiple BCCs and other cancers such as medulloblastoma. Other syndromes that increase BCC risk include Rombo syndrome and Bazex-Dupré-Christol syndrome (Nikolaou, 2012). Vismodegib is a recently developed targeted therapy that inhibits SMO, allowing it to function as an "artificial PTCH" (Montagna & Lopes, 2017). In addition, loss of function in germline *PTPN14* has recently been described as a high risk for BCC pathogenesis in the Icelandic population (O. T et al., 2021). BCC has also been attributed to single-nucleotide polymorphisms (SNPs) in pigment genes such as *MC1R* and *EXOC2* (Nan, 2011). The *TYR, MC1R*, and *OCA* pigment genes have also been strongly associated with fair skin type and increased risk of KC, especially in patients with the red hair phenotype (Box et al., 2001; Nan, 2009; Tagliabue et al., 2015). While BCCs can be locally destructive, they rarely metastasize, with reported metastatic rates ranging from 0.0025% to 0.55% of cases (McCusker et al., 2014). BCC is associated with low mortality, and it has even been shown that BCC might be associated with a survival advantage, possibly linked to health-promoting factors such as changes to a healthier lifestyle or diagnosis in wealthier populations (Eisemann, 2016).

1.1.2 SCC

Similar to BCC pathogenesis, UVR exposure and skin type play a significant role in SCC pathogenesis via the formation of cyclodipyrimidine dimers within keratinocyte DNA. Having a sun-sensitive phenotype is a well-established risk factor for SCC (DR et al., 1998; F & B, 1985; Grodstein, 1995). Acquired mutations within SCCs have a major role in its pathogenesis such as *TP53, NOTCH*, *CDKN2A*, and *PI3K/AKT* (Yilmaz et al., 2017). Although these two different tumors have many distinguishing features, they also have genetic similarities. As in BCC, variations in genes associated with pigmentary

characteristics are also strongly associated with SCC risk, including *MC1R* (Box et al., 2001; Tagliabue et al., 2015), tyrosinase (*TYR*) (Nan, 2009), and interferon regulatory factor 4 (Han et al., 2011). Similar loci have been identified as important in both SCC and BCC formation, such as 6p25 (near *EXOC2*) and 13q32 (near *UBAC2*) (Nan, 2011). Other more recently identified susceptibility loci include 16q24.3 (intronic in the DEF8 pigmentation trait gene), 11q23.3, 2p22.3; 7p21.1 and 9q34.3 (Chahal et al., 2016; S. J. Siiskonen et al., 2016). Furthermore, a stop-gain mutation in the *BRCA2* gene, *BRCA2* K3326*, has been shown to increase risk of SCC (R. T et al., 2018) SCCs are associated with multiple genetic syndromes such as xeroderma pigmentosum, with its associated mutations caused by erroneous DNA repair of pyrimidine dimers (*XPA-XPg* and *XPV* genes); Ferguson-Smith syndrome, where a mutation occurs in *TGFBR1*, impairing its function as a tumor suppressor; oculocutaneous albinism, which has a mutation in the melanin production pathway; and epidermodysplasia verruciformis, whose mutations in *EVER 1* or *EVER 2*, lead to HPV susceptibility and subsequent SCC formation (Jaju, 2016).

SCC formation is frequently thought to start with a precursor lesion known as an actinic keratosis (AK), defined histologically as partial-thickness epidermal dysplasia. AKs are known to be a marker of increased risk for developing both SCC and BCC. A small proportion of AKs undergo malignant transformation, but the actual transformation rate is unknown (Adèle C. Green, 2015). A recent study by Madani et al. showed that among patients with AKs, the risk of SCC increased 1.92% each year, as opposed to 0.83% yearly in controls (Madani et al., 2021). The transformation rate has been reported to be between 0.025%-20% per AK per year, but a more recent systematic review reported a range from 0% to 0.53% per AK per year (A.C. Green & Olsen, 2017; Adèle C. Green, 2015). Once full-thickness epidermal dysplasia has developed, the lesion is categorized as a SCCis, which, if untreated, can eventually progress to invasive SCC with subsequent lymphatic spread and metastasis. It is estimated that 3900–8800 individuals in the United States die of metastatic cutaneous SCC each year (Yilmaz et al., 2017). Clinicopathological features associated with higher recurrence rates and reduced survival include thick, deeply invasive lesions, perineural involvement, and head and neck location (Kyrgidis et al., 2010).

Mortality rates for SCC are poorly documented but are higher than those associated with BCC. Global mortality rates for KCs have been estimated to be 0.52 per 100,000 in developed countries and 0.41 per 100,000 in developing countries (Boyers et al., 2014). Higher mortality is associated

with male sex and Caucasian ethnicity (Wu & Weinstock, 2014). While localized cutaneous SCC carries a relatively high 5-year survival rate, advanced disease was reported in Norway to carry a 64% 5-year survival for men and 51% for women. (Robsahm et al., 2015). Organ transplant status is a known risk factor for SCC formation and is also associated with a worsened prognosis, with mortality rates of 4.94 per 100,000 reported in the U.S. transplant population (Garrett, 2016). The most powerful independent predictors of nodal metastasis and death from SCC have been determined to be a tumor diameter of > 2 cm, followed by invasion beneath the subcutaneous layer, poor differentiation, location on the ear or temple, and lastly, perineural invasion (Schmults, 2013).

1.2 KC incidence and healthcare costs

1.2.1 BCC incidence rates

Basal cell carcinoma (BCC) is the most common cancer in Caucasian populations, whose incidence is reported to be increasing worldwide (Michael R Albert & Weinstock, 2003; Cameron et al., 2018; Lomas, 2012a). In almost all cases, BCC is more common in males than in females, but recent population-based studies from Denmark and the Netherlands have reported a rapid increase in the incidence among young women (Birch-Johansen, 2010; Flohil et al., 2013). This is concerning since BCCs can be locally destructive and have a high healthcare cost (Cameron et al., 2018; Joseph et al., 2001).

BCC epidemiology has been studied most extensively in Australia, where it has by far the highest incidence reported; the incidence rate of 884/100,000 person-years (both sexes combined) reported in 2002 was ten times that recorded in the U.K the same year (Bath-Hextall, 2007). A recent systematic review showed that twelve BCC incidence studies were based on Australian populations, more than any other country (Lomas, 2012a). In Australia, KC causes more than 95,000 hospital admissions (the highest for any cancer in Australia) and more than 500 deaths each year, as noted in a report which combined BCC and SCC in their analysis (Pandeya, 2017). After multiple national public health efforts, BCC incidence has been noted to be reaching a plateau (Giles, 1988; Marks, 1993b; Staples, 1998) or even an incidence decrease (PG & BA, 1998; Raasch & Buettner, 2002; Richmond-Sinclair et al., 2009), showing that public health efforts may be worth pursuing in other countries to lower population morbidity and health-care costs.

BCC incidence increases in Europe by about 20/100,000 person-years every 15 years (5.5% increase per year) (Hannuksela-Svahn, 1999; Lomas, 2012a). Of all countries in Europe, the U.K. might be facing the most significant challenge regarding the increase in BCC incidence. When looking at individual areas in the U.K., Northern England (104.12/100,000 person-years) seems to have a slightly higher incidence compared to Scotland (90.4/100,000 person-years) and Northern Ireland (86.8/100.000 person-years) (Lomas, 2012a). Two Wales-based studies showed a higher BCC incidence in the U.K. compared to the rest of Europe (Holme, 2000; Lloyd Roberts, 1990), and another study showed that the incidence rate could be increasing considerably faster in the U.K. than in the rest of Europe, as it increased from 38.8/100,000 person-years in 1978 to 115.6/100,000 person-years in 1991 (KO, 1994). After the U.K., the countries with the highest BCC incidence in Europe are the Netherlands (87.5/100,000 person-years in 2003) (Holterhues et al., 2010), Denmark

(91.2/100,000 person-years in 2007) (Birch-Johansen et al., 2010), Switzerland and Italy (around 70/100,000 person-years in 1995 for both countries) (Boi, 2003) (Levi, 1995). The lowest rates in Europe have been observed in Croatia (33.6/100,000 person-years between 2003 and 2005. (Lipozenčić, 2010) and Slovakia (38/100,000 person-years in 1994) (Plesko, 2000).

The incidence rates in North America are much higher than in Europe, although direct comparison is often difficult because of varying standardization methods. A steady increase in incidence has been observed both in Canada and the United States. In Canada, incidence rates have been reported in Manitoba (the male incidence was 93·9/100,000 person-years in 2000) (Demers, 2005) and Alberta (147/100,000 person-years in 2006) (Jung, 2010a). The fact that higher incidence rates are now being seen in Canada compared to Europe is interesting, considering their similar latitudes. In North America, there is a much clearer relationship between skin cancer incidence and latitude than in Europe.

As expected, much lower incidence rates have been observed in the northern United States compared to the Southern states. Similar rates have been reported in New Hampshire and Minnesota (170/100,000 person-years) (Harris, 2001; M R Karagas, 1999; Serrano, 1991), compared to much higher rates in Arizona and New Mexico (about 900/100,000 person-years) (Athas, 2003; Harris, 2001).

1.2.2 SCC incidence rates

SCC is the second most common cancer in humans after BCC (Michael R Albert & Weinstock, 2003) (Cameron et al., 2018) (Kallini et al., 2015). As with BCC, the statistics on the incidence of cutaneous SCC are severely limited by registration worldwide, with many simply reporting the first diagnosis of SCC per patient, which has made it impossible to accurately estimate the actual burden of KC (A.C. Green & Olsen, 2017). In addition, most databases do not differentiate between in-situ and invasive forms of SCC, which is significant, as the two carry very different prognoses and are even thought by some to be separate entities rather than existing on a spectrum. This distinction is based on the fact that the age of onset for invasive and in situ SCC is similar, rather than SCCis exhibiting a lower age of onset as expected with actual precursor lesions (K Hemminki, 2003; Kari Hemminki & Dong, 2000). The highest incidence rates of SCC are seen in fair-skinned populations in geographic areas with high UVR. A recent review confirmed this, showing a considerably lower incidence in dark-skinned populations compared to fair-skinned

populations (Lomas et al., 2012). As with BCC, SCC incidence rates are increasing worldwide, which is especially concerning considering that SCC has greater potential to metastasize (A.C. Green & Olsen, 2017).

Australia has the highest SCC incidence globally, with rates of up to 1035/100,000 person-years being reported in some areas (Adèle Green et al., 1996; PG & BA, 1998). As with BCC, SCC incidence in Australia had gradually increased after 1985, with a slow downward trend observed after 2002. Public health efforts in Australia thus might be helping to decrease the incidence of KC (Giles, 1988; Adèle Green et al., 1996; Marks, 1993a; PG & BA, 1998; Raasch & Buettner, 2002; Staples, 1998).

As in Australia, most European studies show an increase in SCC incidence over time, and, as with BCC, the incidence is higher in the U.K. than in continental Europe. The lowest rates in the U.K. have been reported in Yorkshire (14.98/100,000 person-years) as opposed to South-Wales (31.7/100,000 person-years) (Lloyd Roberts, 1990; Lomas, 2012a). The highest overall incidence in continental Europe has been reported in Switzerland (28.9/100,000 in 1997) (Levi, 1995, 2001), with the lowest rates reported in Croatia (8.9/100,000 person-years) (Lipozenčić, 2010). Scandinavian countries have also reported low incidence rates as well as a gradual increase in incidence over time. Norway, Finland, and Denmark have reported rates of less than 10/100,000 person-years (Birch-Johansen, 2010; Hannuksela-Svahn, 1999; Iversen & Tretli, 1999; Østerlind et al., 1988). The highest rates in Scandinavia have been reported in Sweden, with rates of 34.4/100,000 person-years for males and 15.4/100,000 person-years for females (Hussain, 2010; Wassberg et al., 2001).

The SCC incidence trends in North America are less clear. While rates have increased in Canada and the northern United States (Jung, 2010b), in some areas such as Arizona, the incidence has been steady (290/100,000 person-years from 1985-1991) (Harris, 2001), while an increase has been reported in New Mexico and New Hampshire (Athas, 2003; K. MR, 1999).

1.2.3 Increasing health system costs

The increased KC incidence observed worldwide is concerning not only on an individual level but also on a population-wide level since a high disease burden translates into increased healthcare costs. The main costs related to BCC treatment include the following: surgical biopsy and histologic review for diagnosis, surgical treatment (most often excision, Mohs micrographic surgery, or electrodesiccation and curettage), and follow-up care. SCC also has

potential for metastasis, potentially requiring sentinel lymph node biopsy for staging, complete lymph node dissection, imaging, radiation, chemotherapy, and immunotherapy, and can thus be considerably more expensive than BCC treatment. However, what causes BCC treatment to be expensive for healthcare systems is not the individual tumor but rather the enormous potential cost of the total tumor burden. In addition to health-care costs, SCC and BCC treatments can lead to personal direct patient costs, personal income loss, cosmetic and functional impairment, and emotional distress with a reduction in quality of life (A.C. Green & Olsen, 2017).

The United States spends the most on KC treatment each year, followed by Australia, Germany, and the UK (Gordon & Rowell, 2015). In a study conducted over four years, the cost of KC treatment in the Medicare population was $1.7 billion. It was estimated that physician in-office procedures were responsible for 76% of the cost (including biopsies and treatment), with ambulatory surgery accounting for 14% and inpatient expenses representing 9.6% of the whole (J. G. Chen et al., 2001). Another study showed that skin cancer was the most costly of all cancers in the Medicare population, with the five most costly cancers being lung and bronchus, prostate, colon and rectum, breast, and KC (Housman et al., 2003). When specifically looking at skin cancer cost relative to population size, Australia and New Zealand have the greatest associated cost, with Brazil and Canada having the lowest associated cost. Interestingly, Denmark and Sweden had high costs relative to their size, after Australia and New Zealand (Gordon & Rowell, 2015). While melanomas have higher associated mortality and morbidity, studies have shown that in many countries such as the USA, New Zealand, Australia, UK, and Germany, KC costs are higher than the costs for melanoma (Gordon & Rowell, 2015).

1.3 Risk factors and chemoprevention

BCC and SCC have been associated with multiple possible risk factors. These risk factors can roughly be categorized into carcinogens (e.g., UV radiation), genetic susceptibility (e.g., fair skin), and immunosuppression/modulation (e.g., organ transplant status and immunosuppressive medication). Genetic predisposition was reviewed in the previous section on pathogenesis. Some of the less established risk factors for KC include smoking, HPV, and hormonal medications. Two systematic reviews reported an increased risk of SCC, but not BCC, with cigarette smoking (Leonardi-Bee, 2012; F. Song, 2012), while another study did show an increased risk of both SCC and BCC among ever-smokers (F. Song, 2012). Human papilloma virus (HPV) is ubiquitous and is strongly associated with mucosal SCC, but the relationship is less clear with cutaneous SCC (Pfister, 2003). β HPV infection may lead to cutaneous SCC through immortalization of keratinocytes following UVR exposure (de Villiers, 2013; Margaret R. Karagas, 2006), but studies demonstrating HPV DNA within AKs and SCCs have been inconsistent (Andersson et al., 2008; Margaret R. Karagas, 2006). One study showed an association between HPV 5 seropositivity and SCC risk (OR 1.8) (Margaret R. Karagas, 2006). β HPV has a well-established role in producing cutaneous KC in epidermodysplasia verruciformis, but its causal effect in a non-affected population has not been proven (McLaughlin-Drubin, 2015). Regarding hormonal use, studies have been inconsistent, with some reporting an increased risk while others have failed to demonstrate any risk (Birch-Johansen et al., 2012) (Applebaum et al., 2009; Asgari, 2010). In two extensive cohort studies, total alcohol and white wine consumption were associated with increased risk of SCC, although no relationship with BCC was reported (Ansems et al., 2008; S. Siiskonen et al., 2016). Consumption of dietary omega-3 polyunsaturated fatty acids has been reported to have a possible protective effect concerning the development of AKs (Hughes, 2009), and interestingly, obesity was inversely associated with SCC in two studies (Pothiawala, 2012; Zhou, 2016). One explanation for this inverse association is that physical activity has been shown to increase SCC risk, likely because physical activity often directly correlates with increased sun exposure (Lahmann, 2011).

In the following three subsections, we will review the two major established risk factors for KC, UVR, and immunosuppression, as well as the potential for KC chemoprevention and the protective effects of those agents that may work against KC formation.

1.3.1 UVR

UVR is a type of electromagnetic radiation known to have carcinogenic effects in humans. The most relevant types are UVB and UVA since all UVC is blocked by diatomic oxygen or the ozone layer before reaching the Earth's surface. UVA and UVB are used to treat a wide variety of dermatological conditions, such as eczematous dermatoses and psoriasis, mainly by suppressing the function of antigen-presenting cells (APCs) and T cells in the skin (Rangwala & Tsai, 2011). UVB has a wavelength of 280-320nm, while UVA is 320-400nm (S. Q. Wang et al., 2001). Since UVA has a longer wavelength, it penetrates more deeply into the skin compared to UVB. In addition, UVA penetrates glass while UVB does not (Bruls, 1984; S. Q. Wang et al., 2001). UVR carcinogenesis is due to the formation of pyrimidine dimers, most notably in the *TP53* tumor suppressor gene in KC (Brash, 2015) and AKs (W. S. Park et al., 1996). In the past, it was thought that UVA played only a minimal role in skin cancer formation and that UVB was the main culprit since it had been established that UVB induces cellular damage by directly damaging keratinocyte DNA. It is now known that UVA also causes DNA damage, but through a different mechanism. UVA indirectly causes DNA damage by forming radical oxygen species that produce mitochondrial damage with subsequent apoptosis or single stand DNA breaks (S. Q. Wang et al., 2001). While a strong relationship has been shown to exist between individual cumulative sun exposure and KC risk, it is also known that UV exposure does not equally increase the risks of developing BCC and SCC (A.C. Green & Olsen, 2017; Ramos, 2004; Rosso et al., 1996). One study showed that individuals exposed to low doses of UVR over a six-year period developed a BCC/SCC ratio of 4.2, while those individuals exposed to very high levels had a ratio of 2.1, suggesting that high UV doses increased SCC risk more significantly than BCC risk (Ramos, 2004).

The following section will review the potential KC risk effect of different types of UVR exposure, including artificial tanning and UVR used for medical purposes.

1.3.1.1 Psoralen-UVA

Psoralen UVA (PUVA) has been used since 1974 to treat psoriasis and other dermatological conditions (Archier et al., 2012). It has been well established that PUVA increases the risk of AKs and SCC, with some studies also demonstrating an increased risk of melanoma (Tsu Yi Chuang et al., 1992; B. Lindelöf et al., 1991; Olsen, 1992; Reshad, 1984; Stern et al., 1984). BCC risk has been less studied, but one study demonstrated a five-fold increased risk after 100 PUVA treatments. The same study showed that the average period

between PUVA initiation and SCC development was six years, and 4.7 years for BCC (Bernt Lindelöf et al., 1999). PUVA might confer less of an increase in risk in darker skin, including Asian populations, as one study from Japan showed that PUVA poses a lower skin cancer risk in the Japanese population (Torinuki & Tagami, 1988).

1.3.1.2 Narrow-band UVB

Narrow-band UVB (nbUVB) has largely replaced PUVA for the treatment of psoriasis, as it is both safer and more convenient, although probably not as effective (Archier et al., 2012). Interestingly, despite the evidence for in vitro cellular damage following UVB exposure, whether nbUVB actually increases skin cancer risk is not yet certain. Two small studies have demonstrated increased BCC risk using nbUVB (Man, 2005; Raone, 2018), but other studies have not demonstrated an increased risk (Black & Gavin, 2006; Hearn, 2008b; Weischer, 2004). The most extensive study looked at skin cancer risk among 3867 patients receiving nbUVB treatment with 22 years of follow-up and did not demonstrate an increased risk of skin cancer (Hearn, 2008a).

1.3.1.3 Artificial tanning

Tanning beds were first introduced in Iceland in 1973 and the United States in the 1970s and became increasingly widespread and popular in the 1980s and 1990s in both countries (Helgadottir, 2002) (Geislavarnir rikisins, 2020). Approximately 160,000 people are employed in 19,000 such businesses in the United States (Pan & Geller, 2015). The use of indoor tanning beds is highest among adolescents and young adults, with estimated use by 30 million Americans every year, including 2.3 million adolescents. One study from the United States showed that 10.8% of children ages 11-18 use sunless tanners, in addition to avoiding sunscreens and seeking to become tanned (Pan & Geller, 2015). In 2010, the CDC reported that 5.6% of US adults had used an indoor tanning bed within the previous year (Centers for Disease Control and Prevention (CDC), 2012). In Europe and the United States, it has been shown that tanning bed users are most often adolescents or young adults and more often females than males. One Swedish study reported that more than half of all teenagers had used a tanning bed at least four times within 12 months (Bulman, 1995; Helgadottir, 2002; Swerdlow & Weinstock, 1998). In Iceland, tanning bed use surged from the 1980s until 2004 but has since rapidly declined (Helgadottir, 2002) (Geislavarnir rikisins, 2020). About 70% of all Icelandic women have used a tanning bed compared to 35% of men. Individuals between 20-29 years of age were much more likely to actively use

tanning beds than those aged 40-49 (Helgadottir, 2002).

Tanning bed use is associated with potential adverse effects ranging from sunburns, photoaging, and cataracts to increased melanoma and KC risk (Spencer & Amonette, 1995; Swerdlow & Weinstock, 1998). Before the 1980s, artificial tanning devices emitted mainly UVB, producing more long-lasting tanning effects than UVA-based devices. During that timeframe, it was thought that UVB was more carcinogenic compared to UVA. It is now known that UVA also induces DNA damage via indirect mechanisms (Swerdlow & Weinstock, 1998). UVA provides an immediate tanning effect, mainly from the redistribution and oxidation of pre-existing melanin. Contrary to UVB, UVA does not cause increased long-term melanin production and thus does not provide any long-term UV protective effects. Many patients inappropriately "pre-tan" before traveling to develop UV protection, using mainly UVA-producing tanning beds (Miyamura et al., 2011). As discussed earlier, the emergence of PUVA and nbUVB for psoriasis and other skin conditions has shown that UVA is far from safe and that UVB might be safer. It has also been demonstrated that PUVA increases the risk of SCC, with some studies also showing increased risk of melanoma, suggesting that artificial tanning might also increase the risk of developing both types of skin cancer (Tsu Yi Chuang et al., 1992; B. Lindelöf et al., 1991; Olsen, 1992; Reshad, 1984; Stern et al., 1984; S. Q. Wang et al., 2001). More recent studies have demonstrated that artificial tanning beds are associated with an increased risk of SCC, especially in individuals exposed before age 25 (Wehner et al., 2012). An extensive systematic review of more than 9300 cases showed a 67% higher risk of SCC and 29% higher risk for BCC with indoor tanning exposure, with tanning at a young age significantly associated with BCC, concluding that it is critical to prevent young individuals from using tanning beds (Adele Green, 2007). It has been demonstrated that there is a relative risk of developing melanoma of 1.2 in people who had ever used tanning beds, with that risk increasing to 1.87 if tanning beds were used before the age of 35 (Boniol, 2012). Another group reported that 76% of melanomas in people 18-29 years of age could be attributed to prior use of tanning beds (*NTP 12th Report on Carcinogens - PubMed*, 2011).

It has also been shown that cities with a largely white population and a low UV index have a paradoxically high incidence of melanoma (Pan & Geller, 2015). Reykjavik, Iceland's capital, is one such city whose incidence of melanoma has risen and declined in recent years. Travel to more southern countries and diagnostic activity might explain these trends, but the question has been posed whether Iceland's increase in melanoma incidence might also

be attributed to tanning bed use (Hery et al., 2010).

1.3.1.4 Hydrochlorothiazide

Hydrochlorothiazide (HCTZ) is a photosensitizer and thus increases the amount of keratinocyte DNA damage caused by UVA and UVB exposure (Shin et al., 2019). This medication is used worldwide to treat hypertension as well as heart failure, and there is an increasing body of evidence showing a possible relationship between HCTZ and KC risk (Pedersen et al., 2018; Shin et al., 2019). This is of great concern, as certain individuals who might already be at an increased risk of developing KC (fair-skinned individuals in high UVR environments) might unknowingly be predisposed to an even higher level of risk. It is unclear whether this photosensitizing effect is of concern in low UV environments such as Iceland.

1.3.2 Immunosuppressive and immunomodulatory states

One of the immune system's primary functions is to halt the progression and development of cancer. T cells and APCs play a significant role in hindering cancer development. This is evidenced by the increased SCC risk seen with cyclosporine, which shuts down T cell function. Many forms of immunosuppression also increase SCC risk, with the major causes being organ transplants, immunosuppressive medication, and immunosuppressive diseases. Other causes include non-Hodgkins lymphoma, chronic lymphocytic leukemia, HIV, autoimmune disease, and potentially the newer biologic agents (Brewer et al., 2015; Levi, 1996). A review article looking at KC risk with HIV showed that the risk was about 3.63 for men and 2.18 for women, with ART therapy lowering the risk of KC (Zhao, 2016). Other studies looking at autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease have also shown an association of KC with these diseases (Euvrard, 2003; Huizinga, 2011). In contrast, imiquimod activates T cells and APCs and is effective in the topical treatment of AKs, SCCis, and BCC (Rangwala & Tsai, 2011).

1.3.2.1 Organ transplants and immunosuppressive agents

KC has been associated with a mortality of about 5-8% in organ transplant recipients (Mudigonda et al., 2013), with these cancers accounting for over 90% of all skin cancers in this group. 50% of white transplant recipients develop a KC at some point during their lifetime. KC risk increases with the duration and magnitude of immunosuppressive therapy (Euvrard, 2003). SCC is more common than BCC, with transplant patients having up to 250-fold SCC

risk compared to the general population (Euvrard, 2003). In addition, SCCs appear to be considerably more aggressive in the transplant population, having both a 13.4% local recurrence rate and a 5-8% chance of metastasis (Euvrard, 2003). BCC risk in transplant recipients has been less studied, mainly due to the paucity of data in cancer registries. While it has been shown that BCC risk is increased, it does not seem to increase as much as SCC risk, with the usual SCC/BCC incidence of 1:4 in the general population being reversed in severely immunocompromised organ transplant recipients (Berg & Otley, 2002; Euvrard, 2003).

UVR exposure is the essential KC risk factor in organ transplant recipients, initiating carcinogenesis and causing further immune suppression through APC suppression. Thus, UVR avoidance is the primary preventive measure for organ transplant recipients to reduce KC risk (Berg & Otley, 2002). Skin with clinically evident actinic damage in renal transplant recipients has a 4-fold increased risk for SCC development, compared to areas with AKs but without confluent actinic damage (A.C. Green & Olsen, 2017; Adèle C. Green, 2015). Areas of AK in renal transplant recipients had an 18-fold increased risk of developing SCC compared to areas with no AKs, showing the importance of appropriate skin cancer screening in these patients (Wallingford, 2015). In addition to UVR exposure, other important KC risk factors in this population include male sex, older age at transplantation, level of immunosuppression, and Fitzpatrick skin type (Mudigonda et al., 2013).

Organ-specific differences in KC incidence have been noted, with the risk being directly proportional to lower CD4 counts (Euvrard, 2003). Heart transplant recipients seem to be at the highest risk in almost all studies, mostly attributed to the increased immunosuppression required for these patients. Liver transplant patients have the lowest risk, probably because they need lower immunosuppression than kidney and heart transplant recipients (Berg & Otley, 2002).

Many different types of immunosuppressive therapy have been associated with increased KC risk. However, most of the available data pertains to the immunosuppressive agents specifically used to prevent organ transplant rejection, such as prednisone, azathioprine, and cyclosporine, which were used in the protocols of the 1970s. In the 1990s, mycophenolate mofetil, tacrolimus and sirolimus became increasingly popular (Berg & Otley, 2002). Glucocorticoids have a wide variety of immunosuppressive effects and have been reported to increase SCC risk by roughly 2-fold (A. Jensen, 2009; M. R. Karagas, 2001), and the risk of BCC by about 1.25-fold (A. Jensen, 2009).

Calcineurin inhibitors (CNIs) are medications that include cyclosporine (CsA), tacrolimus, and sirolimus. CNIs inhibit Langerhans cells, dermal dendritic cells, and T-cell signaling and proliferation through decreased IL-2 function (Rangwala & Tsai, 2011). CsA might also have carcinogenic effects independent of its immunosuppressive effects, as was suggested in a study looking at mice with severe combined immunodeficiency, in whom CsA enhanced tumor development independent of its immunosuppressive effects (Berg & Otley, 2002). Of the three agents, sirolimus has the lowest risk of KC development (Guba et al., 2002; Luan, 2002), although tacrolimus might be associated with lower KC risk compared to CsA, but this is debatable (Berg & Otley, 2002). In order to lower KC risk for patients on CsA therapy, the dose can be lowered, although this has been associated with more frequent organ rejections (Dantal et al., 1998). Azathioprine is both a mutagen and a photosensitizer (Berg & Otley, 2002) and has been shown to increase KC risk for SCC in particular (Rangwala & Tsai, 2011). This risk might be higher than the risk seen with CsA (Berg & Otley, 2002), and the combination of the two agents has been shown to exponentially increase SCC risk (P. Jensen, 2000).

1.3.2.2 TNF α-inhibitors

Etanercept was the first TNF α inhibitor (TNFi) approved by the FDA; today, there are five different TNFis used for various diseases (Gerriets, 2004). TNF is produced chiefly by macrophages, with downstream effects ultimately being T and B cell activation, followed by the secretion of various cytokines, which play a role in diseases such as psoriasis, rheumatoid arthritis, and Crohn's disease. TNFis have revolutionized the treatment of these diseases, providing an alternative to more toxic and less effective medications such as methotrexate, cyclosporine, and azathioprine, among others (Gerriets, 2004). Their exorbitant cost, however, severely limits their use (Schabert et al., 2013). TNFis are not without risk and have been shown to suppress T-cell responses in a way that can predispose individuals to develop infections such as tuberculosis, herpes zoster, and hepatitis B. Infliximab, which is more potent than adalimumab and etanercept, might increase this risk more than other TNFi agents (Murdaca et al., 2015). Despite the increased risk of infection, TNFis have not been shown to increase the risk of solid organ malignancy (Dreyer et al., 2013; Rangwala & Tsai, 2011). It is unclear whether TNFis directly increase the risk of KC, as there have been conflicting study results; some studies have shown an increased risk of both SCC and BCC, especially in patients with psoriasis. Some have postulated that increased tumor development might be related to the increased PUVA or nbUVB exposure in these patients (Raaschou, 2016; Van Lümig et al., 2015).

1.3.2.3 Statins

Statins are cholesterol-lowering medications, which produce their effect by inhibiting HMG-CoA reductase. These drugs may potentially increase CD4+CD25+ regulatory T cell activity, thereby impairing the host antitumor Th1 response, which could theoretically increase the risk of developing KC (Yang et al., 2017a). While some studies have shown an association between statins and KC risk, reports in the literature have been inconsistent (Yang et al., 2017a).

1.3.3 KC Chemoprevention and other protective agents

Certain medications have been hypothesized to lower KC risk. Metformin, a drug used widely to treat type II diabetes (Saraei, 2019), has been shown to decrease skin cancer risk in some populations (C. H. Tseng, 2018). Metformin activates the *TP53* tumor suppressor gene and inhibits mTOR, thereby arresting the cell cycle and cellular growth. As a result, metformin can directly inhibit the mutations that cause the rapid cell growth seen with SCC and BCC and could theoretically decrease the risk of these cancers (Saraei, 2019).

Another group of drugs that may lower KC risk are non-steroidal anti-inflammatory drugs (NSAID) and aspirin. Summary estimates from nine studies in a systematic review showed significantly reduced risk of SCC and BCC among NSAID users but not aspirin users (Muranushi, 2015). Topical diclofenac has also been shown to be effective in treating AKs (Nelson, 2011). NSAIDs and prostaglandins (Muranushi, 2015) inhibit COX-2, which has consistently been shown to be overexpressed in SCC tumor cells. Another agent that has shown chemopreventive effects for KC is nicotinamide, which has been shown to reduce the incidence of BCC, SCC, and AKs (A. C. Chen et al., 2015). Nicotinamide acts as a precursor for NAD+, an essential cofactor for ATP production, thereby enhancing DNA repair and lowering the amount of immunosuppression caused by UVR (A. C. Chen et al., 2015). Finally, retinoids have also been shown to decrease KC risk, especially SCC. Retinoids induce growth arrest of keratinocytes, leading to normal cellular differentiation, thereby significantly reducing SCC burden, especially in organ transplant recipients (Harwood, 2005).

1.4 What does this study add?

We know that SCC and BCC incidence are on the rise worldwide, although the exact reasons are unclear. The wide variety of risk factors and behavioral patterns seen in different populations make it difficult to tease out the exact reasons for the rise in skin cancer. However, the Icelandic population is unique in many ways, and studying the epidemiology of KCs in this population can shed new light on our understanding of the behavior of these cancers. There is no capital in the world further north than Reykjavik, which has low daily ambient UV radiation levels and a homogeneous fair-skinned population. In addition to this, the island is small, with minimal variation in daily ambient UV exposure (Helgason et al., 2003; Vidarsdottir et al., 2008). Since BCC and SCC have been shown to have relationships with fair skin and high UVR environments, Iceland provides an interesting contrast to Australia‘s population, which has the highest reported rates of KC in the world (Pandeya et al., 2017b).

Alarmingly, the rates of melanoma have also increased in Iceland through the 1980s and 1990s, mostly in young women, although this incidence increase later declined. (Helgadottir, 2002). In 1986-1990, 10-20% of women diagnosed with melanoma were younger than 45 years of age, but in 1996-2000, the proportion increased to 50-65%. It is unclear what caused this increase in incidence, but background UVR has been determined to be an unlikely factor, with high-risk behaviors among women being a more likely explanation (Helgadottir, 2002).

The Icelandic Cancer Registry (ICR) is a high-quality registry that documents all histologically confirmed skin cancers in that country from 1981 onward. Unlike many other population-based cancer registries, it includes cutaneous BCC. In addition, the ICR separately classifies SCCis from invasive SCC, allowing more detailed epidemiologic analysis. (Sigurdardottir et al., 2012). Furthermore, only the first BCC and SCC cases are reported in many registries, and subsequent tumors are excluded. Consequently, true BCC incidence and tumor burden remain unknown and are probably underestimated (Lomas, 2012b). In order to look at KC relationships with different medications, it is possible to link the ICR to the Icelandic Prescription Medicine Register, held by the Icelandic Directorate of Health, a population-based registry that records all outpatient prescriptions, to look at relationships between different medications and cancer. This is possible due to unique personal identification numbers that are assigned to every Icelandic-born individual. This can be used to connect various databases and virtually

eliminates loss of follow-up in retrospective studies (The Icelandic Directorate of Health Web Site, Https://Www.Landlaeknir.Is/English, 2020).

In addition to ascertaining the actual tumor burden of KC in the Icelandic population, studying epidemiological trends in this low UVR setting will provide important information regarding the behavior of KC in a genetically predisposed population in a low risk environment. It is unknown whether many reported risk factors, such as exposure to HCTZ and immunosuppressive therapies, are relevant in a low UVR environment. We have the unique opportunity to combine histological confirmation of keratinocyte cancers with tumor registry verification over an extensive time period for an entire population while simultaneously looking at multiplicity to calculate total tumor burden, so as to gain further understanding of the potential risk factors for KC.

2 Aims

The aims of this study were to provide an update on keratinocyte cancer incidence rates and tumor burden in an unselected, geographically isolated population that is exposed to a low level of ultraviolet radiation.

In addition, we aimed to further delineate the relationship between SCC/BCC and hydrochlorothiazide (HCTZ), TNF-alpha inhibitors (TNFi), metformin and statins. These four medications have in some studies been associated with altering the risk of BCC and SCC through UV sentization, immunosuppression and immunomodulation (respectively).

Study 1. Assess the incidence trends and total tumor burden of BCC in a whole population using joinpoint analysis.

Study 2. Assess the individual incidence and total tumor burden of in-situ and invasive SCC, using joinpoint analysis.

Study 3. Assess the association between the photosensitizer HCTZ, and invasive SCC, SCCis and BCC in a low UV environment.

Study 4. Assess the association between statins, and invasive SCC, SCCis and BCC in a low UV environment.

Study 5. Assess the association between TNFis, and invasive SCC, SCCis and BCC in a low UV environment.

Study 6. Assess metformin's potential as a chemoprotective agent for BCC, SCCis and invasive SCC.

Future studies

Using the information from the above studies, we further potentially aim to assess the effect of public health efforts such as increased tanning bed regulation and physician education on the incidence of keratinocyte carcinoma.

3 Materials and methods

3.1 The epidemiology of basal cell carcinoma and squamous cell carcinoma (Studies I and II)

The Icelandic Cancer Registry (ICR) contains comprehensive records of all cases of pathologically confirmed KC in Iceland from 1981 (Sigurdardottir et al., 2012). We included all patients diagnosed with first and subsequent KC between 1981-2017, with an associated ICD code and pathologic diagnosis. Iceland was divided into two regions: 1) Reykjavik and the adjacent Reykjanes peninsula, and 2) all other areas in Iceland, mainly small towns and rustic countryside. KC diagnosed in individuals under 30 years of age was re-analyzed by an Accreditation Council for Graduate Medical Education accredited dermatopathologist (Arni Kjalar Kristjansson) before being included in the dataset.

All KCs between January 1981 and December 2017 were included after reviewing all tumors in individuals ≤ 30 years of age. World standardized rates (WSR) were used to present incidence rates of confirmed malignancies for the 37-year period (Segi M, 1960), expressed per 100,000 person-years. The cumulative risk of KC occurrence before ages 40 and 65 was calculated and before 80 years, which was defined as lifetime risk. This was done using age-specific rates, multiplied by the proportion of survivors and expressed as a percentage, cumulative risk=1-exp (-cumulative rate) (Muir C, Waterhouse J, 1987). Due to Iceland's small population (357,000 individuals), random variation was expected. Therefore we used moving averages with 5-year intervals when showing changes with time instead of looking at individual years. For both single and multiple KC, we also present age-specific incidence rates.

To account for the fact that the same KC might be histologically diagnosed multiple times in multiplicity calculations, all records of KC diagnosed within four months in the same anatomic location in the same individual were excluded. In addition, we calculated the median interval between the 1st and 2nd KC and the median interval between all KCs that occurred.

Trends and joinpoints were calculated when plausible. It was not always possible for all anatomic sites due to low case numbers. Joinpoint version 4.6.0.0 was used (Kim et al., 2000). Joinpoint regression is a valuable

tool for analyzing changes over time. It has widely been used to estimate rate changes of skin cancer incidence but has also been shown to have practical implications in other fields, such as implementing new traffic laws (Gillis & Edwards, 2019). Joinpoint analysis assumes that data can be divided into smaller segments, with each segment having unique properties. A linear slope is calculated for each segment, which can be compared to the linear slopes of other segments of the dataset (Gillis & Edwards, 2019). In addition, non-linear models can be calculated using annual percent change calculations in joinpoint. These can be used to measure a trend over a pre-specified fixed interval, allowing the calculation of a single number to describe the average incidence change over a period spanning multiple years (*AAPC Definition — Joinpoint Help System*, n.d.). We assessed trends using this method by calculating the annual percentage change (WAPC) and the corresponding 95% CI (Kim et al., 2000). In our joinpoint analysis, we stratified according to age (< 50 years and ≥ 50 years) so that we could compare our analysis with a previous Icelandic study on melanoma (Hery et al., 2010).

In the very early years of the study period, KC did not have a chance of being registered as second or third lesions, as KC registration started first in 1981. We, therefore, conducted a sensitivity analysis by looking at the proportion of multiple tumors in the first few years of the study to see whether the early years differed significantly from subsequent years.

3.2 Medication as risk factors (Studies III, IV, V and VI)

We used a population-based nested case-control design for this study, which has several advantages over traditional case-control studies. With a nested case-control design, there is a predetermined clearly defined cohort, in this case, the Icelandic population. Using a nested case-control design while linking nationwide health registries, the typical limitations for most case-control studies, such as the risks of having a non-representative control group or information bias, are eliminated (Ernster, 1994). With traditional case-control design, there is always the possibility that the control group does not belong to the same underlying population, with an increased risk of residual confounding variables. (*9.2 - Comparison of Cohort to Case/Control Study Designs with Regard to Sample Size | STAT 507*, n.d.).

Cases consisted of all individuals diagnosed for the first time with KC of the skin with histological confirmation in Iceland in the years 2003-2017. Ten unaffected population controls were linked to each case, matched by year of

birth and sex. These were randomly selected from the National Register of Iceland.

In order to extract data about KC diagnosis and prescription drug utilization, two nationwide databases were used. First, as discussed earlier, the ICR records all skin cancer cases diagnosed with histologic verification (Sigurdardottir et al., 2012). The Directorate of Health runs The Icelandic Prescription Medicine Register and records all electronic outpatient prescriptions from 2002 onward (*The Icelandic Directorate of Health Web Site, Https://Www.Landlaeknir.Is/English*, 2020). Due to the retrospective nature of the data, smoking status, information regarding underlying comorbidities, and socioeconomic status were not available for analysis. Record linkage between databases was possible by using the unique Icelandic personal identification number.

The date of KC diagnosis served as the index date. Patients were considered exposed if they had filled one or more prescriptions at a minimum of two years before this date. To account for possible lag time, prescriptions filled less than two years before the index date were disregarded. This was not done in the TNFi analysis, as there were too few recorded prescriptions, which would have resulted in the study being underpowered. Optimally a lag time should be used when conducting such an analysis, as the formation or prevention of cancer is not immediate after immunomodulation. In similar studies, it has been shown that increased lag time is associated with increasing KC risk (A. Ø. Jensen et al., 2008). Cancer formation early after the index date is less likely to result from the immunomodulatory effect and more likely to be a coincidental occurrence. This applies especially to HCTZ, as photosensitization is a chronic process that takes years (S. Q. Wang et al., 2001).

Cumulative exposure was recorded in milligrams and daily dose units (DDUs) for all patients. A DDU is defined by the average daily maintenance dose of a medication used for its primary indication (*The Defined Daily Dose System (DDD) for Drug Utilization Review - PubMed*, n.d.). BCC, Invasive SCC, and SCCis were evaluated separately in all studies. Never-users served as controls. For HCTZ and metformin, a trend analysis was performed to assess a dose-response relationship for each tumor sub-type. This was not done for TNFis due to low case numbers, nor was it done for statins since the overall association with KC was weak. Interquartile ranges (IQR) were calculated and reported in tables.

In all studies, patients taking azathioprine, mycophenolate mofetil, and

cyclosporine were subsequently excluded as these immunosuppressive medications dramatically increase the risk of keratinocyte carcinoma (Berg & Otley, 2002) (Wisgerhof et al., 2010). For all medications, we adjusted for the use of tetracyclines, and topical and oral retinoids as these medications can theoretically modify the potential risk of KC (Harwood, 2005). Of note, various other medications have been reported to have possible associations with KC. We decided against excluding multiple patient groups, and we also emphasized avoiding the inclusion of too many covariates in the multivariate models, as this could have harmed the generalizability of the data and resulted in overfitting (Z. Zhang, 2014). After calculating the results of our HCTZ analysis (Study III), all subsequent studies (studies IV, V, and VI) included HCTZ in the multivariate model. After the statin and TNFis analysis (studies IV and V), those medications were included in the multivariate model for the metformin analysis (Study VI). This inconsistency of the multivariate models between studies was unavoidable due to the chronological order of our analysis.

The dose-response trend tests' P values were calculated using weighted linear regression, which regressed ORs based on median dosage for each dose category (1-500, 501-1500, and >1500 DDUs). The inversed variance of the log-effect size was used as weight. For incidence trends, p-values were calculated using the chi-square test, which met all assumptions. A p-value of <0.05 was considered statistically significant. Conditional logistic regression analyses were performed with 95% confidence intervals (CI) to calculate multivariate odds ratios (ORs).

3.3 Ethics

The studies were approved by: The National Bioethics Committee (VSNb2018030013/03.03), The Icelandic Cancer Registry (ICR), The Landspitali University Hospital medical director, the medical director of Akureyri Hospital, and the Directorate of Health (1802220/5.6.1/gkg).

4 Results

4.1 Epidemiology of Keratinocyte carcinoma

4.1.1 Basal cell carcinoma (Study I)

The results in this chapter have been previously published by Adalsteinsson et al. as Paper I in the British Journal of Dermatology (Paper I. J. A. Adalsteinsson et al., 2020). The total number of first diagnosed BCCs, after excluding 32 cases diagnosed outside of the country, was 7,226. No cases diagnosed in individuals <30 years of age were excluded after review. The sensitivity analysis did not show a significant difference in multiplicity proportions according to how early the lesions were diagnosed after KC registration. Therefore, no years were excluded from the analysis. There were 3,100 cases in men (42.9%) and 4,126 (57.1%) in women. The average age at diagnosis of the first diagnosed tumor for the study period was 67.2 for men and 65.2 for women ($p<0.001$). The Reykjavik area had more tumors than rural areas, or 71% of all BCCs in men and 72% in women ($p=0.21$). The most common anatomical location was head/neck for both men and women (62% and 55% respectively) ($p<0.01$). The second most common was the trunk (29% for men and women) ($p=0.56$), and the third was legs (3% for men, 8% for women) ($p<0.01$) (Paper I. J. A. Adalsteinsson et al., 2020).

4.1.1.1 Age-standardized incidence rates – Stratified by sex

In the first year of the study period, 1981, the age-standardized incidence rates (per 100,000) were 22.2 for women and 25.7 for men (difference not statistically significant). By the end of 2017, the rates had increased approximately 2.33 fold for men and 3.74 fold for women (**figure 1**). The incidence difference between the sexes became statistically significant after the 1998-2002 time period, as **figure 1** demonstrates from the non-overlapping 95% CIs. At the end of the study period, the WSR was 1.39-fold higher for women than for men (83.1 and 59.9 respectively). Women demonstrated the most significant increase in WSR between 1995 – 2004, or 1.49 fold (39.8 to 59.2). The increase in WSR was more stable over time for men, increasing 1.19 fold during the same period (35.5 to 42.4) (Paper I. J. A. Adalsteinsson et al., 2020).

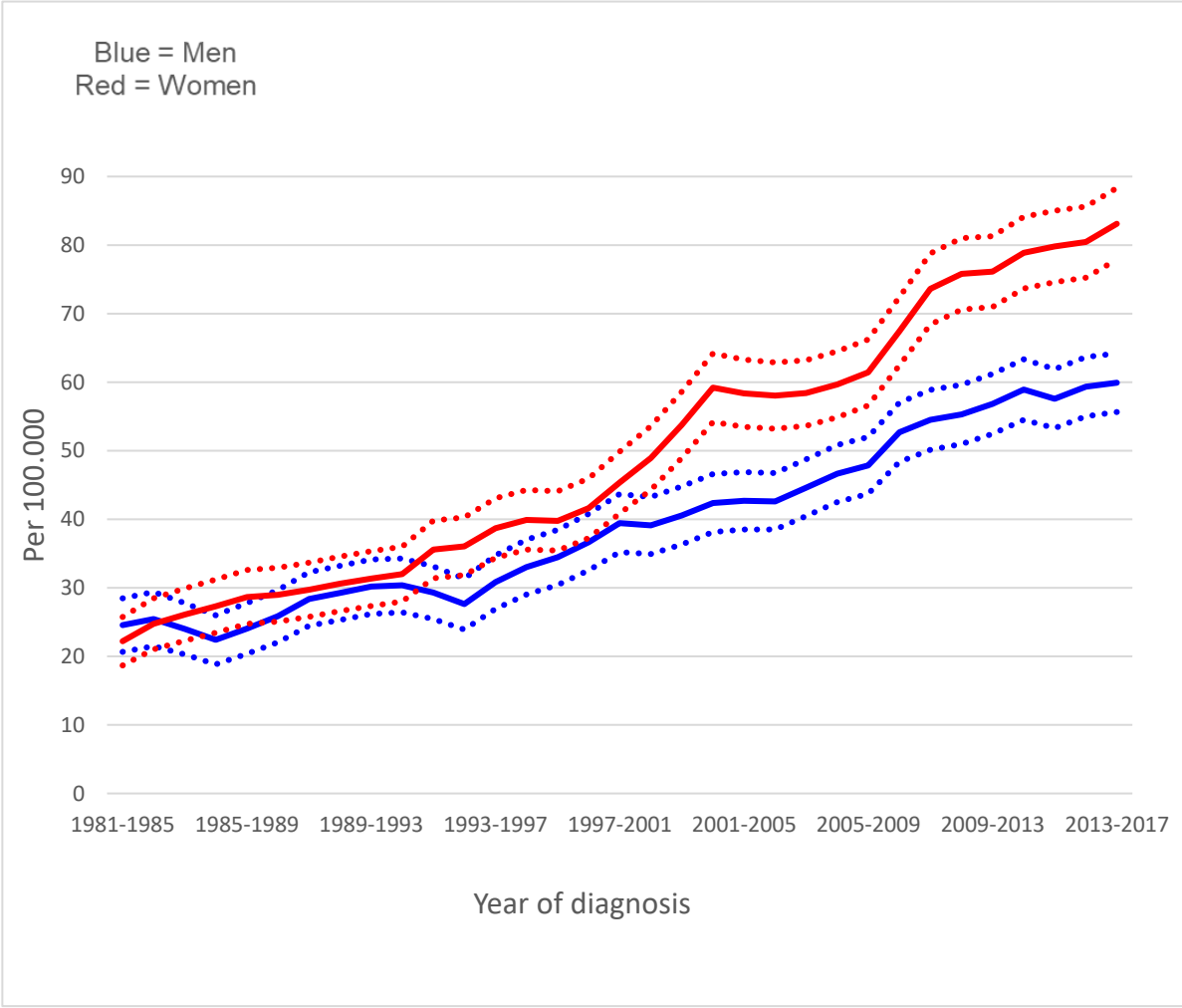


Figure 1: Histopathologically confirmed BCC, age-standardized (world) incidence (5-year moving averages) from 1981-2017 for men (blue line) and women (red line), with 95% CIs. This figure has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper I. J. A. Adalsteinsson et al., 2020).

4.1.1.2 Age-standardized incidence rates – Stratified by anatomic location

The WSR increased for both men and women from 1981 until 2017 for all body sites (**figure 2)**. Women had a higher number of total BCCs than men, mostly due to a rapid increase in truncal and leg lesions than head and neck lesions. 72% of BCCs were located on the head and neck in both men and women in the 1981-1990 period. In 2009-2017 this percentage had decreased to 49% for women and 57% for men ($p<0.01$) primarily due to a proportional increase in leg and truncal lesions in women (Paper I. J. A. Adalsteinsson et al., 2020).

4.1.1.3 Age distribution

Looking at **Figure 3,** we can see how the KC incidence changed in various age groups throughout the study period. The incidence increase mainly was accounted for by men >70 years of age, but women also accounted for the incidence increase even in the 25-40 year age group (Paper I. J. A. Adalsteinsson et al., 2020).

4.1.1.4 Reykjavik and rural areas

BCC age-standardized rates for both Reykjavik and rural areas increased over time. In rural areas, rates were lower for both sexes (**figure 4**). The difference in incidence between rural men (50.0, 95% CI [44.7-55.3]) and Reykjavik men (62.2, 95% CI [58.2-66.2]) was statistically significant in the 2009-2017 period. There was a marginally significant difference between Reykjavik women (83.8, 95% CI [79.0-88.5]) and rural women (72.4, 95% CI [65.7-79.2]) (Paper I. J. A. Adalsteinsson et al., 2020).

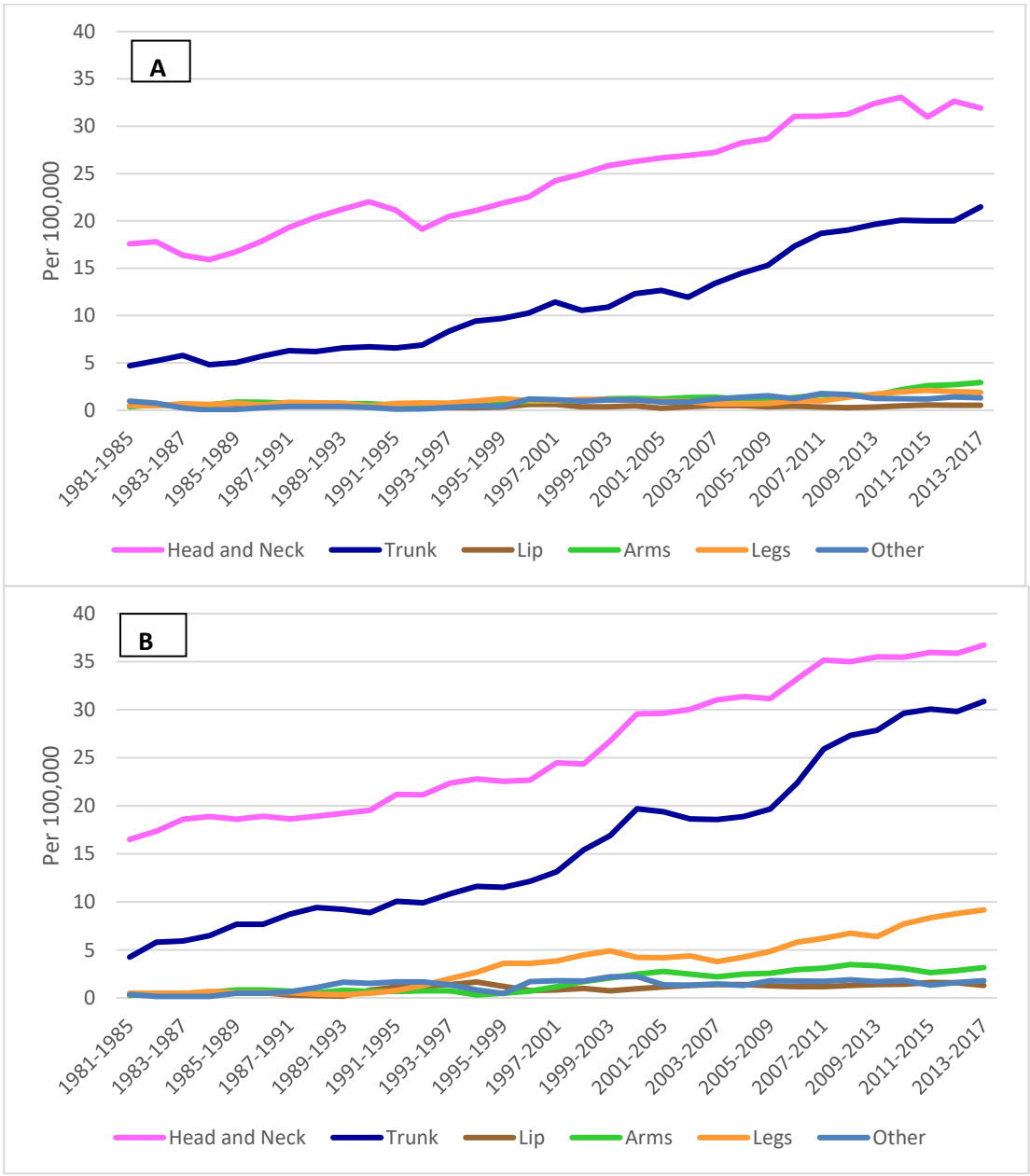
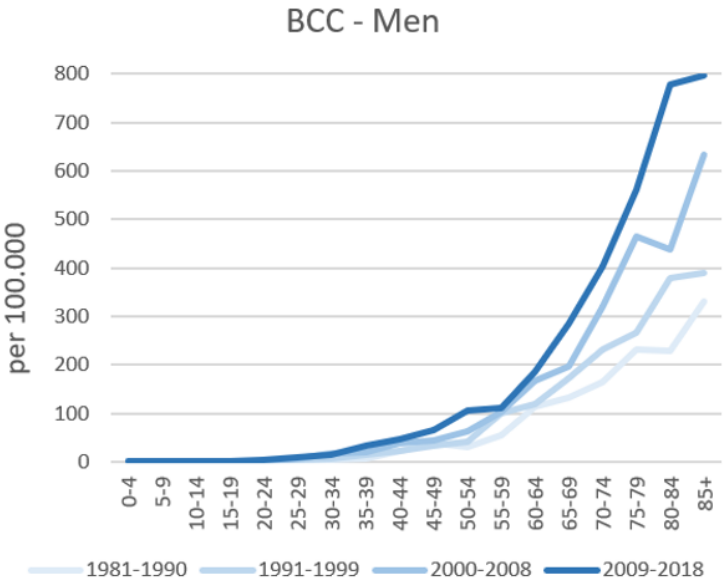


Figure 2: Trends in age-standardized (world) incidence (5-year moving averages) of BCC according to sex, anatomical location, and time. A. In men. B. In women. This figure has been previously published by Adalsteinsson et al. as Paper I in the British Journal of Dermatology (Paper I. J. A. Adalsteinsson et al., 2020).



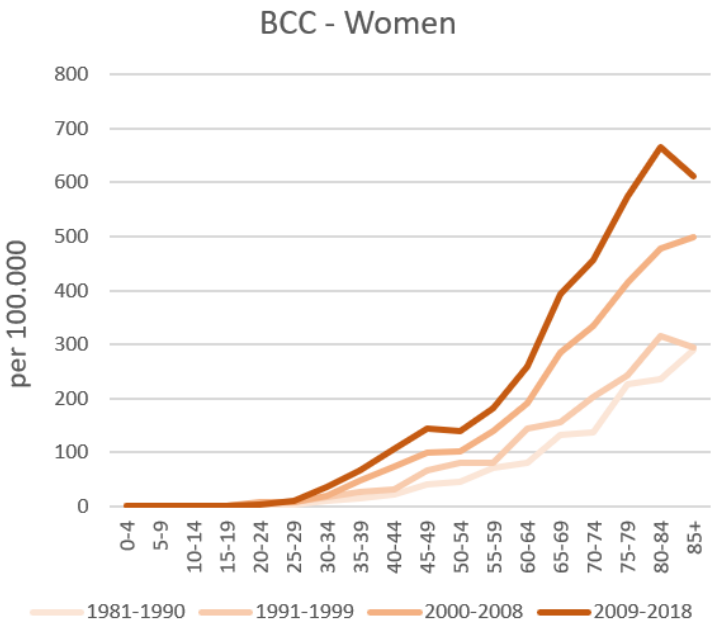


Figure 3: BCC age distribution of incidence over time, stratified by ten-year study periods for men (above) and women (below).

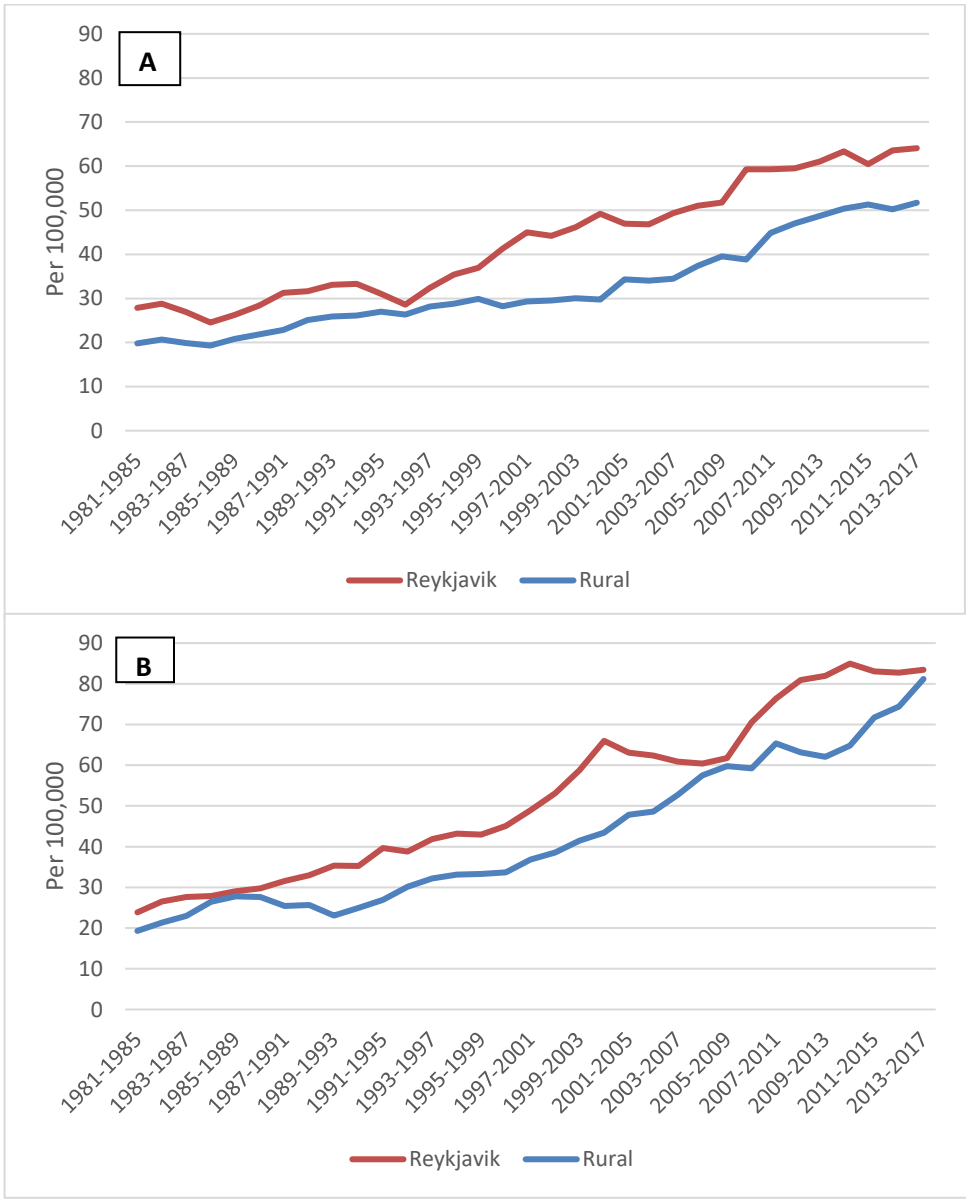


Figure 4: Trends in age-standardized (world) incidence (5-year moving averages) of BCC according to time-period, sex, and residence (Reykjavik vs. rural areas). A. In men. B. In women. This figure has been previously published by Adalsteinsson et al. as Paper I in the British Journal of Dermatology (Paper I. J. A. Adalsteinsson et al., 2020).

4.1.1.5 Joinpoint analysis

The WAPC was 2.99% for men and 4.12% for women for the entire study period. Slopes for BCCs of the head and neck for the <50 and ≥ 50 years of age groups are depicted in **figure 4**. No joinpoints occurred. There was a marginally significant difference between the slopes in the <50 years of age group, 0.11 (95% CI [0.05-0.17]) for males and 0.24 (95% CI [0.17-0.31]) for females. In the ≥ 50 group, there was no significant difference between the slopes, 2.89 (95% CI [2.38-3.40]) for males and 3.26 (95% CI [2.66-3.86]) for females (Paper I. J. A. Adalsteinsson et al., 2020).

Lesions of the trunk in the <50 years of age group are depicted in **figure 5.** Joinpoints occurred for men in 1988 and women in 1993. Joinpoints were not observed in the ≥50 years of age group. A more notable difference between the sexes was observed for the age <50 category compared to age ≥50, similar to head/neck lesions. A statistically significant joinpoint occurred for women <50 years of age in 2004 for leg lesions (slope increased from 0.0 to 0.36) and for women ≥ 50 years of age in 1992 (slope increased from 0.00 to 1.34). There was no corresponding increase in the number of leg lesions in men (Paper I. J. A. Adalsteinsson et al., 2020).

4.1.1.6 Multiplicity

The total number of BCCs during the entire study period was 12,432 lesions in 7,226 individuals when accounting for multiple tumors. On average, a similar number of lesions were diagnosed in men and women (1.7 and 1.73 respectively). Most individuals (92%) had between 1 and 3 lesions (men and women). During the first period of the study (1981-1990), a slightly higher proportion of men had multiple lesions, or 35%, than women (33%) (p=0.74). During the last period (2009-2017), the multiplicity proportions had decreased to 25% for both sexes (Paper I. J. A. Adalsteinsson et al., 2020).

The range is depicted in brackets. The median interval between 1st and 2nd BCC was 2.2 years for women [0-34] and 2.1 years [0-30] for men. The overall median interval between all developed BCCs was 1.4 years [0-34] for women and 1.3 years [0-30] for men. This difference was not statistically significant. **Table 1** demonstrates age-specific rates (ASR) analyzed by age group and sex. Overall, women had higher ASR for both single and multiple tumors, the exception being the 65+ years of age single BCC category, where men had the higher ASR (Paper I. J. A. Adalsteinsson et al., 2020)

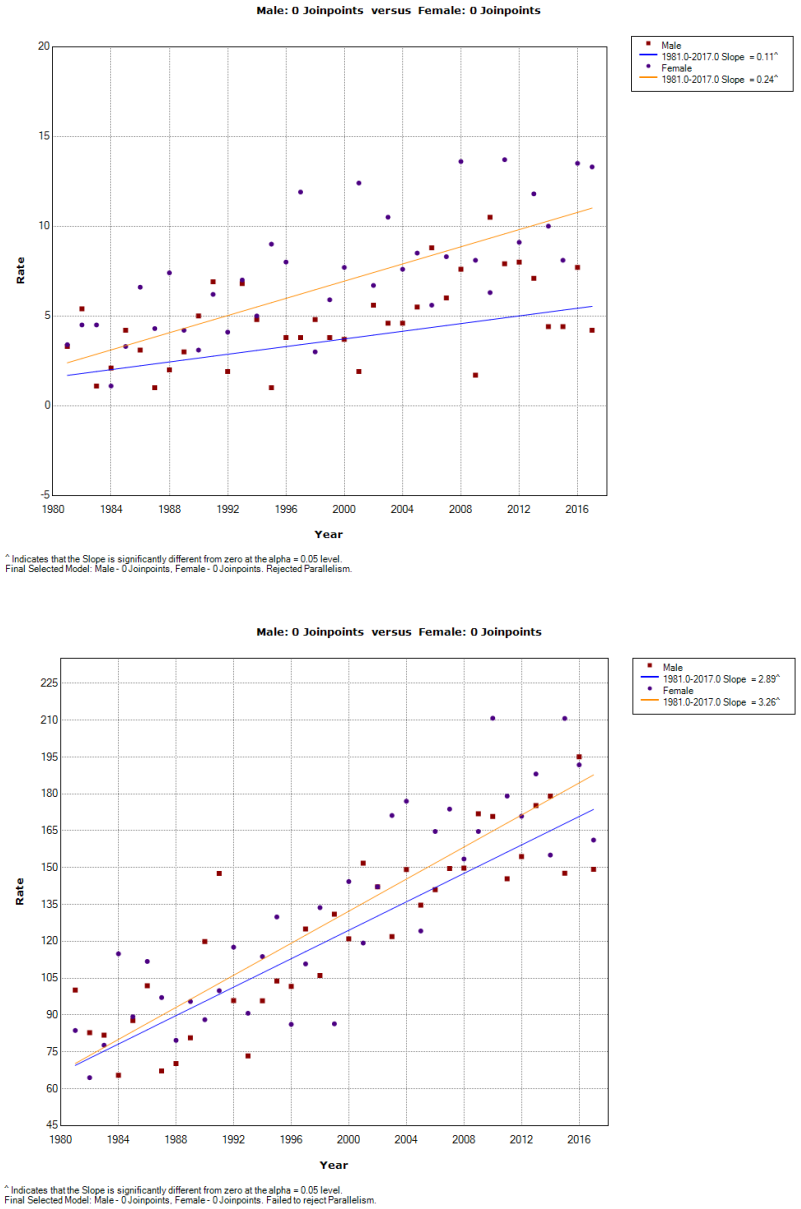


Figure 5: Joinpoint analysis of BCCs of the head and neck for men (blue) and women (orange) <50 (4A) and >=50 (4B), using age-standardized rates (world) per 100.000. This figure has been previously published by Adalsteinsson et al. as Paper I in the British Journal of Dermatology (Paper I. J. A. Adalsteinsson et al., 2020).

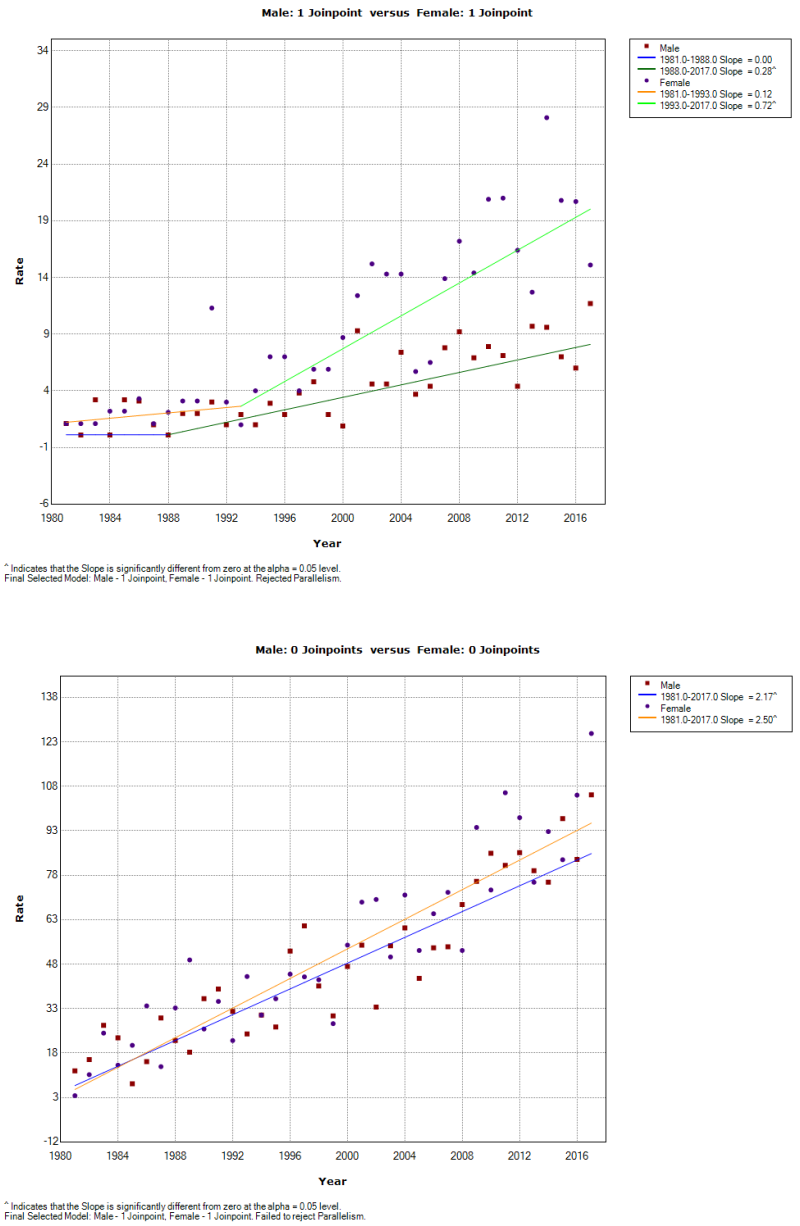


Figure 6: Joinpoint analysis of BCCs of the trunk for men (blue) and women (orange) <50 (5A) and >=50 (5B), using age-standardized rates (World) per 100.000. This figure has been previously published by Adalsteinsson et al. as Paper I in the British Journal of Dermatology (Paper I. J. A. Adalsteinsson et al., 2020).

Table 1: BCC age-specific incidence rates (ASR) per 100.000 1981-2017, stratified by sex and age. The WSR is reported at the bottom for each sex in each category. This table has been previously published by Adalsteinsson et al. as Paper I in the British Journal of Dermatology (Paper I. J. A. Adalsteinsson et al., 2020).

	All BCCs		**Single BCC**		**Multiple BCCs**	
Male	**(n)**	**Rate [95% CI]**	**(n)**	**Rate [95% CI]**	**(n)**	**Rate [95% CI]**
<40	139	4.3 [3.6-5.0]	109	3.4 [2.7-4,0]	30	0.9 [0.6-1.3]
40-64	1049	72.5 [68.1-76.9]	712	49.2 [45.6-52.8]	337	23.3 [20.8-25.8]
65+	1912	347.0 [331.5-362.6]	1352	245.4 [232.3-258.5]	560	101.6 [93.2-110.1]
WSR	3100	42.4 [40.8-43.9]	2173	29.5 [28.2-30.8]	927	12.9 [12.0-13.7]
Female	**(n)**	**Rate [95% CI]**	**(n)**	**Rate [95% CI]**	**(n)**	**Rate [95% CI]**
<40	278	8.9 [7.9-10.0]	211	6.8 [5.9-7.7]	67	2.2 [1.6-2.7]
40-64	1528	108.0 [102.6-113.4]	1024	72.4 [67.9-76.8]	504	35.6 [32.5-38.7]
65+	2320	351.0 [336.7-365.3]	1604	242.7 [230.8-254.6]	716	108.3 [100.4-116.3]
WSR	4126	53.9 [42.2-55.7]	2839	36.7 [35.2-38.1]	1287	17.3 [16.3-18.3]

4.1.1.7 Lifetime- and Cumulative risk

In the 2009-2017 time period, the lifetime risk for women is 10.1%, compared to 7.3% in men ($p<0.01$). This is an increase from the 1981-1990 period when the lifetime risk was 3.2% for women and 2.8% for men ($p=0.1$). The risk for women <40 years of age had the highest proportional increase, 6-fold (from 0.1% to 0.6%). In comparison, the increase was 3-fold for men (from 0.1% to 0.3%) (J. A. Adalsteinsson et al., 2020).

4.1.2 Squamous cell carcinoma (Study II)

The results in this chapter have been previously published by Adalsteinsson et al. as Paper II in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021). During the study period, there were 1,471 first diagnosed invasive SCCs and 1,534 first diagnosed SCCiss. No cases diagnosed in individuals <30 years of age were excluded after histopathologic review. During this period, first diagnosed SCCis WSR increased from 2.0 to 22.3 in women and from 1.2 to 19.1 in men; first diagnosed invasive SCC WSR increased from 0.3 to 13.2 in women and 4.6 to 14 in men (per 100,000). There were 560 first diagnosed SCCiss in men (36.5 %) and 974 in women (63.5%) (male/female ratio = 0.57), with 70% of male and 75% of female cases diagnosed in the Reykjavik area (p=0.035). There were 769 first diagnosed invasive SCCs in men (52.3%) and 702 in women (47.7%) (male/female ratio = 1.1). 67% and 70% of male and female cases, respectively, were diagnosed in the Reykjavik area (p=0.22). The median age at diagnosis was similar in men and women for SCCis (76 [IQR: 15] vs. 75 [IQR: 18], p>0.05) and invasive SCC (77 [IQR: 15] vs. 78 [IQR: 16], p>0.05). The median age at diagnosis for in-situ was lower than for invasive SCC among both males (p<0.01) and females (p<0.01) (J. A. Adalsteinsson et al., 2021).

The frequencies of in-situ and invasive SCC arising at different anatomic locations in both sexes are summarized in table 1. Head and neck was the most common location for both invasive (74% males, 53% females, p<0.01) and SCCis (54% males, 45% females, p<0.01). Women had invasive (14%) and in-situ (20%) leg lesions more frequently than men (2% and 6%, respectively, p<0.01). Lip lesions were more likely to be invasive than in-situ. Invasive lip lesions accounted for 6% of invasive SCC in men and 4% in women, with 1% of in-situ lesions occurring on the lip in both men and women (p<0.01).

4.1.2.1 Age-standardized incidence rates – Stratified by sex

SCCis WSR consistently increased, from 1.2 to 11.6 in men and from 2.7 to 18.9 in women per 100,000 (**figure 7**). Women had a higher SCCis WSR than men from 1981, but it was not until 1999-2003 that the differences became statistically significant (J. A. Adalsteinsson et al., 2021).

Looking at invasive SCC, men had a higher WSR throughout most of the study period. However, the sex difference was only statistically significant in 1993-1997. During this time, the WSR increased from 4.3 to 13.2 for men and from 2.3 to 11.0 for women. By the end of the study period, men had a

similar incidence of invasive and SCCis (13.2 [11.8-14.6] and 11.6 [10.2-12.9], p>0.05), while women have a higher WSR of in-situ than invasive SCC (18.9 [17.1-20.6]) and 11.0 [9.7-12.2], p<0.05) (J. A. Adalsteinsson et al., 2021).

4.1.2.2 Age distribution

Figure 8 demonstrates how SCC incidence changed in various age groups throughout the study period. The incidence increase in younger women with in-situ or invasive SCC was the same as that of BCC. The highest incidence increase for SCCis was accounted for by women >75 years of age. In contrast, the highest incidence increase for invasive SCC was accounted for by men >75 years of age (J. A. Adalsteinsson et al., 2021).

4.1.2.3 Age-standardized incidence rates – Stratified by anatomic location

Figure 9 summarizes SCCis incidence trends. Head and neck was the most common location in men and women. Head/neck proportion of all lesions increased from 47% to 56% in men and decreased in women from 57% to 43%. This was mainly because of increased truncal, leg, and arm lesions (J. A. Adalsteinsson et al., 2021).

Figure 10 summarizes incidence trends for invasive SCC. Similarly to what was seen for SCCis The head and neck was the most commonly affected location in men and women. However, the proportional increase of head and neck invasive SCC in men was much lower than that of SCCis. Head and neck lesions accounted for 83% of all lesions in the 1981-1985 period, decreasing to 74% by the study's end. In contrast, the proportion of head and neck SCCis in men increased over the same period. In women, the proportion of invasive head and neck SCC also decreased from 67% in 1981-1985 to 46% in 2013-2017 (J. A. Adalsteinsson et al., 2021).

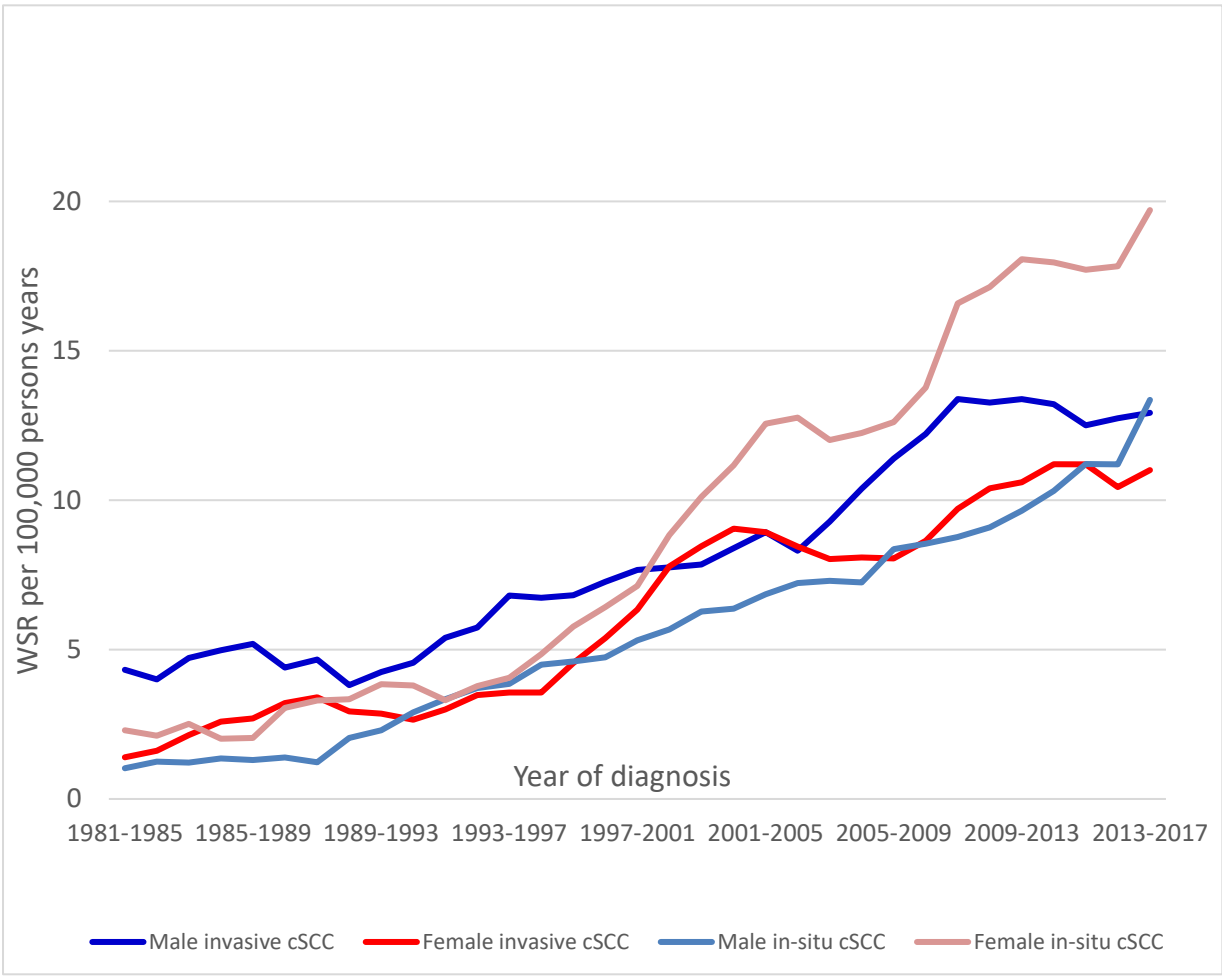


Figure 7. The WSR per 100,000 person-years of histologically confirmed in-situ and invasive cutaneous squamous cell carcinoma in Iceland for men and women from 1981 to 2017 (5-year averages). This figure has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021).

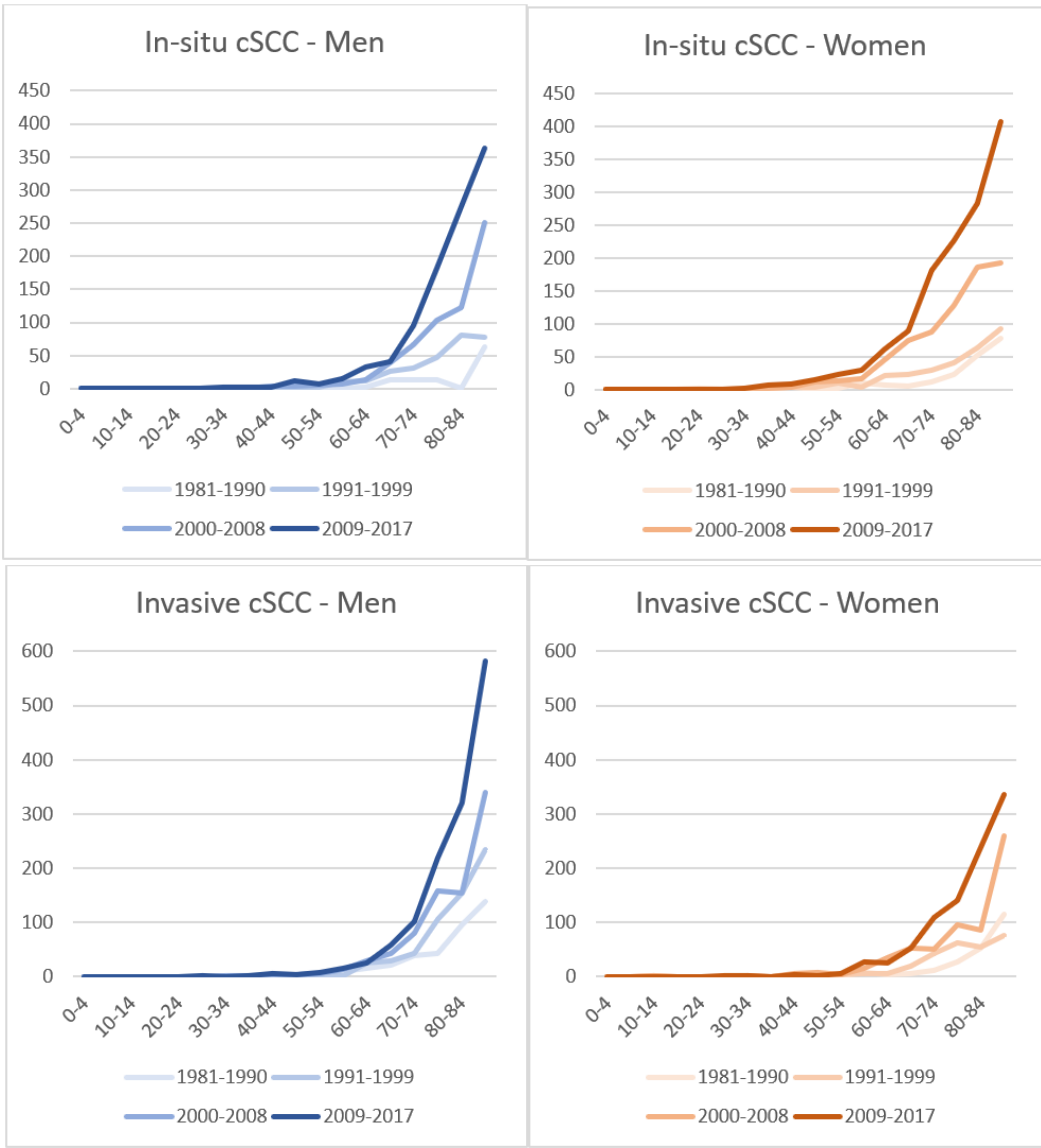
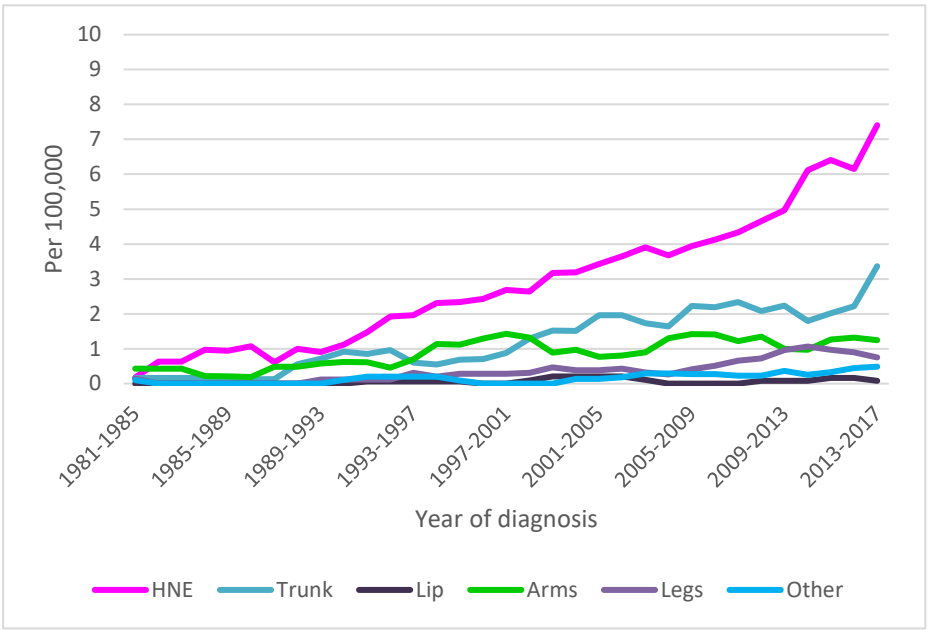


Figure 8: Age-specific incidence rates per 100,000 for men and women, for both in-situ and invasive SCC. Age-specific incidence rates are on the y-axis, and age is on the x-axis. This figure has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021).



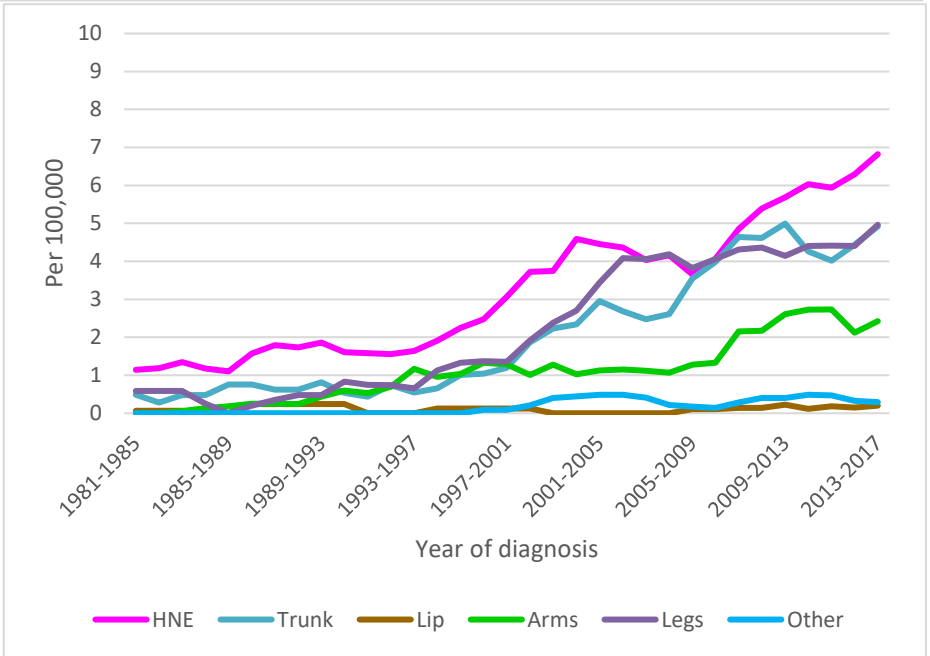
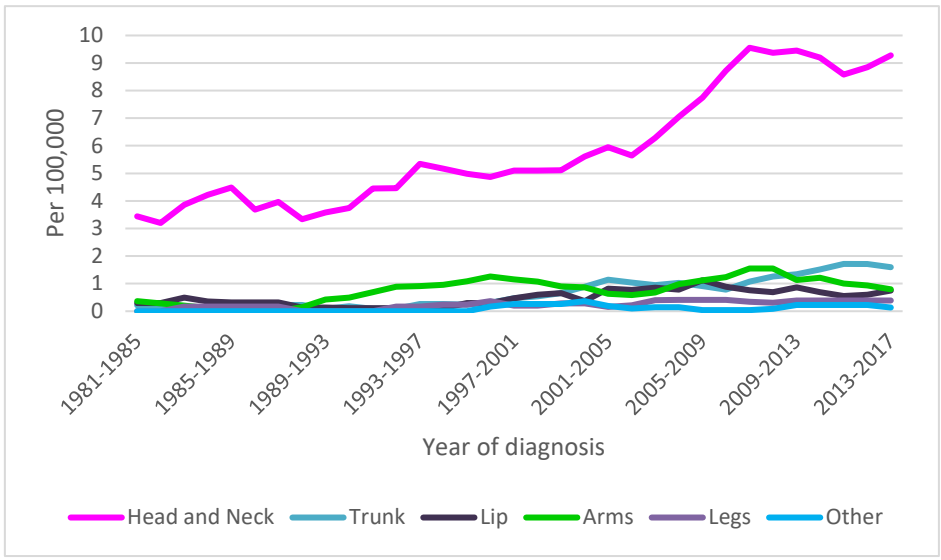


Figure 9: Trends in age-standardized (world) incidence (5-year moving averages) of in-situ squamous cell carcinoma from 1981-2017 according to sex, anatomical location, and time. Men (above) and women (below). This figure has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021).



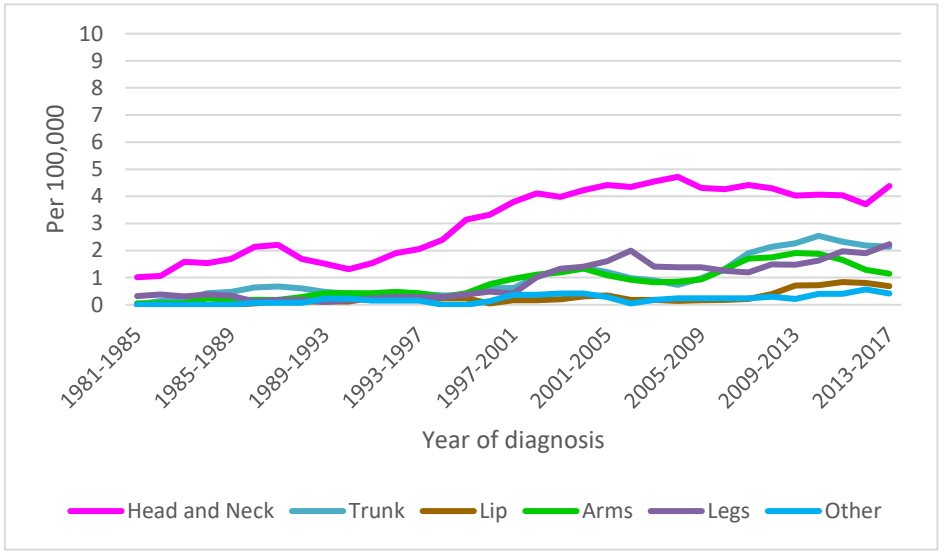


Figure 10: Trends in age-standardized (world) incidence (5-year moving averages) of invasive squamous cell carcinoma from 1981-2017 according to sex, anatomical location, and time. Men (above) and women (below). This figure has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021).

Table 2: Frequency of SCCis and invasive SCC among men and women for different anatomic locations for the study period, 1981 to 2017. This table has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021).

SCCis frequency			
Anatomic location	**Men** (n=560)	**Women** (n=974)	**p-value**
Lip	5 (1%)	9 (1%)	0.95
Head/neck	304 (54%)	438 (45%)	<0.01
Trunk	122 (22%)	194 (20%)	0.38
Arms	79 (14%)	120 (12%)	0.31
Legs	32 (6%)	195 (20%)	<0.01
Other and unknown	18 (3%)	18 (2%)	0.09
Invasive SCC frequency			
Lip	44 (6%)	27 (4%)	0.11
Head/neck	566 (74%)	372 (53%)	<0.01
Trunk	63 (8%)	100 (14%)	<0.01
Arms	71 (9%)	87 (12%)	0.06
Legs	18 (2%)	98 (14%)	<0.01
Other and unknown	7 (1%)	18 (3%)	0.01

Table 3: Trends in age-standardized (World) incidence (10-year averages) of in-situ and invasive squamous cell carcinoma from 1981-2017 according to sex, geographical area, and time per 100.000. This table has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021).

SCCis incidence				
Time-period	**Men**		**Women**	
	Reykjavik-Reykjanes	**Outside capital area**	**Reykjavik-Reykjanes**	**Outside capital area**
1981-1990	1.3 [0.5-2.1]	1.0 [0.3-1.6]	3.2 [2.1-4.3]	1.7 [0.7-2.8]
1991-1999	4.1 [2.8-5.4]	3.6 [2.1-5.1]	5.0 [4.2-5.8]	3.2 [2.1-4.3]
2000-2008	7.5 [5.9-9.0]	6.2 [4.4-8.0]	12.9 [10.9-14.8]	8.8 [6.4-11.2]
2009-2017	13.3 [11.6-15.1]	8.0 [6.1-9.8]	20.5 [18.4-22.7]	15.2 [12.4-18.0]
Invasive SCC incidence				
1981-1990	3.8 [2.5-5.0]	5.0 [3.2-6.9	2.7 [1.7-3.7]	1.4 [0.7-2.1]
1991-1999	6.0 [4.5-7.5]	5.9 [4.0-7.7]	3.6 [2.5-4.7]	3.6 [2.1-5.1]
2000-2008	9.3 [7.6-10.9]	9.7 [7.4-12.1]	8.5 [6.1-10.8]	8.4 [6.1-10.8]
2009-2017	14.5 [12.7-16.3]	10.9 [8.7-13.2]	11.5 [9.9-13.0]	9.9 [7.7-12.1]

4.1.2.4 Reykjavik and rural areas

SCCis WSR increased for all geographical areas in men and women (**table 2**). Although slightly higher overall in Reykjavik, this difference was generally insignificant. However, by the end of the study period, SCCis WSR were higher in Reykjavik than in rural areas for men and women (**table 3**) (Paper II. J. A. Adalsteinsson et al., 2021).

4.1.2.5 Joinpoint analysis

The AAPC was 7.1% (95% CI [5.9-8.4]) for SCCis in males, 7.0% (95% CI [5.8-8.2]) for SCCis in females, 3.8% (95% CI [3.1-4.6]) for invasive SCC in males and 5.2% (95% CI [4.0-6.4]) for invasive SCC in females. We saw a higher increase in in-situ incidence than invasive SCC (Paper II. J. A. Adalsteinsson et al., 2021).

Figure 11 summarizes joinpoint analysis for all sites as well as head and neck lesions. SCCis joinpoints occurred in 1987 for men and 1995 for women. After the joinpoints, the slope was 0.76 (95% CI [0.60-0.93]) for women and 0.41 (95% CI [0.36-0.47]) for men, which was statistically significant. For invasive SCC, a joinpoint occurred in 1994 for women, changing the slope from 0.15 (95% CI [0.03-0.28]) to 0.44 (95% CI [0.32-0.55]). The slope for men was 0.31 (95% CI [0.26-0.37]) throughout the study period. For SCCis, joinpoints occurred in 1991 for men and 1994 for women, but the slopes [95% CI] were similar (0.25 [0.18-0.31]) and 0.29 [0.22-0.36], respectively). For invasive SCC, no joinpoints occurred, with the slope steeper for men (0.21 [0.17-0.26]) than for women (0.15 [0.12-0.17]) (Paper II. J. A. Adalsteinsson et al., 2021).

Figure 12 summarizes joinpoint analysis for the trunk and legs. For SCCis, joinpoints occurred in 1994, 2009, and 2012 for men and 1997 for women. Notably, 2009 and 2012 joinpoints for men occurred because of a single year with a low incidence. For invasive SCC, joinpoints occurred in 2006 for women and 1998 for men. After the joinpoint occurred, the slopes were 0.08 [0.05-0.11] for men and 0.26 [0.12-0.40] for women, which was statistically significant. The incidence of SCCis leg lesions was stable throughout the study period for men. However, a steep increase in leg lesions was noted for women after a joinpoint occurred in 1997 (Paper II. J. A. Adalsteinsson et al., 2021).

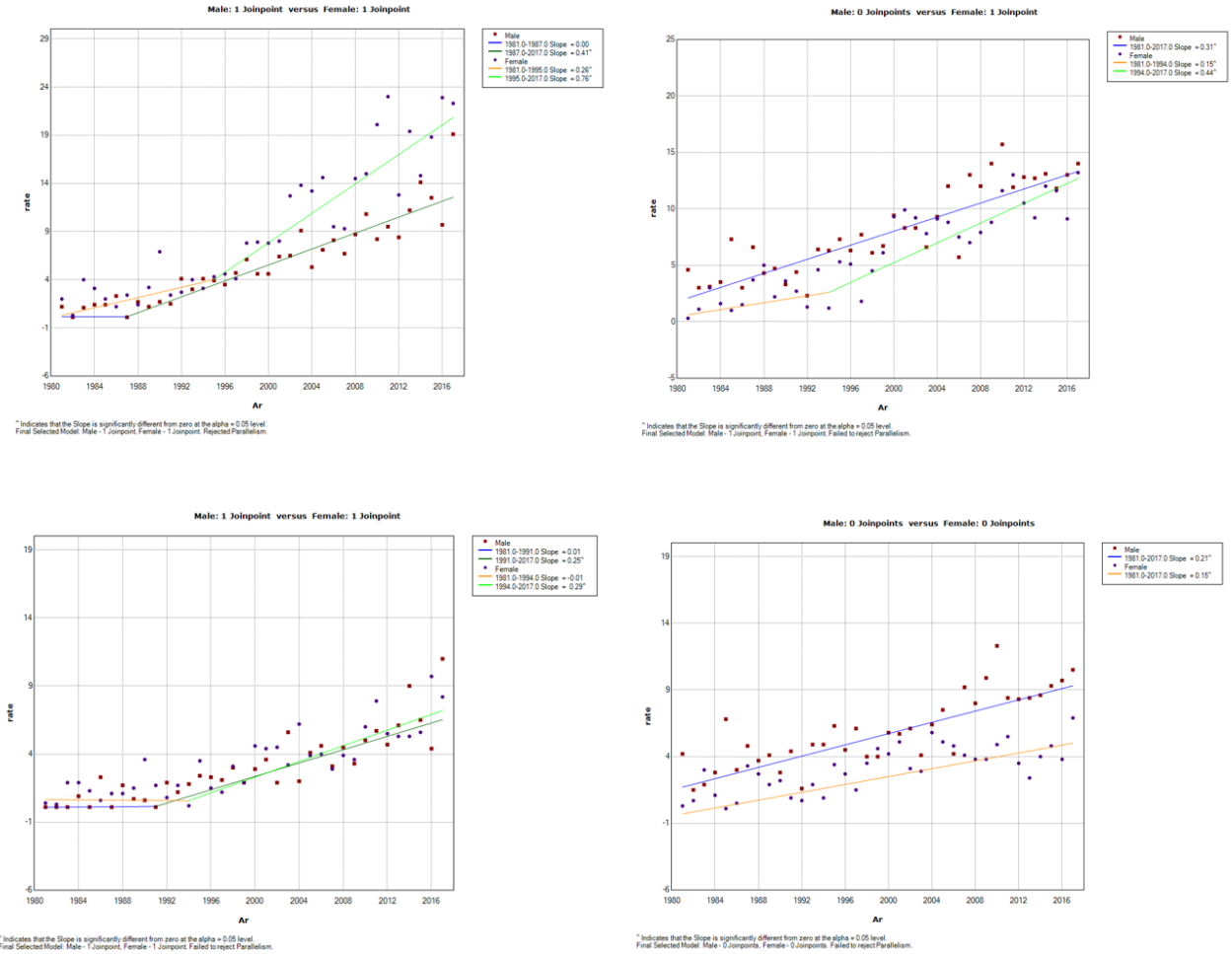


Figure 11. Joinpoint analysis for men and women. All anatomic sites for SCCis (upper left) and invasive SCC (upper right). Head and neck cancer incidence for SCCis (bottom left) and invasive SCC (bottom right), using age-standardized rates (world) per 100,000. This figure has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021).

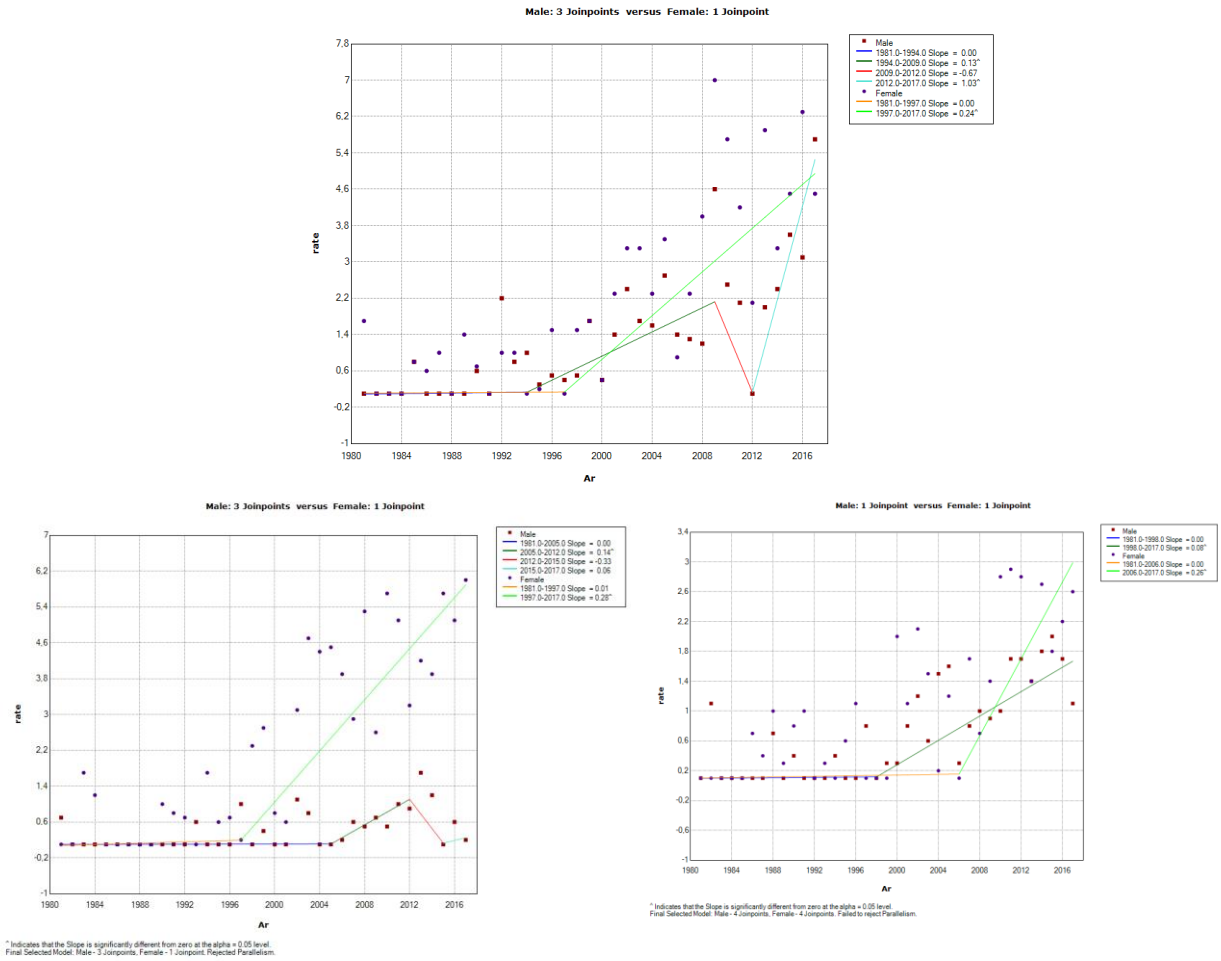


Figure 12. Joinpoint analysis in men and women. Truncal SCCis (above), truncal invasive SCC (bottom left), and in-situ lesions of the legs (bottom right) using age-standardized rates (world) per 100,000. This figure has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021).

4.1.2.6 Multiplicity

The total number of SCCis lesions during the study period was 2,443 in 1,534 cases. The median interval between 1st and 2nd SCCis was 1.3 for women and 1.5 years for men. The median interval between 1st and 2nd invasive SCC was 1.6 for women and 2.3 years for men. Women had 1.71 [1-20] lesions on average compared to 1.39 [1-15] ($p<0.01$) in men. 29% of women and 19% of men had ≥2 lesions ($p<0.01$). The total number of invasive SCC during the study period was 2,144 lesions in 1,471 cases. Women and men had a similar number of lesions on average, or 1.49 [1-29] and 1.43 [1-13], respectively ($p=0.45$). 22% of men and 18% of women had ≥2 lesions ($p=0.09$). Women had a significantly higher number of in-situ lesions on average compared to invasive lesions ($p<0.01$), while men had a similar average number of in-situ and invasive lesions ($p=0.24$) (Paper II. J. A. Adalsteinsson et al., 2021).

Table 2 shows age-specific incidence rates by sex and age. Women had higher SCCis age-specific rates for single and multiple lesions for all ages. Invasive SCC age-specific rates were similar between sexes for ages < 65 years, whereas in the 65+ category, men had significantly higher age-specific rates for developing single or multiple invasive SCCs (Paper II. J. A. Adalsteinsson et al., 2021).

4.1.2.7 Lifetime- and Cumulative risk

The lifetime invasive SCC risk (95% CI) in the 2009-2017 period was similar in men (1.7% [1.5-1.9]) and women (1.6% [1.4-1.8]). SCCis lifetime risk in women (2.8% [2.6-3.0]) was significantly higher than in men (1.6% [1.4-1.8]). SCCis lifetime risk for women increased 9.3 fold since 1981-1990 when it was 0.3%. The cumulative invasive SCC risk was 0.3% for both men and women <65 years. The cumulative SCCis risk was 0.7% for women <65 years of age and 0.4% for men <65. This was an increase from 0.0% in men and 0.1% in women during the 1981-1990 (Paper II. J. A. Adalsteinsson et al., 2021).

Table 4: Single and multiple SCCis and invasive SCC age-specific incidence rates per 100,000 during 1981-2017, stratified by sex and age. Age-standardized (world) incidence rate per 100,000 is reported for each sex in each category. This table has been previously published by Adalsteinsson et al. in the British Journal of Dermatology (Paper II. J. A. Adalsteinsson et al., 2021).

	All SCCis		Single SCCis		Multiple SCCis	
	(n)	Rate [95% CI]	(n)	Rate [95% CI]	(n)	Rate [95% CI]
Male						
<40	7	0.1 [0.0-0.3]	6	0.1 [0.0-0.2]	1	0.0 [0.0-0.1]
40-64	100	6.9 [5.6-8.3]	77	5.4 [4.2-6.6]	23	1.6 [0.9-2.2]
65+	453	69.5 [62.8-76.2]	373	56.9 [50.9-62.9]	80	12.6 [9.7-15.5]
WSR	560	6.7 [6.1-7.3]	456	5.4 [4.9-5.9]	104	1.3 [1.0-1.6]
Female						
<40	21	0.5 [0.3-0.8]	18	0.5 [0.2-0.7]	3	0.1 [0.0-0.2]
40-64	214	15.0 [13.0-17.1]	155	10.8 [9.1-12.5]	59	4.2 [3.1-5.3]
65+	739	91.0 [83.8-98.2]	519	62.3 [56.4-68.1]	220	28.7 [24.6-32.9]
WSR	974	10.5 [9.8-11.2]	692	7.4 [6.8-8.0]	282	3.1 [2.7-3.5]
	All invasive SCCs		**Single invasive SCCs**		**Multiple invasive SCCs**	
	(n)	Rate [95% CI]	(n)	Rate [95% CI]	(n)	Rate [95% CI]
Male						
<40	6	0.1 [0.0-0.3]	5	0.1 [0.0-0.2]	1	0.0 [0.0-0.1]
40-64	114	7.9 [6.4-9.3]	91	6.3 [5.0-7.6]	23	1.6 [0.9-2.2]
65+	649	98.0 [90.2-105.8]	507	76.8 [69.9-83.8]	142	21.2 [17.6-24.8]
WSR	769	8.9 [8.3-9.6]	603	7.0 [6.4-7.6]	166	1.9 [1.6-2.2]
Female						
<40	7	0.2 [0.0-0.3]	6	0.2 [0.0-0.3]	1	0.0 [0.0-0.1]
40-64	118	8.2 [6.7-9.6]	91	6.3 [5.0-7.6]	27	1.9 [1.2-2.6]
65+	577	67.6 [61.6-73.7]	1604	56.0 [50.5-61.5]	99	11.6 [9.1-14.1]
WSR	702	6.9 [6.3-7.5]	575	5.6 [5.1-6.1]	127	1.3 [1.0-1.6]

4.2 Medications as risk factors

4.2.1 Hydrochlorothiazide (Study III)

The results in this chapter have previously been published as paper III in the Journal of the American Academy of Dermatology (Paper III. Jonas A. Adalsteinsson et al., 2020). 1,013 patients with invasive SCC, 1,167 with SCCis, and 4,700 with BCC were identified and age- and sex-matched with 10,367, 11,961 and 47,292 controls respectively. **Table 5** contains patient characteristics. Females constituted 58%, 64%, and 49% of patients with BCC, SCCis, and invasive SCC, respectively.

The relationship between HCTZ exposure and KC risk is reported in **table 6** and **figure 13**. Of individuals with invasive SCC, 8.9% were users of HCTZ as compared to 8.6% of controls. There was no difference in invasive SCC risk between HCTZ users and controls at low and moderate doses. Cumulative HCTZ doses greater than 1,500 DDUs (37,500 mg) were associated with an increased risk of invasive SCC (OR [95% CI]: 1.69 [1.04 – 2.74]. Of individuals diagnosed with SCCis, 10.0% were users of HCTZ compared to 8.2% of controls. HCTZ users demonstrated a significant increase in SCCis risk as compared to controls (OR [95% CI]: 1.24 [1.01 – 1.52]). Of individuals diagnosed with BCC, 7.4% were users of HCTZ compared to 6.5% of controls. HCTZ use was associated with an increased risk of developing BCC (OR [95% CI]: 1.14 [1.02 – 1.29]). Dose-response relationship was statistically significant for BCC ($p = 0.02$) but not for SCCis ($p = 0.64$) or invasive SCC ($p = 0.1$) (**figure 13)**.

With subgroup analysis (**table 7**), HCTZ use was associated with a significant increase in the risk of SCCis in males and people aged 50 and above (OR [95% CI]: 1.45 [1.03 – 2.04] and (OR [95% CI]: 1.23 [1.00 – 1.52], respectively). HCTZ use was also associated with a significant increase in BCC risk in people >50 (OR [95% CI]: 1.15 [1.02 – 1.30]) (Paper III. Jonas A. Adalsteinsson et al., 2020).

Table 5: Characteristics of patients with BCC, in SCCis and invasive SCC, and age and sex-matched controls (Paper III. Jonas A. Adalsteinsson et al., 2020).

	BCC		SCCis		Invasive SCC	
	Case	Control	Case	Control	Case	Control
	(n = 4,700)	(n = 47,292)	(n = 1,167)	(n = 11,961)	(n = 1,013)	(n = 10,376)
Age, Median (IQR)	69 (56- 79)	69 (56- 79)	77 (67 - 84)	77 (67 - 84)	79 (71 - 85)	79 (70 - 85)
Male sex	1,988 (42.3%)	20,022 (42.3%)	425 (36.4%)	4368 (36.5%)	521 (51.4%)	5309 (51.2%)
HCTZ Never use	4,354 (92.6%)	44,226 (93.5%)	1051 (90.1%)	10982 (91.8%)	923 (91.1%)	9473 (91.4%)
HCTZ Ever use	346 (7.4%)	3,066 (6.5%)	116 (10.0%)	979 (8.2%)	90 (8.9%)	894 (8.6%)

Table 6: Association between HCTZ use and risk of BCC, SCCis, and invasive SCC (Paper III. Jonas A. Adalsteinsson et al., 2020).

	Cases	Controls	OR (95% CI)	Adjusted OR (95% CI)*
BCC				
Never Use	4,354	44,226	1.00	1.00
Ever Use	346	3,066	1.15 (1.02 - 1.30)	1.14 (1.02 - 1.29)
Cumulative Dosage				
1-500 DDU (25-12,500 mg)	210	1,981	1.08 (0.93 - 1.25)	1.07 (0.93 - 1.24)
501-1500 DDU (12,525-37,500 mg)	87	734	1.22 (0.97 - 1.53)	1.21 (0.97 - 1.52)
>1500 DDU (>37,500 mg)	49	351	1.43 (1.06 - 1.94)	1.42 (1.05 - 1.92)
Trend Test	p=0.02			
SCCis				
Never Use	1051	10,982	1.00	1.00
Ever Use	116	979	1.24 (1.01 - 1.53)	1.24 (1.01 - 1.52)
Cumulative Dosage				
1-500 DDU (25-12,500 mg)	68	639	1.12 (0.86 - 1.45)	1.11 (0.86 - 1.45)
501-1500 DDU (12,525-37,500 mg)	32	215	1.55 (1.06 - 2.26)	1.55 (1.06 - 2.26)
>1500 DDU (>37,500 mg)	16	125	1.34 (0.79 - 2.28)	1.35 (0.79 - 2.29)
Trend Test	p=0.64			
Invasive SCC				
Never Use	923	9,473	1.00	1.00
Ever Use	90	894	1.03 (0.82 - 1.30)	1.02 (0.81 - 1.29)
Cumulative Dosage				
1-500 DDU (25-12,500 mg)	49	568	0.88 (0.65 - 1.20)	0.87 (0.64 - 1.18)
501-1500 DDU (12,525-37,500 mg)	21	205	1.05 (0.67 - 1.66)	1.05 (0.66 - 1.66)
>1500 DDU (>37,500 mg)	20	121	1.67 (1.03 - 2.71)	1.69 (1.04 - 2.74)
Trend Test	p=0.1			

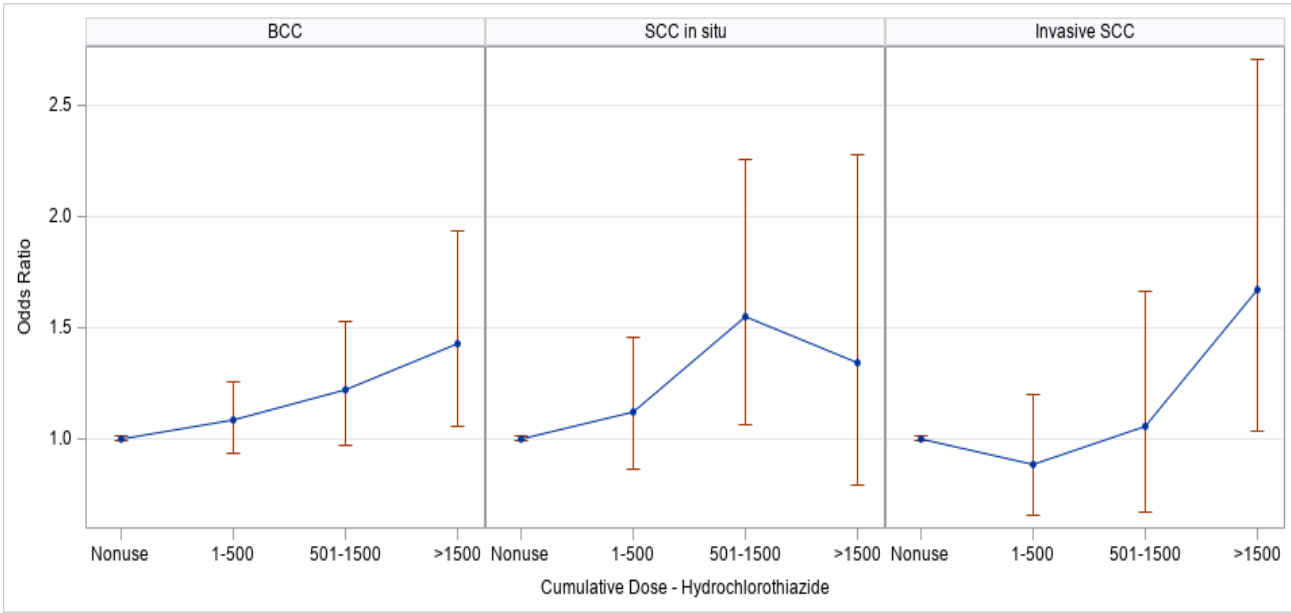
*Model adjusted for the use of the following photosensitizing medications: tetracyclines, oral retinoids, and topical retinoids.

Table 7: Associations of HCTZ use and KC by subgroup (Paper III. Jonas A. Adalsteinsson et al., 2020).

Subgroup	Case patients (exposed/ unexposed)	Controls (exposed/ unexposed)	OR (95% CI)	Adjusted OR (95% CI)*
BCC				
Male	136/1852	1226/18796	1.13 (0.94 - 1.37)	1.12 (0.93 - 1.36)
Female	210/2502	1840/25430	1.16 (1.00 - 1.36)	1.16 (0.99 - 1.35)
< 50 y	7/740	73/7445	0.97 (0.44 - 2.12)	0.72 (0.61 - 0.86)
≥ 50 y	339/3614	2993/36781	1.16 (1.03 - 1.30)	1.15 (1.02 - 1.30)
SCCis				
Male	44/381	328/4040	1.45 (1.04 - 2.04)	1.45 (1.03 - 2.04)
Female	72/670	651/6942	1.14 (0.88 - 1.48)	1.13 (0.87 - 1.47)
< 50 y	1/63	4/671	2.65 (0.27 - 26.29)	2.21 (0.21 - 22.94)
≥ 50 y	115/988	975/10311	1.24 (1.00 - 1.52)	1.23 (1.00 - 1.52)
Invasive SCC				
Male	39/482	389/4920	1.01 (0.71 - 1.43)	1.01 (0.71 - 1.43)
Female	51/441	505/4553	1.05 (0.77 - 1.43)	1.03 (0.75 - 1.41)
< 50 y	0/35	0/380	-	-
≥ 50 y	90/888	894/9093	1.03 (0.82 - 1.30)	1.021 (0.810 - 1.29)

*Model adjusted for the use of the following photosensitizing medications: tetracyclines, oral retinoids, and topical retinoids

Figure 13: Dose-response relationships between cumulative HCTZ dosage and risk of BCC, SCCis, and invasive SCC (Paper III. Jonas A. Adalsteinsson et al., 2020).



*Continuous trend test resulted in a p-value of 0.02, 0.64, and 0.1, respectively.

4.2.2 Statins (Study IV)

The results in this chapter have previously been published in the Archives of Dermatological Research (Paper IV. Jonas A. Adalsteinsson, Muzumdar, Waldman, Hu, Wu, Ratner, Feng, et al., 2021). 4,700 patients with BCC, 1,167 patients with SCCis and 1,013 patients with invasive SCC were identified and paired with 47,292, 11,961 and 10,367 controls respectively (**table 8**). Statin use was not associated with BCC but was associated with an increased risk of invasive SCC and SCCis (adjusted OR [95% CI]: 1.29 [1.11-1.50]; 1.43 [1.24-1.64]; 1.03 [0.95-1.12] respectively). Subgroup analysis was performed. It demonstrated that statins were significantly associated with invasive SCC and SCCis in patients over 60 but not in those under 60 (**table 9**).

Table 8: Demographics of patients with BCC, SCCis, and invasive SCC and age and sex-matched controls (Paper IV. Jonas A. Adalsteinsson, Muzumdar, Waldman, Hu, Wu, Ratner, Feng, et al., 2021).

	BCC		**SCCis**		**Invasive SCC**	
	Case (n=4,700)	**Control (n=47,292)**	**Case (n=1,167)**	**Control (n=11,961)**	**Case**	**Control**
Age: Median (IQR)	69 (56 - 79)	69 (56 - 79)	77 (67 - 84)	77 (67 - 84)	79 (71 - 85)	79 (70 - 85)
Male sex	1988 (42.30%)	20022 (42.34%)	425 (36.42%)	4368 (36.52%)	521 (51.43%)	5309 (51.21%)
Use of Statin	1093 (23.26%)	10661 (22.54%)	405 (34.70%)	3350 (28.01%)	365 (36.03%)	3185 (30.72%)

Table 9: Association between statin exposure and risk of BCC, SCCis, and invasive SCC with subgroup analysis (Paper IV. Jonas A. Adalsteinsson, Muzumdar, Waldman, Hu, Wu, Ratner, Feng, et al., 2021).

	Cases (exposed/ unexposed)	**Controls (exposed/ unexposed)**	**OR (95% CI)**	**Adjusted OR (95% CI) ***	**Adjusted OR (95% CI)****
BCC	1,093/3,607	10,661/36,631	1.05 (0.97 - 1.14)	1.05 (0.97-1.13)	1.03 (0.95 - 1.12)
Cumulative Dose					
1-500 DDU	315	3,000	1.07 (0.95 - 1.22)	1.07 (0.94-1.21)	1.06 (0.93 - 1.20)
501-1500 DDU	363	3,448	1.08 (0.96 - 1.21)	1.07 (0.95-1.20)	1.06 (0.94 - 1.19)
>1500 DDU	415	4,213	1.01 (0.90 - 1.13)	1.00 (0.81.13)	0.99 (0.88 - 1.11)
Subgroup					
Male	588/1400	5696/14326	1.07 (0.96 - 1.20)	1.07 (0.95-1.19)	1.05 (0.94 - 1.18)
Female	505/2207	4965/22305	1.03 (0.92 - 1.16)	1.03 (0.92-1.15)	1.01 (0.91 - 1.13)
<60 years old	61/1364	680/13703	0.90 (0.69 - 1.19)	0.89 (0.67-1.17)	0.87 (0.66 - 1.14)
≥60 years old	1032/2243	9981/22928	1.07 (0.98 - 1.16)	1.06 (0.98-1.15)	1.05 (0.98 - 1.14)
Simvastatin	574/3607	5527/36631	1.07 (0.97 - 1.18)	1.06 (0.96-1.17)	1.05 (0.95 - 1.16)
Atorvastatin	220/3607	2081/36631	1.07 (0.92 - 1.24)	1.06 (0.91-1.23)	1.05 (0.91 - 1.23)
SCCis	405/762	3,350/8,611	1.45 (1.26 - 1.67)	1.44 (1.25-1.66)	1.43 (1.24 - 1.64)
Cumulative Dose					
1-500 DDU	97	864	1.33 (1.05 - 1.67)	1.32 (1.05 - 1.65)	1.31 (1.05 - 1.65)
501-1500 DDU	126	1,091	1.37 (1.12 - 1.69)	1.36 (1.11 - 1.67)	1.35 (1.09 - 1.66)
>1500 DDU	182	1,395	1.63 (1.34 - 1.97)	1.61 (1.33 - 1.96)	1.59 (1.32 - 1.93)
Subgroup					
Male	170/255	1505/2863	1.33 (1.07 - 1.67)	1.31 (1.05-1.64)	1.30 (1.04 - 1.63)
Female	235/507	1845/5748	1.53 (1.28 - 1.83)	1.53 (1.27-1.83)	1.51 (1.26 - 1.81)
<60 years old	9/133	74/1466	1.55 (0.72 - 3.30)	1.50 (0.70-3.23)	1.47 (0.68 - 3.15)

≥60 years old	396/629	3276/7145	1.45 (1.25 - 1.67)	1.44 (1.25-1.66)	1.43 (1.24 -1.65)
Simvastatin	226/762	1760/8611	1.50 (1.26 - 1.78)	1.49 (1.25-1.76)	1.47 (1.23 - 1.74)
Atorvastatin	68/762	569/8611	1.35 (1.02 - 1.78)	1.34 (1.01-1.77)	1.34 (1.01 - 1.77)
Invasive SCC	365/648	3,185/7,182	1.31 (1.13 - 1.51)	1.31 (1.13-1.51)	1.29 (1.11 - 1.50)
Cumulative Dose					
1-500 DDU	86	759	1.28 (1.00 - 1.63)	1.28 (1.00 - 1.63)	1.27 (1.00 - 1.62)
501-1500 DDU	125	1038	1.36 (1.10 - 1.68)	1.36 (1.10 - 1.68)	1.35 (1.09 - 1.67)
>1500 DDU	154	1388	1.28 (1.04 - 1.57)	1.28 (1.04 - 1.57)	1.26 (1.02 - 1.54)
Subgroup					
Male	215/306	1936/3373	1.25 (1.02 -1.52)	1.25 (1.02-1.52)	1.24 (1.01 - 1.51)
Female	150/342	1249/3809	1.38 (1.11 - 1.73)	1.38 (1.11-1.73)	1.37 (1.10 - 1.71)
<60 years old	Jul-88	59/969	1.19 (0.49 - 2.88)	1.28 (0.53-3.10)	1.24 (0.51 - 3.02)
≥60 years old	358/560	3,126/6,213	1.31 (1.12 - 1.52)	1.30 (1.12-1.52)	1.29 (1.11 - 1.50)
Simvastatin	203/648	1679/7182	1.37 (1.15 - 1.64)	1.37 (1.15-1.65)	1.35 (1.13 - 1.62)
Atorvastatin	68 /648	577 /7182	1.28 (0.97 - 1.69)	1.28 (0.97-1.69)	1.27 (0.96 - 1.68)

*Adjusted for HCTZ.

**Adjusted for HCTZ and photosensitizing medications (tetracyclines, oral retinoids, and topical retinoids).

4.2.3 TNF-inhibitors (Study V)

The results in this chapter have been previously published as paper V in the Journal of the American Association of Dermatology (Paper V. Jonas A. Adalsteinsson, Muzumdar, Waldman, Hu, Wu, Ratner, Ungar, et al., 2021). Age and sex matching was performed on 4,700 patients with BCC, 1,013 with SCC and 1,167 with SCCis and 47,293, 10,367 and 11,961 controls respectively (**Table 10**). TNFis were associated with an increased risk of SCCis (aOR [95% CI]: 3.13 [1.15-8.55]) (**Table 11**). There was no association with an increased risk of SCC. Exposure was not associated with increased risk of BCC. Sub-analysis revealed a slightly increased risk in individuals receiving TNFis for >3 years (OR [95% CI]: 2.28 [1.10-4.74]) (**Table 11**), but not >3 years (Paper V. Jonas A. Adalsteinsson, Muzumdar, Waldman, Hu, Wu, Ratner, Ungar, et al., 2021).

Table 10: Summary of patients with SCC, SCCis, and BCC and age and sex-matched controls (Paper V. Jonas A. Adalsteinsson, Muzumdar, Waldman, Hu, Wu, Ratner, Ungar, et al., 2021).

	SCC		SCCis		BCC	
	Case (n=1013)	**Control (n=10367)**	**Case (n=1167)**	**Control (n=11961)**	**Case (n=4700)**	**Control (n=47293)**
Age, median (IQR)	79 (71 - 85)	79 (70 - 85)	77 (67 - 84)	77 (67 - 84)	69 (56 - 79)	69 (56 - 79)
Male sex	521 (51.43%)	5309 (51.21%)	425 (36.42%)	4368 (36.52%)	1988 (42.30%)	20023 (42.34%)
Use of photosensitizing medication	403 (39.78%)	3597 (34.70%)	483 (41.39%)	4430 (37.04%)	1735 (36.91%)	15810 (33.43%)
Use of HCTZ	90 (8.88%)	894 (8.62%)	116 (9.94%)	979 (8.18%)	346 (7.36%)	3065 (6.48%)
Use of TNFi	3(0.30%)	16(0.15%)	5(0.43%)	19(0.16%)	12(0.26%)	70(0.15%)

Table 11: Association between TNFi exposure and incidence of BCC and SCC with subgroup analysis. (Paper V. Jonas A. Adalsteinsson, Muzumdar, Waldman, Hu, Wu, Ratner, Ungar, et al., 2021).

	Cases exposed/unexposed	Controls exposed/unexposed	Adjusted OR (95% CI)*
SCC	3/1,010	16/10,351	1.80 (0.51-6.34)
Male	1/520	7/5,302	1.37 (0.16-11.66)
Female	2/490	9/5,049	2.10 (0.44-10.09)
< 50 y	1/34	0/380	NA
≥ 50 y	2/976	16/9,971	1.19 (0.27-5.31)
≤ 3 years cumulative usage	1	8	1.26 (0.16-10.12)
> 3 years cumulative usage	2	8	2.28 (0.48-10.79)
SCCis	5/1,162	19/11,942	3.13 (1.15-8.55)
Male	1/424	3/4365	5.02 (0.45-55.69)
Female	4/738	16/7577	2.84 (0.93-8.63)
< 50 y	0/64	2/673	NA
≥ 50 y	5/1,098	17/11269	3.37 (1.22-9.28)
≤ 3 years cumulative usage	1	4	3.48 (0.36-33.51)
> 3 years cumulative usage	4	15	3.05 (0.99-9.37)
BCC	12/4,688	70/47,223	1.68 (0.91-3.11)
Male	4/1984	21/20002	1.82 (0.62-5.36)
Female	8/2704	49/27221	1.62 (0.76-3.42)
< 50 y	1/746	9/7509	1.00 (0.12-8.13)
≥ 50 y	11/3942	61/39714	1.78 (0.93-3.38)
≤ 3 years cumulative usage	9	39	2.28 (1.10-4.74)
> 3 years cumulative usage	3	31	0.94 (0.29-3.08)

* Odds ratio adjusted for the use of oral and topical retinoids, tetracyclines, and HCTZ.

4.2.4 Metformin (Study VI)

The results in this chapter have been previously published as paper VI in the Journal of the American Association of Dermatology (Paper VI. Jonas A. Adalsteinsson, Muzumdar, Waldman, Wu, et al., 2021). 4,700 individuals with BCC, 1,167 with SCCis and 1,013 with invasive SCC were identified and matched with 47,293, 11,961 and 10,367 controls respectively (**table 12**).

The relationship between metformin use and KC risk is summarized in **table 13**. 4.0% of individuals with BCC and 5.3% of controls were exposed to metformin. Use was associated with a significantly lower risk of BCC (Adjusted OR [95% CI]: 0.71 [0.61-0.83]). When looking at SCCis, 7.5% compared to 6.2% of controls were exposed to metformin. Metformin use was not significantly associated with SCCis (Adjusted OR [95% CI]: 1.06 [0.84-1.35]). Finally, looking at SCC, 7.2% compared to 6.6% of controls were exposed to metformin. Metformin use was not significantly associated with invasive SCC (Adjusted OR [95% CI]: 1.01 [0.78-1.30]). Dose-response relationships were not statistically significant for BCC, SCCis, or invasive SCC (p = 0.87, 0.94, and 0.88, respectively) (Jonas A. Adalsteinsson, Muzumdar, Waldman, Wu, et al., 2021).

Table 12: Characteristics of individuals with BCC, SCCis, and SCC and age and sex-matched controls (Paper VI. Jonas A. Adalsteinsson, Muzumdar, Waldman, Wu, et al., 2021).

	BCC		SCCis		SCC	
	Case (n=4,700)	**Control (n=47,293)**	**Case (n=1,167)**	**Control (n=11,961)**	**Case (n=1,013)**	**Control (n=10,367)**
Age, Median (IQR)	69 (56 - 79)	69 (56 -79)	77 (67 - 84)	77 (67 - 84)	79 (71 - 85)	79 (70 - 85)
Male Sex	1988 (42.30%)	20023 (42.34%)	425 (36.42%)	4368 (36.52%)	521 (51.43%)	5309 (51.21%)
Metformin ever use	189 (4.02%)	2500 (5.29%)	87 (7.46%)	740 (6.19%)	73 (7.21%)	687 (6.63%)
Metformin never use	4511 (95.98%)	44793 (94.71%)	1080 (92.54%)	11221 (93.81%)	940 (92.79%)	9680 (93.37%)

Table 13: Association between metformin and BCC, SCCis, and SCC. Doses are depicted in grams (g) (Paper VI. Jonas A. Adalsteinsson, Muzumdar, Waldman, Wu, et al., 2021).

	Cases	Controls	OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)**	Adjusted OR (95% CI)***	Adjusted OR (95% CI)****
BCC							
Never Use	4511	44793	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever Use	189	2500	0.75 (0.64 - 0.87)	0.74 (0.63-0.86)	0.73 (0.63 - 0.85)	0.71 (0.61 - 0.83)	0.71 (0.61 - 0.83)
Cumulative Dose							
1-500 DDUs (2-1000g)	79	1041	0.75 (0.60 - 0.95)	0.75 (0.59-0.94)	0.74 (0.58 - 0.93)	0.72 (0.57 - 0.91)	0.72 (0.57 - 0.91)
501-1500 DDUs (1002-3000g)	60	816	0.73 (0.56 - 0.95)	0.72 (0.54-0.93)	0.71 (0.54 - 0.93)	0.69 (0.53 - 0.90)	0.69 (0.53 - 0.90)
>1500 DDUs (>3000g)	50	643	0.77 (0.57 - 1.03)	0.76 (0.57-1.01)	0.75 (0.56 - 1.00)	0.73 (0.54 - 0.98)	0.73 (0.54 - 0.98)
Continuous Trend Test	p = 0.87						
SCCis							
Never Use	1080	11221	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever Use	87	740	1.22 (0.97 - 1.54)	1.20 (0.95-1.52)	1.20 (0.95 - 1.51)	1.06 (0.84-1.35)	1.06 (0.84-1.35)
Cumulative Dose							
1-500 DDUs (2-1000g)	25	281	0.92 (0.61-1.40)	0.91 (0.60-1.38)	0.91 (0.60-1.37)	0.83 (0.55 -1.27)	0.84 (0.55 -1.27)
501-1500 DDUs (1002-3000g)	43	273	1.64 (1.18-2.27)	1.61 (1.16-2.24)	1.59 (1.15-2.22)	1.40 (1.00 -1.96)	1.40 (1.00 -1.96)
>1500 DDUs (>3000g)	19	186	1.06 (0.65-1.71)	1.05(0.65-1.69)	1.05 (0.65-1.71)	0.91 (0.56-1.48)	0.90 (0.56-1.47)
Continuous Trend Test	p = 0.94						
SCC							
Never Use	940	9680	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever Use	73	687	1.10 (0.85- 1.42)	1.10 (0.85-1.42)	1.09 (0.85 - 1.41)	1.01 (0.78-1.30)	1.01 (0.78- 1.30)
Cumulative Dose							
1-500 DDUs (2-1000g)	24	267	0.93 (0.61-1.42)	0.93 (0.60-1.42)	0.92 (0.60-1.40)	0.86 (0.56-1.32)	0.86 (0.56 -1.32)
501-1500 DDUs (1002-3000g)	33	234	1.47 (1.01-2.14)	1.47 (1.01-2.14)	1.47 (1.01-2.14)	1.35 (0.92-1.97)	1.35 (0.92 -1.97)
>1500 DDUs (>3000g)	16	186	0.89 (0.53-1.50)	0.89 (0.53-1.50)	0.89 (0.53-1.50)	0.79 (0.47-1.34)	0.79 (0.47-1.34)
Continuous Trend Test	p = 0.88						

*Adjusted for HCTZ. **Adjusted for HCTZ and photosensitizing medications. ***Adjusted for HCTZ, photosensitizing medications, and statins. ****Adjusted for HCTZ, photosensitizing medications, statins, and TNFis

Table 14: Associations of metformin use and KC risk by subgroup (Paper VI. Jonas A. Adalsteinsson, Muzumdar, Waldman, Wu, et al., 2021).

Subgroup	Case patients (exposed / unexposed)	Controls (exposed / unexposed)	OR (95% CI)	Adjusted OR (95% CI)
BCC				
Male	100/1888	1314/18709	0.75 (0.61-0.93)	0.71 (0.57-0.88)
Female	89/2623	1186/26084	0.75 (0.60-0.93)	0.72 (0.57-0.90)
< 60 y	27/1398	309/14074	0.88 (0.59-1.31)	0.86 (0.57-1.30)
≥ 60 y	162/3113	2191/30719	0.73 (0.62-0.86)	0.69 (0.59-0.82)
SCCis				
Male	39/386	345/4023	1.18 (0.83-1.68)	1.06 (0.74-1.52)
Female	48/694	395/7198	1.25 (0.92-1.71)	1.06 (0.77-1.47)
< 60 y	4/138	32/1508	1.34 (0.46-3.88)	1.04 (0.34-3.21)
≥ 60 y	83/942	708/9713	1.21 (0.96-1.54)	1.06 (0.83-1.36)
SCC				
Male	50/471	435/4874	1.12 (0.88-1.64)	1.12 (0.81-1.54)
Female	23/469	252/4806	0.94 (0.61-1.46)	0.83 (0.53-1.30)
< 60 y	2/93	23/1005	1.17 (0.27-5.177)	1.10 (0.23-5.35)
≥ 60 y	71/847	664/8675	1.10 (0.85-1.42)	1.01 (0.77-1.31)

Subgroup analysis is shown in **table 14**. Metformin use was associated with a decreased risk of BCC in both men and women (Adjusted OR [95% CI]: 0.71 [0.57-0.88] and 0.72 [0.57-0.90] respectively). In addition, individuals over the age of 60 had a decreased risk of BCC with metformin exposure (Adjusted OR [95% CI]: 0.69 [0.59-0.82]) (Paper VI. Jonas A. Adalsteinsson, Muzumdar, Waldman, Wu, et al., 2021).

5 Discussion

5.1 Main findings

- **KC epidemiology**
    - We observed a steep rise in KC incidence in a country with very low background UVR (Weather-Atlas/Reykjavik, n.d.). This initial increase was associated with a surge in tanning bed use, increased level of travel abroad, and increased dermatology access. Today, tanning bed use in Iceland has decreased, but the incidence is still increasing.
    - This observed rise was explicitly present in women, especially young women, and was most pronounced for BCC and SCCis. Iceland is the only population to our knowledge in which women are reported to have a statistically higher incidence of BCC and SCCis than men.
    - In women, the rise was most prominent on anatomic sites that are not typically sun-exposed in Iceland, such as the legs and trunk, strongly suggesting that indoor tanning devices, travel abroad, and increased dermatology access played a significant role in the incidence increase.
    - In men, most lesions were on the head and neck, and almost none occurred on the legs, signifying the possibility of significant behavioral differences between men and women. Men might be more susceptible to chronic outdoor UVR exposure.
    - Men were more likely to develop more serious, invasive SCC, and women were more likely to develop multiple superficial and less severe BCCs and SCCiss.
    - Lesions of the lip were more likely than lesions on other anatomic sites to be invasive rather than in-situ.
    - The total KC tumor burden worldwide is most likely underestimated by a large margin.

- **Risk in association with medication**
    - This is the first whole population study to our knowledge looking at the relationship between selected medications and SCCis.
    - In a country where KC is sharply rising, we observed a relationship between increased KC risk with three different medications and identified a single medication associated with lower BCC risk.
    - We saw an increased risk of all KC subtypes with the photosensitizer HCTZ, signifying that HCTZ use places patients at increased risk for developing skin cancer even in a low UV environment. This risk is likely much higher in high UVR environments such as Australia and the USA.
    - We observed an increased risk of both invasive and SCCis, but not BCC, in patients taking statins. Simvastatin was associated with both SCCis and invasive SCC, but atorvastatin was only associated with SCCis. It is unclear whether this result simply signifies that patients on statins represent a population with a higher baseline risk for skin cancer.
    - TNFis were associated with SCCis, but not invasive SCC. It is unclear whether this is due to T-cell suppressive functions or whether past PUVA/nbUVB exposure could play a role. Regardless, physicians who prescribe TNFis should be aware of this association.
    - Metformin was strongly associated with decreased risk of BCC, but not SCC. The fact that SCC risk was unchanged makes potential confounding less likely. This association needs to be further studied in prospective controlled trials, but metformin could be a preventive option for patients who develop multiple BCCs and are poor surgical candidates.

5.2 Epidemiology of keratinocyte carcinoma (Studies I-II)

This is the first whole population study to our knowledge looking at the nationwide incidence of BCC, invasive SCC, and SCCis, while simultaneously assessing multiplicity proportions. Skin cancer used to be rare in the Icelandic population. However, KC has become some of the most prevalent cancers in this population, and its gender specific incidence has now surpassed that of lung and colon cancer, and comes very closely behind breast and prostate cancer (*Icelandic Cancer Institute - Cancer Age Standardized Incidence Rates*, n.d.). These trends are concerning since Reyjavik has low background UVR. In fact, Reykjavik's background UVR is lower than those of all other capital cities. In addition, Iceland has a higher proportion of cloudy days than sunny days, which is considered unusual by many who travel there, making for a relatively protective UV environment compared to many other countries (*Weather-Atlas/Reykjavik*, n.d.). At the beginning of the study period, the WSR for KC was lower than in most other countries. By the end of the study period, while the overall WSR for KC was still low, it had surpassed those of other countries, including Malta, Lithuania, Slovenia, and Croatia (de Vries et al., 2012; Jurciukonyte et al., 2013; Lomas, 2012b).

Our study emphasizes a dramatic disparity in skin cancer incidence between men and women. While KC incidence did increase for both genders, invasive SCC incidence increased a staggering 44-fold in women throughout the study period, compared to 5-fold for women over a similar time in a recent study from the Netherlands (Tokez et al., 2020). The extent to which KC increased in women was also noteworthy, as they are considered to be at much lower risk for KC than men. There are a few potential explanations that will be discussed later in this chapter, but there is no clear correlation between KC incidence and latitude on the European continent (Lomas, 2012b).

5.2.1 The relationship between sex and anatomic site

One of the more unique aspects of our results is the dramatic disparity observed between men and women in multiple features within the analysis. Men had a higher overall KC incidence at the beginning of the study period; however, we observed much steeper incidence slopes for women in the joinpoint analysis, with women also being younger when diagnosed with KC. By the end of the study period, women had surpassed men in most categories. In 2017, women had a considerably higher incidence of BCC and SCCis than men and had almost caught up with men in their invasive SCC incidence. This is highly unusual when considered in the broader context of other similar population-wide studies looking at KC. Men have been shown in multiple studies to consistently have a higher risk and incidence of both SCC and BCC than women, especially in areas with high overall background UVR. In those areas, men are often reported to have twice the incidence of women, including the southern United States and Australia (Athas, 2003; T Y Chuang et al., 1990; Harris, 2001; M R Karagas, 1999; Serrano, 1991). To our knowledge, a statistically significant higher incidence of BCC and SCCis in women compared to men has not been reported in a whole population study (Devine et al., 2018; Jurciukonyte et al., 2013; Leiter et al., 2017; Lomas et al., 2012; Mclean et al., 2012; Musah et al., 2013; Muzic et al., 2017; Pandeya et al., 2017a; Rogers et al., 2015; Rudolph et al., 2015).

Joinpoint analysis demonstrated a more rapid increase in all subtypes of KC, even invasive SCC, in women. The steepest slopes in women were observed after 1995, suggesting the advent of damaging behavioral changes in the 1980s or perhaps the early 1990s. The head and neck region was the dominant site for men for all subtypes of KC, but women demonstrated much more variety in the locations of their lesions, with a more generalized distribution of all KC subtypes. We noticed much steeper joinpoint slopes for SCCis compared to invasive SCC for women. If these lesions are pathologically related, we should see a similar trend for invasive SCC in women; however, we did not observe such a trend within our cohort. It could be that SCCis in women is over-diagnosed or that diagnosing a significant number of in-situ lesions prevents their progression into invasive disease. Further study will be required to explain these results. We also noticed steeper slopes for the lesions of the legs and trunk in women compared to the head and neck. In addition, **figures 3** and **8** highlight how women are becoming younger when diagnosed with their first BCC and SCC compared to men. This result was especially pronounced for BCC, as women as young as 35 account for this increased incidence. Women also had a higher tumor burden,

especially BCC and SCCis, and were more likely to develop multiple tumors. This has never been demonstrated before in any population, and we, therefore, suspect that the total tumor burden of KC may be substantially underestimated worldwide. Despite women's higher tumor burden and steeper KC incidence increase overall, men still tend to develop more serious disease. Men were much more likely to develop invasive SCC on the head and neck, especially those >70 years of age, who accounted for most of the increased incidence throughout the study period. These differences could result from important behavioral differences between men and women.

5.2.2 Artificial tanning and travel abroad

As discussed in the introduction, it is known that UVA based artificial tanning devices induce DNA damage via indirect mechanisms (Swerdlow & Weinstock, 1998), having the potential to induce keratinocyte and melanocyte mutations, leading to KC or melanoma (Tsu Yi Chuang et al., 1992; B. Lindelöf et al., 1991; Olsen, 1992; Reshad, 1984; Stern et al., 1984; S. Q. Wang et al., 2001). It has also been hypothesized that artificial tanning exposure at a young age might exponentially increase KC risk later in life. (M. Zhang et al., 2012),(Hery et al., 2010),(S. T., n.d.) Green et al. published a systematic review in 2007 summarizing more than 9300 cases, showing a 67% higher risk of SCC and a 29% higher risk of BCC with artificial UVR exposure. Specifically, exposure at a young age had a strong association with BCC development. Therefore, it is critical to continue public awareness efforts to prevent young individuals from using tanning beds (Adele Green, 2007).

There are multiple potential explanations for the differences we observed between men and women. One interesting observation is the absence of a relationship between latitude and KC incidence in Europe, either because 1. The Icelandic population is more genetically susceptible to KC. 2. The Icelandic population engages in high-risk behaviors such as artificial tanning and travel abroad with binge tanning 3. Icelanders have greater access to dermatology care and screening, leading to KC diagnosis. It is highly likely that reason 1 is valid, but that alone could not explain the markedly increased KC incidence in Iceland, as increased background UVR is unlikely to account for such a rapid increase in leg and truncal lesions. In Iceland, these anatomical sites are usually concealed under clothing, even during the summer. Availability of dermatology screening might play a role, but for this to be true, in the first years of the study, there would need to have been a sizeable undiagnosed reservoir of KC in the population that increased screening is now detecting. It is unknown whether such a reservoir exists for BCC or SCC but it

is likely, since recent evidence suggests that up to 50% of BCCs might demonstrate indolent or extremely slow growth (Winden et al., 2021). There has been a recent discussion about melanoma overdiagnosis due to increased screening. Since melanoma in situ is on a spectrum with severely dysplastic nevi, it may be challenging to ascertain which lesions truly have metastatic potential and which ones do not (Welch et al., 2021). Therefore, melanomas are believed to have such a reservoir of tumors that are now being diagnosed that might not have metastatic potential. It is conceivable that a subset of KC might demonstrate indolent behavior, growing slowly over many years without necessarily being detected, similar to atypical nevi, although this is unproven. For all of these reasons, while genetics and screening play a likely role in this incidence increase, we think high-risk tanning behaviors are likely culprits as they potentially explain some of the specific patterns we observed.

The frequency of travel abroad amongst Icelanders has increased considerably since the 1970s, from about 65,941 yearly voyages in 1970 to 937,315 in 2006. There are a few arguments against the possibility of foreign travel playing an exclusive role in the increased incidence of KC. Young adults and adolescents in Iceland make fewer trips abroad than older adults but have a much higher cumulative tanning bed exposure (Hery et al., 2010). A 2001-2002 survey showed that 16% of women and 12% of men aged 20–39 years had used an artificial tanning device > 100 times during their lifetime compared to only 2% and 1% among women and men aged 50 years or more. (Helgadottir, 2002)·(Hery et al., 2010)·(S. T., n.d.) These findings could certainly explain why an incidence surge was observed in younger individuals. The fact that we observed joinpoints in 1988 and 1993 for truncal lesions for both men and women <50 years of age, without any joinpoints occurring in individuals ≥ 50 years, further suggests a behavioral change that might have been more prevalent in the <50 age group. These joinpoints occurred both during the height of travel abroad and the height of tanning bed use (1979-2004). We know that artificial tanning use was much more prevalent in the younger group, while travel abroad was more significant in the older age groups. Unfortunately, sex-specific travel data in Iceland is not available in the literature.

5.2.3 Occupational exposure and rural areas

KC rates in our study were lower overall in rural areas compared to in Reykjavik, but it is noteworthy that melanoma incidence in Iceland has shown a similar trend (Andradottir, 2019) (Hery et al., 2010). This could be explained by higher numbers of dermatologists in Reykjavik, leading to higher rates of screening. In both Australia and the US, the opposite is true. In rural areas in these countries, background UVR can be extremely high, and individuals are therefore thought to be at an increased KC risk in large part due to occupational sun exposure (Szewczyk et al., 2016). A systematic review published in 2020 showed that outdoor workers are almost certainly at increased risk for KC compared to the general population (Loney et al., 2021). This also explains why men have much higher rates of KC in the US and Australia compared to Iceland, as men in these countries are more likely to be outdoor workers and susceptible to high levels of background UVR (Fennell et al., 2017).

Artificial tanning use is similar between Reykjavik and rural areas, but Icelanders in rural areas might be less likely to see a dermatologist regularly due to low access in these regions. (Hery et al., 2010) (S. T., n.d.). Men have been reported to be less likely to use sunscreens daily. (Watts et al., 2018), although this matters less in Iceland's low UVR environment. Preventive efforts in Iceland have been effective in minimizing artificial tanning use. It could be that public health efforts are more effective in Iceland than in other countries with high background UVR or that it is easier for Icelandic individuals to minimize high-risk tanning (binge tanning, artificial tanning) than to limit chronic UV exposure.

Men in Iceland are more likely to be outdoor workers in rural areas. The greater number of cloudy days and low UVR create a sun-protective environment for men. However, men who work chronically outdoors, wear concealing clothing, and do not use sun protection would still be much more likely to develop lesions on the head and neck, possibly explaining why head and neck KC, and especially invasive SCC, was much more common in Icelandic men. Interestingly, throughout the entire study period, men showed almost no tendency to develop lesions on the legs, while in women, truncal and leg SCCis became almost as frequent as lesions on the head and neck. For women with invasive SCC, the head and neck was still the most common anatomical location, but the distribution of locations was much more homogeneous than in men. Since women are more likely to wear lighter clothing and engage in high-risk UVR behaviors than men, these differences can be easily accounted for (Szewczyk et al., 2016). However, tanning bed use

alone cannot explain the increase in men's invasive head and neck SCC. Therefore, it is likely that travel abroad and possible detection bias from increased skin cancer screening could explain the increased incidence of skin cancer.

5.2.4 Multiplicity and cumulative risk

This is the first whole population study looking at the multiplicity of BCC as well as SCCis. Our results indicate that the total tumor burden worldwide may be substantially underestimated, primarily due to the inability to account for multiple tumors in most national cancer registries, which document the first but not subsequently diagnosed tumors. While this might make sense for most cancer diagnoses, such as colon and lung cancer, as developing a second primary is extremely unlikely, this works poorly when monitoring skin cancer incidence, as most patients have an excellent survival rate and are highly likely to develop multiple skin cancers during their lifetime. One meta-analysis concluded that the risk for patients with a first BCC or SCC to develop subsequent skin cancer of the same type was at least ten times higher than the risk of a first KC among persons of the same age and sex in the corresponding general population (Marcil & Stern, 2000). Tracking multiple tumors makes it possible to accurately estimate a population's total tumor burden and the median interval between tumors. Our results indicate that multiplicity rates are as high as 1.7 for BCC and SCCis in females, substantially higher than the 1.3 recently estimated in a European study(de Vries et al., 2012). BCC and SCCis might therefore be an even more significant healthcare issue in Europe than was previously thought. The median interval between 1st and 2nd in-situ and invasive SCCs in women was only 1.3 and 1.6 years, respectively compared to 1.5 and 2.3 years in men. While women could be developing skin cancers at a faster rate, this could also be due to more frequent dermatology visits. We also noticed decreased KC multiplicity throughout the study period, likely due to shortened follow-up times for individuals diagnosed in later periods.

Iceland's lifetime risk for women developing a BCC is 10.1%, compared to 7.3% in men. This is still considerably lower than in other countries such as the US, where the lifetime risk in white populations is estimated at 30% (Miller & Weinstock, 1994). The lifetime risk for women tripled in Iceland from the 1980's onward, and the cumulative risk for women <40 years of age increased 6-fold, with no signs of this incidence increase slowing down. The lifetime risk of developing in-situ and invasive SCC is still much lower than BCCs, but it is rapidly rising. For example, the SCCis lifetime risk for women increased 9.3 fold from the 1981-1990 period until the end of the study period. The big question is, when and how will this increase end?

5.2.5 The relationship between BCC, SCCis, and invasive SCC

Prior studies looking at incidence rates of SCCis are limited and most often performed in small selected study populations. The highest rates were reported in a Hawaiian population, most likely due to a high concentration of Caucasians living in an environment with high UVR (Farmer, 1994). It is currently unknown whether all in-situ lesions have the potential to progress to invasive disease or whether that potential only applies to a subset. One study reported that among patients with at least 2 KC diagnoses, those who had a previous SCCis diagnosis had a 2-fold risk of developing invasive SCC (Xiong et al., 2013). A partial explanation might be that these patients share similar risk factors, such as a history of increased UVR exposure. However, this seems not entirely the case. A meta-analysis found that the risk of SCC after a BCC diagnosis was 6% at three years. In that same study, the authors reported that the risk of developing another BCC was eight times higher than the risk of that first SCC (Marcil & Stern, 2000). This has also been the authors' clinical experience. Patients who develop multiple BCCs do not necessarily develop SCCs, or at least not until much later in their lives. We did not calculate the subsequent risk of KC diagnosis after the development of a primary tumor in our study. However, we did notice a lower average age of diagnosis for SCCis than invasive SCC for both men (1.9 years) and women (2.7 years), supporting the notion that SCCiss are at least in part precursor lesions to invasive disease. Theoretically, the interval between SCCis formation and the subsequent development of invasive SCC could be 2-3 years.

The incidence of SCCis was higher for almost all anatomical locations compared to invasive SCC in the 2013-2017 period. The exceptions were the lip for both sexes and head/neck in males, where invasive SCC was more common than SCCis. It has been theorized that SCCis is probably underdiagnosed in men, as they likely present later with more invasive disease (Tokez et al., 2020). Assuming that invasive and SCCis are related on a histologic spectrum, our findings imply either a delay in diagnosis for lip and head and neck SCC, or that the invasive growth phase occurs more rapidly in these anatomic locations, as could very well be the case for lip SCC, which was more likely to be invasive in both men and women. This explanation seems less plausible for head and neck SCC, as we only observed this finding in men. Men have indeed been shown to seek medical care later than women, resulting in a delay in diagnosis and a higher likelihood of aggressive disease(Hollestein et al., 2012; Venables et al., 2019). One other explanation for the decreased head and neck lesions in women compared to men might be greater hair scalp density on average, which might be protective. Higher rates

of SCCis were noted in Reykjavik compared to rural areas, likely due in part to greater dermatology access, but higher rates of invasive SCC were not noted in Reykjavik, suggesting that lesions may be diagnosed there that would not otherwise be diagnosed if those patients lived in a rural area.

We will compare our results with a recent study from the Netherlands (Tokez et al., 2020), the first to publish nationwide SCCis incidence rates but without evaluating multiplicity rates. They also noted increasing SCCis rates, especially in women, with a female/male ratio of 1.4 (Tokez et al., 2020). In our study, the ratio was 1.63, showing an even higher discrepancy between genders, possibly due to the low UVR in Iceland providing relative protection for men. Tokez et al. also suggested possible underdetection of in situ SCC among men, as we did (Tokez et al., 2020). However, “underdetection” may not be the correct terminology to use in this context. Must these lesions be diagnosed as early as possible? What is the risk of progression into invasive disease? These are questions to which we do not yet have answers.

5.2.6 Prevention methods

This chapter discusses various prevention methods that might be employed to reduce the public risk of KC. As mentioned in the previous chapters, the incidence increase observed in Iceland is likely due to a combination of preventative factors (such as binge UVR exposure), where prevention methods can be employed and increased dermatology screening. Primary prevention is the most efficacious and cost-effective form of prevention and is intended to reduce the actual incidence of a disease (Verkouteren et al., 2017). In the case of KC, primary prevention mostly centers around minimizing the population's UVR exposure. This can be done through tanning booth regulations, public awareness efforts, or minimizing the effect of UVR through the use of sunscreens, sun protection, dietary supplements, and retinoids. UVR is not the sole cause of KC, but the genetic risk cannot be modified using primary prevention methods. It is unclear how quickly the results of new primary prevention programs would become evident as we do not know the actual delay between UVR exposure and KC risk (Verkouteren et al., 2017). Secondary prevention aims to detect skin cancer soon after it occurs, otherwise known as screening. Tertiary prevention is intended to decrease the impact of disease on someone who has already been diagnosed but does not necessarily cure the disease process. The necessity of tertiary prevention is scarce when it comes to KC, especially BCC and SCCis. However, some patients with high-risk invasive SCC, especially lesions >2cm located on the lips, ears, genitals, will be at higher risk of metastasis, in which case radiotherapy, retinoids, chemotherapy, or sonic-hedgehog inhibitors can be used (Verkouteren et al., 2017). Interestingly, the success of behavioral intervention is most often measured by the reduction in tanning or sunburns rather than the reduction in actual skin cancer or precancerous lesions. This is easier to measure and has been employed in Iceland for many years, but suboptimal, as the true benefit of the intervention remains unknown (Janda & Green, 2014).

We will begin by discussing primary prevention methods, starting with public behavioral intervention.

5.2.6.1 Tanning booth regulations

To better understand the potential role of tanning beds in skin cancer development, we need to better understand their history, both in Iceland and abroad. As mentioned earlier, tanning bed usage in Iceland surged in the

1980s and 1990s. A 2002 Reykjavik study showed that 70% of women but only 35% of men had used a tanning bed within the previous 12 months (J. A. Adalsteinsson et al., 2020; Helgadottir, 2002). At that time, tanning bed usage in Iceland was twice as high as in Swedish adults and three times as high as in British adults (Helgadottir, 2002). An increase specifically in truncal lesions in women was reported in Iceland, with a rapid increase after 1992 attributed to tanning bed use (Hery et al., 2010). After this surge in melanoma incidence (**figure 14**), public health efforts were initiated to inform the public about the potential risks of tanning beds. After these educational efforts were initiated, melanoma incidence subsequently declined (**figure 14**). Such a decline in KC incidence was not noted in our study, however. It is conceivable that UVR might have a more immediate effect on melanoma risk than KC, with the risk of melanoma dropping 2-3 years after exposure while, for KC, the risk associated with artificial tanning might be long-lasting. The lag time between UVR exposure and increased KC risk is unclear, but studies have suggested it may be as little as two years (Hery et al., 2010) (Stern et al., 1979).

Women of all ages, especially adolescents, are more likely to have used a tanning bed (Andradottir, 2019), but the numbers have decreased more recently. In a Capacent-Gallup study from 2018, only 8% of adults reported using a tanning bed within the previous 12 months. **Figures 15** and **16** summarize the decline in tanning bed usage in Iceland from 2005 among adults, young adults, and adolescents. The total number of adults and adolescents that had experienced a sunburn in the previous year also declined during that time (Andradottir, 2019). From 1973 to 1988, the number of tanning salons in Iceland increased from 3 to 56, with 207 total available tanning beds. This increase continued until 2005 when the total number of tanning beds in Reykjavik was 277. This number decreased until 2017, stabilized at 90, but has steadily increased again, most recently being 97 in 2020 (**figure 17**). While tanning bed use decreased temporarily during the COVID-19 epidemic in Iceland, usage seems to be increasing again since the public restrictions were lifted (Geislavarnir rikisins, 2020).

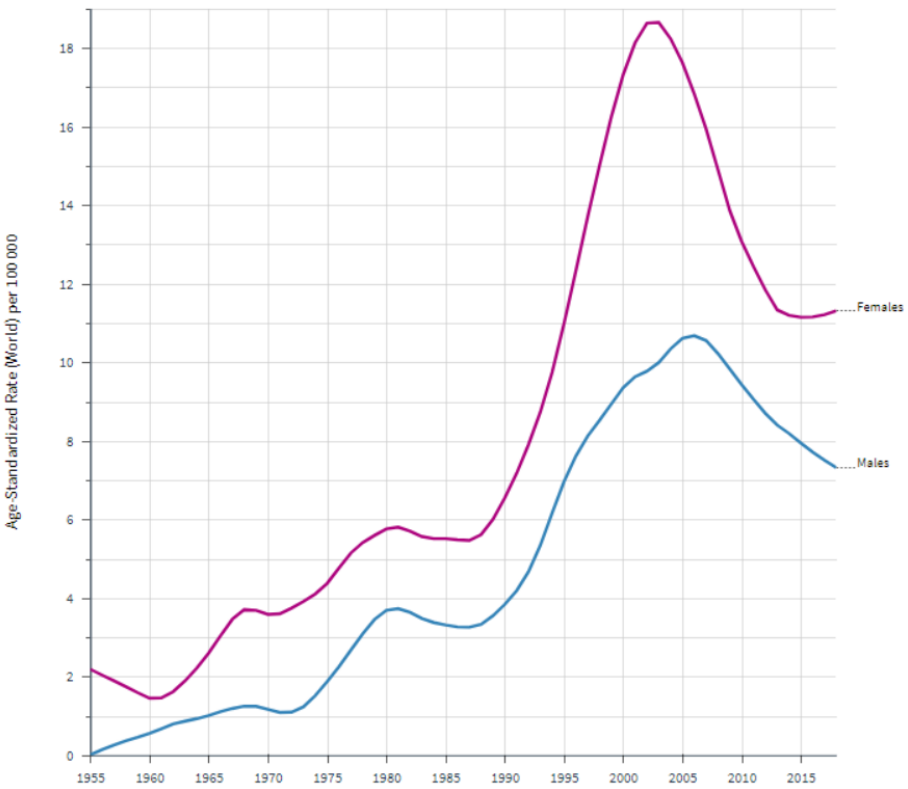


Figure 14: Data summarizing melanoma age-standardized incidence in Iceland for all ages from 1990 until 2018 (Nordcan, 2021).

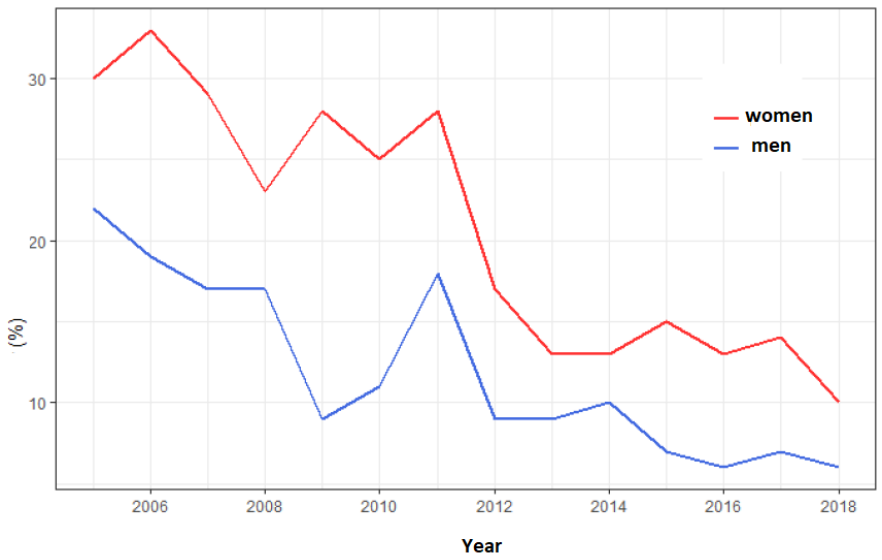


Figure 15: The percentage of adults in Iceland having used a tanning bed in the previous 12 months according to yearly Gallup questionnaires (Andradottir, 2019).

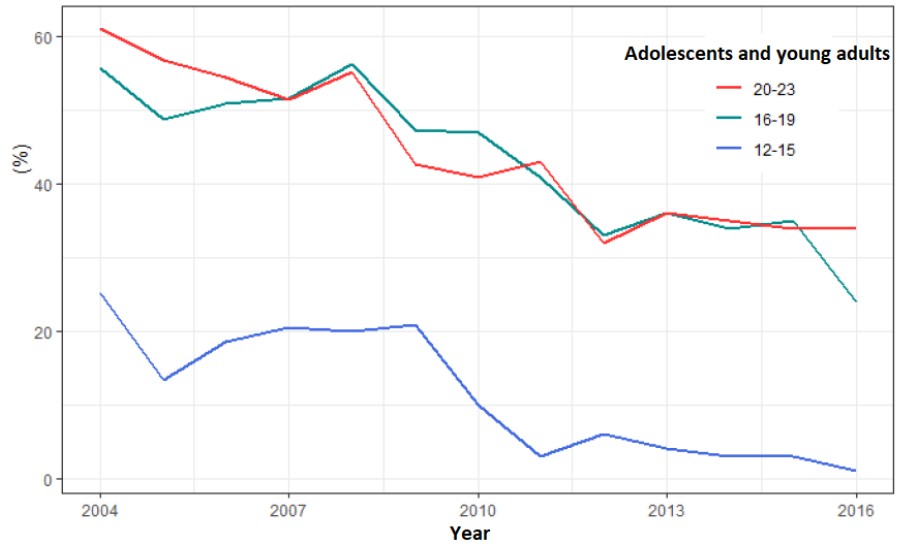


Figure 16: The percentage of adolescents and young adults in Iceland having used a tanning bed in the previous 12 months according to yearly Gallup questionnaires, stratified by age (20-23 in red, 16-19 in green, 12-15 in blue) (Andradottir, 2019).

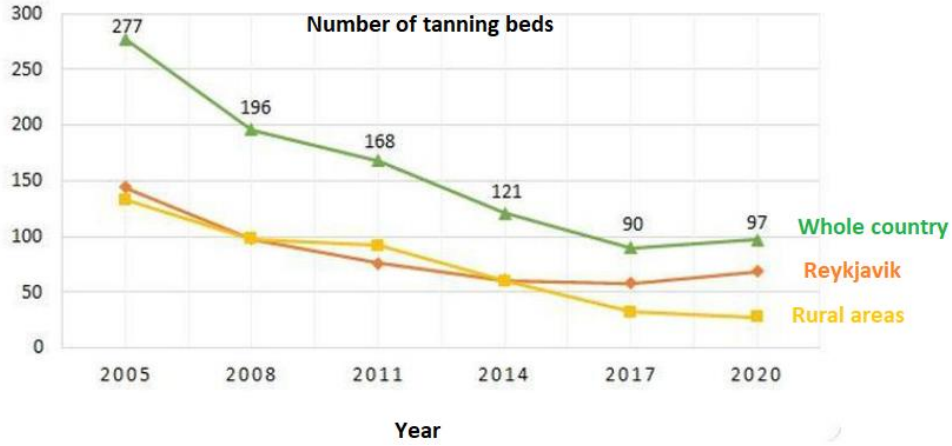


Figure 17: The number of tanning beds in Iceland from 2005 until 2020. The whole country (green), Reykjavik (orange), and rural areas (yellow) (Geislavarnir rikisins, 2020).

Numerous countries have now restricted tanning bed use, banning use for children 18 years or younger. Brazil was the first country to pass such a law in 2009, and 8 states in the United States have implemented indoor tanning legislation since 2003 (Pawlak et al., 2012). Due to a sharp increase in melanoma incidence in Iceland, people were encouraged to attend skin cancer screenings and avoid artificial tanning starting in 1991. These public health efforts were continued for 17 years (Tryggvadottir, n.d.)**.** A 2009 Capacent-Gallup questionnaire examined public views on the ban for minors (**figure 18**). Reassuringly, most people approved of such a law, and in 2011 the Icelandic government passed the first law banning artificial tanning for minors in the country (Capacent Gallup, 2009). Tanning booths emitting the highest amounts of UV radiation must also be labeled with a warning. In addition, artificial tanning devices can now only be used for up to 60 minutes at a time (Lög um geislavarnir, með síðari breytingum nr. 82/2010, n.d.).

Some countries have taken a different path concerning tanning regulations, most notably Australia and the United States. Australia has the most stringent artificial tanning legislation of any country worldwide. In 2016, Australia issued an outright ban on tanning beds. They were able to achieve this legislation by using incremental change to secure their public health reforms despite substantial public opposition. Considerable healthcare cost savings are expected from this ban (Sinclair, 2014) (Gordon, Sinclair, et al., 2020). In the United States, the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA) all classify UVA and UVB emitting devices to be in the highest risk category of known human carcinogens, alongside tobacco smoke (Swerdlow & Weinstock, 1998). Despite this, tanning beds still have low regulation rates in the United States as different states have different regulations. Twelve states have an absolute ban for minors with California being the first state to issue such a ban in 2012. Nine states have no laws regulating tanning access (Pan & Geller, 2015), and there is currently no federal law definitively banning artificial tanning device use. Other states have implemented laws requiring parental consent, but studies have shown these to be ineffective due to poor compliance. The FDA requires that artificial tanning devices carry a black box warning, clearly indicating the increased risk of skin cancer associated with their use. In 2010, indoor tanning devices also became subject to a 10% excise tax. As a result, about 1/3 of U.S. tanning salons lost clients. (Pan & Geller, 2015).

One study from 2020 estimated the long-term health and economic consequences of banning indoor tanning devices in North America and Europe. Their primary outcomes were numbers of melanomas and KC, as well as health care and productivity costs. For the next generation of youths and young adults during their remaining lifespans, banning indoor tanning devices could be expected to provide 423,000 additional life years and prevent 7.3 million KCs (-7.8%) and 240,000 melanomas (-8.2%) in North America, with economical cost savings of $31.1 billion. The cost savings of banning tanning for minors in terms of skin cancer treatment would be approximately 1/3 of the corresponding benefits of a total ban (Gordon, Rodriguez-Acevedo, et al., 2020). While the actual effects of such measures are unclear, similar strategies can perhaps be utilized in Iceland and other countries as an incremental means of decreasing tanning bed use and an eventual permanent ban.

5.2.6.2 Other public behavioral interventions

Beyond strict tanning booth regulations, other methods exist to decrease public UVR exposure, including public education, environmental policy changes, media campaigns, social media awareness, and counseling by dermatologists and primary care physicians (Janda & Green, 2014) (*NICE. NICE Public Health Guidance 6: Behaviour Change... - Google Scholar*, n.d.). Public views regarding tanning can be powerful, and intervention can quickly fail, especially in young adults and adolescents, if social norms dictate that tanning is desirable. As previously discussed, this has certainly been the case in Icelandic high schools, as evident from the high proportion of teenagers using tanning beds. The consensus is that educational interventions aimed at adolescents and young adults can be effective in minimizing tan-seeking behavior in this population (Janda & Green, 2014) (*NICE. NICE Public Health Guidance 6: Behaviour Change... - Google Scholar*, n.d.) (J. S. Lin et al., 2011) (Moyer, 2012). As previously mentioned, targeting younger individuals is crucial, as UVR exposure at a young age has been hypothesized to increase KC risk exponentially. However, these efforts should also be directed explicitly toward high-risk groups, including patients with a history of KC, immunosuppressed individuals, or patients with a history of organ transplant (Mudigonda et al., 2013) (Berg & Otley, 2002). Another potentially successful policy change could focus on recommending sun-protective clothing for outdoor workers as well as in primary schools (Janda & Green, 2014). In our study population, the most important groups to target would be men who are outdoor workers, encouraging the use of sun-protective hats with a wide brim, and teenagers in high schools, especially girls, emphasizing the risks of tanning bed use.

Health policies that control or prevent invasive SCC have been cost-effective, similar to the cost-effectiveness of banning tanning beds. SCC incidence is exceptionally responsive to various prevention measures that would also be likely to bring economic benefit. Governments would receive a return on investment with such public intervention programs (Drago et al., 2016) (Muranushi, 2015) (Adèle Green et al., 1999) (Muranushi et al., 2016) (Gordon & Rowell, 2015). It is, of course, possible that policy efforts aimed at preventing obesity, smoking, and excessive alcohol use might compete with programs aimed at preventing skin cancer, leading to other challenges. Furthermore, tanning salon owners and others declare that vitamin D deficiency can cause a wide variety of problems, including cancer and cardiovascular disease, and that dermatologists have therefore gone too far in telling people to avoid UVR, although the literature does not support this. Such

arguments have led to confusion amongst the public, leading to further difficulties in implementing behavioral change efforts (Gordon & Rowell, 2015). Recently, Passeron et al. showed that diligent sunscreen use does not compromise vitamin D levels in healthy individuals but that high sun-protective behaviors in people with photosensitivity disorders, using protective clothing, and shade-seeking behavior are likely to compromise vitamin D status (Passeron et al., 2019). To assess whether the public would be receptive to behavioral change using sun protection programs, one study looked at a sample of 211 Caucasian women, randomly assigning them to a sun protection program or a stress management (control) program. The intervention produced significant behavioral modifications, including a higher intention to sun-protect and greater adherence to sun-protective behavior, and a lower desire to sunbathe (Jackson & Aiken, 2006). Another study demonstrated a decreased incidence of BCC in younger individuals after public intervention efforts in Australia (Staples, 1998).

5.2.6.3 Minimizing the effect of UVR with sun protection

Sun protection can take many forms, from sun protective clothing and topical sunscreens to oral medications such as beta-carotene. While oral retinoids have been shown to decrease SCC risk, they may be sun sensitizing, which can minimize benefit if the patient fails to adhere to sun-protective behaviors. Sunscreen efficiency is measured by the sun protective factor (SPF), which is calculated by applying sunscreen at 2mg/cm^2, a much higher dose than most individuals apply. UVB is then used to measure the minimal dose required to cause clinically apparent erythema. To be recommended for use in skin cancer prevention, a sunscreen must be both “broad spectrum” and have a minimum of 15 SPF (Geisler et al., 2021) (Reinau et al., n.d.) To be considered broad-spectrum, a sunscreen must absorb 90% of UVR above 370nm, including UVB, UVA1, and a portion of UVA2. An SPF of 15 means that a person can spend 15 times longer in the sun without burning than they would if they did not wear sunscreen. Unfortunately, most individuals underapply sunscreens by a considerable amount (Gabros et al., 2020).

Sunscreens contain UVR filters that are termed either organic (chemical) or inorganic (mineral); these are terms recommended by the FDA, as mineral filters can also be considered “chemicals” because they absorb UV photons (Geisler et al., 2021). In general, inorganic (mineral) sunscreens are more effective at blocking UVB, UVA1, and UVA2, and their use should therefore be encouraged. Oxybenzone is the most commonly used organic filter and absorbs UVB and short UVA but is usually combined with another organic filter.

Oxybenzone has been a topic of controversy in recent years, as it has been hypothesized to damage coral reefs, as has been shown in vitro. This has confused the public, causing distrust in sunscreens and resulting in decreased use (Geisler et al., 2021), even though the oxybenzone levels measured in the sea are 1/1000 of those shown to be toxic in vitro, and coral reef deaths are more likely due to global warming. Inorganic (mineral) filters have, therefore, rapidly become more popular. These are mostly zinc and titanium-based and can be identified by looking at the active ingredients or seeing the label "mineral" on the sunscreen bottle. Notably, this label does not apply to iron oxide, which is not classified as an active ingredient by the FDA. As a result, consumers must often go by the term "tinted", which should also be listed on the sunscreen label. Iron oxide has the benefit of being able to block visible light, in addition to UVR, providing additional benefit for patients with photodermatoses, such as melasma and porphyrias. Tinted sunscreens reduce visible light penetration by 93% to 98% (Boukari et al., 2015). These sunscreens always have a brown discoloration, while purely zinc/titanium-based sunscreens will be white. Products containing zinc or titanium often cause a chalky white appearance, causing many consumers to shy away from them and to use micronized versions instead, which provide less photoprotection (Geisler et al., 2021) (Gasparro et al., 1998) Addition of photolyases and antioxidants to sunscreens could provide additional protective benefit. Photolyases are enzymes that repair pyrimidine dimers, while antioxidants reduce ROS formation and therefore reduce indirect DNA damage caused by UVA (Krutmann et al., 2020) (D. Y. Wang et al., 2019). Sun-protective clothing can also be effective, with particular benefits over sunscreens, including the convenience of application and protection against a broad spectrum of radiation, as opposed to specific UV wavelengths only (Adam, 1998). The term ultraviolet protection factor (UPF) is used for clothing rather than SPF and is dependent on the fabric quality and density of its weave (Adam, 1998).

Do sunscreens work for KC prevention? Most evidence points towards "yes". The use of sunscreens for KC prevention is safe and efficacious and confirmed in nonrandomized studies and randomized controlled trials. One trial from Australia showed a 40% reduction in cutaneous SCC formation after topical use of a broad spectrum SPF 15 based sunscreen compared with placebo. (Adèle C. Green, 2007) (Van Der Pols et al., 2006). The rate of AK formation has also been shown to be reduced with sunscreen use (Darlington et al., 2003) (Thompson et al., 1993). Thompson et al. published a randomized controlled trial in 1993 in the New England Journal of Medicine, looking at 588

people 40 years of age and older in Australia, using either sunscreen or placebo over a single summer. They observed a reduction in AKs of 0.6 in the sunscreen group and a dose-response relationship with the amount of sunscreen used and reduction in the development of new lesions (Thompson et al., 1993). Sunscreen use is also cost-effective. One study using primary data from a randomized controlled trial of regular sunscreen use showed that sunscreens are cost-effective for skin cancer prevention (Gordon et al., 2009). Interestingly, Van Der Pols et al. showed much more significant benefit in SCC prevention than BCC prevention after using sunscreens, which makes sense in the context of the higher risk of developing SCC than BCC with PUVA exposure. UVR might play a much more significant direct role in SCC pathogenesis, while BCC pathogenesis might be fueled to a greater extent by an underlying genetic predisposition (Van Der Pols et al., 2006).

Studies have also looked at oral agents for sun protection. One looked at oral beta carotene, 30mg/d, but did not note any effect on AK prevention (Darlington et al., 2003). Other photoprotective agents such as oral polypodium extract (Heliocare) and afamelanotide (an analog of alpha-melanocyte-stimulating hormone) are known to be photoprotective but have not been studied in skin cancer prevention (Geisler et al., 2021). Nicotinamide, an active form of vitamin B_3, was shown in a phase 3 randomized trial to reduce rates of AK development by 13% at 12 months at a dose of 500mg twice a day. No differences were observed in BCC or SCC development (A. C. Chen et al., 2015). While nicotinamide is safe and gives some photoprotection, many patients do not find it worth the trouble to take a pill twice a day for a minuscule effect. Taking 1500mg daily has no benefit over 500mg daily (Yiasemides et al., 2009).

Further studies are needed to truly understand the benefits of nicotinamide supplements. Oral retinoids and acitretin have been shown to suppress SCC development at low doses. However, retinoids are photosensitizing and not practical for primary prevention except in carefully selected individuals at high risk for skin cancer. While acitretin has been reported to treat and prevent BCC successfully, large studies are lacking (Lebwohl et al., 2003). A recent comprehensive review found weaknesses in the evidence supporting most oral chemoprotective options for SCC. Other agents that have shown promise include nonsteroidal antiinflammatory drugs (including topical diclofenac for AK prevention) (Muranushi, 2015) as well as field therapy using topical agents like 5-fluorouracil, imiquimod or photodynamic therapy(Mounessa et al., 2016).

5.2.6.4 Screening as a method for secondary prevention

The major goal of secondary prevention is to detect skin cancer as early as possible. BCC mostly causes local destruction of skin and soft tissue without mortality risk. SCCis has the theoretical risk of progressing into invasive disease, which has metastatic potential. Screening for BCC alone has thus been determined unlikely be cost effective in otherwise healthy individuals, and the U.S. Preventive Services Task Force in 2016 concluded that evidence is lacking for skin cancer screening in healthy adults. (Gordon & Rowell, 2015) (Verkouteren et al., 2017). However, other lesions are screened for, including melanoma. Furthermore, detecting KC early may reduce scarring and disfigurement, a clinical benefit which cannot be ignored (Marcil & Stern, 2000).

In high-risk patients, screening has been shown to temporarily increase skin cancer incidence, although there should eventually be a return to previous levels (Verkouteren et al., 2017). Our study did not document any decrease in KC incidence over time, so screening alone is unlikely to explain our results, in contrast to the results of an Icelandic melanoma study which observed an incidence increase among young women that normalized a few years later (Hery et al., 2010). To make screening more cost effective, it could be restricted to high-risk patients with a history of skin cancer or immunosuppression. Focused screenings in high risk patients however can theoretically lead to the “prevention paradox”, causing the cases that occur in healthy individuals to be missed (Verkouteren et al., 2017).

Most KCs in our study were located on the head and neck, a location easily monitored by patients and family members. While increased education regarding early detection might be useful for more obvious lesions, the rapid rise of truncal and leg lesions noted in our study might make self-examinations less useful in detecting lesions in sites that are harder to monitor. The optimal follow up time for patients at high risk for multiple BCCs is not known; it is easier to justify closer clinical follow up for patients with a history of SCC, due to the greater risk for morbidity and mortality (Marcil & Stern, 2000). Our data suggest that women in Iceland are more diligent with skin cancer screening, allowing lesions that might have otherwise gone unnoticed to be diagnosed.

An argument has been made that the rapid rise in cutaneous melanoma diagnoses, without a corresponding increase in mortality, is similar to that seen in prostate cancer, whose screenings have not necessarily led to

reduced mortality (Welch et al., 2021) (Ilic et al., 2013). However, Boniol et al documented decreased melanoma mortality following screening efforts, and a return to normal mortality levels after screening efforts were decreased to baseline levels (Boniol et al., 2015). Since melanoma in situ is on a spectrum with severely dysplastic nevi, it is unclear which lesions have metastatic potential and which ones do not (Welch et al., 2021). While it may be a matter of some importance whether to call a melanocytic lesion a severely dysplastic nevus, or a true melanoma in situ with metastatic potential, a similar dilemma does not exist for the diagnosis of BCC. It is not clear whether all BCCs inherently behave similarly, or whether there is a subset of SCCiss and BCCs that remain clinically indolent (Welch et al., 2021).

Ultimately, while the evidence strongly suggests that primary prevention using public behavioral interventions and sunscreens is an effective means of preventing skin cancer, the true benefits of screening remain unclear.

5.3 Risk in association with medication (Studies III-VI)

In a country where KC is on a sharp rise, we observed an increased risk of KC with three different medications commonly used in the Icelandic population and identified a single medication associated with lower BCC risk. A myriad of medications is prescribed every day in this country and worldwide, each having unique effects, some of which could potentially modify underlying cancer risk. Limitations plague most published studies looking at medication association with underlying cancer or disease: they are often small or use inconsistent definitions of medication exposure (medication alone or a combination with another medication). Additionally, multiple studies lump SCC and BCC together within their analysis. This is problematic as SCC and BCC are different cancers with clear divergence in their mutations, histopathology, and clinical behavior. It is of the utmost importance to understand the relationships between medication use and skin cancer risk to prescribe more appropriate medications for individuals at risk and on a population-wide level. Could medications perhaps be contributing to the epidemic we are observing? Could any medication potentially decrease KC risk in high-risk individuals, or more broadly, within the population? If so, could physician education and awareness lead to a change in prescribing habits, thereby limiting a further increase in the incidence of KC?

5.3.1 Hydrochlorothiazide (Study III)

Our results support an association between HCTZ, a thiazide diuretic, and all three subtypes of KC (Paper III. Jonas A. Adalsteinsson et al., 2020). Our analysis included over 1,000 patients with SCC, 1,100 patients with SCCis, and 4,700 patients with BCC and was unique for a few reasons. This was the first study examining the relationship between SCCis and HCTZ in a population exposed to meager background UVR. This is important, as HCTZ is one of the most commonly prescribed antihypertensives in Iceland and the rest of Europe and North America. In the US, antihypertensive medication use for blood pressure control has increased tremendously over the past ten years, with combination regimens being very common (Gu et al., 2012). Furthermore, accumulated evidence has hinted at a possible association between HCTZ and KC risk over the past few years. A meta-analysis from 2019 concluded that out of all thiazide diuretics, HCTZ had the strongest photosensitizing effect and a positive association with cutaneous SCC (Shin et al., 2019). The photosensitizing mechanism is thought to stem from UVR inducing dissociation of the chlorine substituent of thiazide's chemical structure, which causes the formation of reactive oxygen species and free radicals, subsequently leading

to DNA damage. One study showed that HCTZ significantly increased such damage by increasing the formation of thymine-thymine dimers and cyclobutene pyrimidine dimers in keratinocytes (Kunisada et al., 2013). Such an effect increases the risk of SCC and less so BCC, but no studies have specifically evaluated SCCis risk (Shin et al., 2019). Due to this effect and with HCTZ being commonly prescribed in Iceland, whether HCTZ can also increase the risk of KC in a low UV environment must be considered. Three other population-based case-control studies have evaluated the association between HCTZ and KC, with conflicting results. Two of these were nationwide studies, one from Denmark and one from Korea (E. Park et al., 2020) (Pedersen et al., 2018) (A. Ø. Jensen et al., 2008). Jensen at all found that HCTZ increased the risk of SCC with an OR of 1.79 and melanoma by 1.43 among users of combined amiloride and hydrochlorothiazide therapy. They found little association with BCC, consistent with theories that BCC is less associated with UVR than SCC (Pedersen et al., 2018). These results were in concordance with another study, based on data from a large prospective population-based follow-up study in Rotterdam, which concluded that thiazide use was not associated with BCC, but that use of high ceiling diuretics (furosemide and bumetanide) was. High ceiling diuretics contain a sulfa group and can theoretically increase reactive oxygen species formation in the skin (Ruiter et al., 2010). However, a more recent study showed the reverse: HCTZ was associated with BCC with an odds ratio of 1.29 and SCC with an OR of 3.98 (Pedersen et al., 2018). One supplemental analysis looked at high-ceiling diuretics, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers. The study did not demonstrate any dose-response relationship between HCTZ and KC (Pedersen et al., 2018). Based on these studies, and after our HCTZ results were published, the FDA approved label changes on August 20, 2020, to HCTZ, noting “a small risk” of KC (*FDA Approves Label Changes to Hydrochlorothiazide to Describe Small Risk of Non-Melanoma Skin Cancer | FDA*, n.d.). While this is a step in the right direction, no guideline-driven changes or other clinical recommendations have yet been developed based on these findings (Armstrong & Senior Associate Editor, 2014). The Icelandic population is exceptionally homogenous with minimal variance in Fitzpatrick skin type, while Denmark is more genetically heterogeneous (Helgason et al., 2003). In addition, Iceland is small, with a surface of only 39,769 square miles, with an approximately 3-degree range in longitude from its southernmost to northernmost tip. As a result, the average daily UVR is consistent throughout the country. (*Ísland Er Minna En Talið Var*, 2015). This is important when studying the effects of photosensitizing medication, as Fitzpatrick skin type is universally agreed upon

to be a major risk factor for KC risk. A slight difference in skin pigmentation between individuals taking HCTZ and not taking HCTZ could skew the entire dataset. In contrast to all other published studies, Park et al. concluded that HCTZ might have a chemoprotective effect for KC as well as melanoma; they found a significantly lower risk of both cancers in their population, with a hazard ratio of 0.85 for HCTZ users for melanoma, and 0.96 for KC, as they combined SCC and BCC within their analysis. For high cumulative doses >50.000mg, they noted a hazard ratio of 0.2 for KC and 0.18 for melanoma (E. Park et al., 2020). While we disagree that HCTZ could potentially be chemoprotective, these results are nevertheless interesting. Korea is, like Iceland, ethnically homogeneous, but the incidence of KC in South Koreans is only a fraction of the incidence in the Icelandic population, or about 2.5% (E. Park et al., 2020) (J. A. Adalsteinsson et al., 2020). Although it is difficult to directly compare incidence rates between studies using different modes of standardization, it could well be that HCTZ does not exert a photosensitizing effect in darker skin types, Fitzpatrick III and higher, which would be extremely important to note when discussing potential changes in clinical guidelines. Our results suggest that in ethnicities with lighter skin tones, relatively low levels of UVR are sufficient to see an increased risk of KC with HCTZ use. Optimally, we would have wanted to stratify our analysis, specifically looking at abroad travel and tanning bed use, but this was not possible. It is unclear whether background UVR in Iceland is enough to produce a meaningful increase in KC risk or if this increased risk pertains only to Icelanders who engage in high-risk tanning behaviors. Even so, our results are concerning, as in Reykjavik, the average daily UV exposure is 957 J/m2, which is almost half of the exposure in Denmark (1691 J/m2), and only about one-third of the exposure seen in South Korea and the United States of America (2535 J/m2 and 2736 J/m2) (Lucas et al., 2010). It is interesting to compare our results directly to those of the Danish study, as the OR of developing KC in Iceland seems lower than the risk in Denmark (E. Park et al., 2020). It appears that the risk of KC development with HCTZ use may be greater in high UVR environments, and guidelines for its use should therefore keep in mind not only the individual patient but also the environment in which that patient lives. More recently, Schneider et al. published a high-quality cohort study using an active comparator group, finding that long-term HCTZ use increased the absolute and relative risks of SCC (RR 1.95), but not BCC or melanoma. Interestingly, they also looked at bendroflumethiazide (BFT), which was not meaningfully associated with the risk of any skin cancers. BFT might thus be an alternative thiazide option for patients with an extensive skin cancer history (Schneider et al., 2021).

Our study was the first to analyze the association between HCTZ and the risk of SCCis separate from that of invasive SCC, and we identified independent associations between HCTZ and invasive SCC as well as SCCis. We noted an increased risk of invasive SCC only in patients taking a high cumulative dose, or >1500 DDUs (37,500mg). Our sub-analyses did not show an association with invasive SCC, most likely because the study was not powered to detect association with many small sub-analyses. It is important to note that while there was a higher risk of SCCis with the >1500 DDU category, it was not significant. While it is possible that the study was not powered for this dose category, it is essential to look beyond p-values and confidence intervals when interpreting these results. **Figure 13** strongly suggests a dose-response with HCTZ and KC risk for BCC but not SCCis and invasive SCC. This dose-response was not significant for SCCis because of a slight drop in risk in the highest dose category and a drop in risk in the lowest dose category for invasive SCC. Looking at the figure, a longer CI can be seen with each dose increase category, which increases the chance of random variation, and decreases the chance of statistical significance. For SCCis, HCTZ use was associated with increased risk in males and individuals aged 50 and above, which is important to note for possible risk stratification. If SCCis and invasive SCC share the same pathogenesis and exist on a spectrum, we could combine our SCC and SCCis analysis to have more power to detect minor differences in our results. However, we cannot make such an assumption, as it is unknown whether this applies to all SCCis.

As mentioned earlier, an association between HCTZ and BCC development is less established in the literature, perhaps because BCCs have longer promoter periods than SCC or a weaker association with UVR exposure (Paper I. J. A. Adalsteinsson et al., 2020) (Ferreira et al., 2014). Our results showing an increased risk of BCC with HCTZ use are convincing, with a clear dose-response relationship as depicted in **figure 13**. This association was also significant for “ever-users” of HCTZ. However, statistical significance was only achieved for the >1500 DDU category, possibly because longer periods of HCTZ exposure might be necessary to observe an increased BCC risk or because of our study’s inability due to low power to detect minor differences in the other dose categories. As with SCCis, people aged 50 and older had significantly increased BCC risk with HCTZ use. The Danish study also demonstrated a dose-dependent increase in BCC risk with HCTZ use (E. Park et al., 2020).

Our findings support the association of HCTZ with KC, with a more pronounced risk in individuals with prolonged exposure. The link between KC

and other Eighth Joint National Committee (JNC-8) first-line antihypertensive medications, including ACE inhibitors, ARBs, and calcium channel blockers, has not been previously noted (E. Park et al., 2020). Alternative first-line agents should therefore be considered in hypertensive patients at high baseline risk of KC. Physicians in Iceland need to be educated about the potential risks of tanning and baseline sun exposure to mitigate the ongoing epidemic of KC. When HCTZ is started, this risk should be discussed with patients, and sun avoidance and protection encouraged. For patients in countries with high background UVR, such as the United States and Australia, average sun protection behaviors may not eliminate the risk associated with HCTZ exposure, as demonstrated by the increased risk even in Iceland's low UVR environment. It has yet to be demonstrated whether HCTZ discontinuation decreases subsequent KC risk; the risk/benefit ratio of using HCTZ must be determined carefully in each case. It appears that the groups most likely to benefit from HCTZ avoidance in Iceland would be men >50 years of age, in whom HCTZ could increase the risk of developing invasive head/neck SCC, and females of all ages who engage in high-risk tanning behaviors (Paper II. J. A. Adalsteinsson et al., 2021) (Paper I. J. A. Adalsteinsson et al., 2020).

5.3.2 Statins (Study IV)

In this study, we demonstrated that statin exposure is associated with an increased risk of SCC, but not BCC (Paper IV. Jonas A. Adalsteinsson, Muzumdar, Waldman, Hu, Wu, Ratner, Feng, et al., 2021). Statins inhibit HMG-COA reductase, and thereby decrease cholesterol, as discussed earlier. These agents can increase CD4+CD25+ regulatory T cell activity, and thus impair the host antitumor Th1 response, which could theoretically increase KC risk. They have also been associated with inhibiting the Ras signaling pathway (Yang et al., 2017a) (B. M. Lin et al., 2018). Furthermore, high cholesterol levels have been associated with cancer development, as in prostate cancer (B. M. Lin et al., 2018).

Reports in the literature are inconsistent, however. In direct contradiction to the previously mentioned results, statins have also been shown to have pleiotropic properties with possible tumor-suppressive effects (B. M. Lin et al., 2018). One prospective study in women did not show any association between statin use and melanoma risk (Jagtap et al., 2012). Only one other population-wide study has been conducted, which analyzed the impact of statins on both SCC and BCC, but not SCCis, in Denmark (Arnspang et al., 2015). No increased risk with SCC was seen 1.01 (CI: 0.91–1.11), but the authors noted a slight increase in BCC risk, attributed to residual confounding (Arnspang et al., 2015). Similarly, the Nurses' Health Study and Health Professionals' Follow-up Study did not show any association between high cholesterol or statins with BCC, SCC, or melanoma (B. M. Lin et al., 2018). A large meta-analysis focusing on statin use and KC risk also found no evidence of association. However, this study pooled all BCCs and SCCs into the same dataset instead of doing a separate analysis for each tumor subtype, which confounds the results since statins are immunomodulatory and might have different effects on each tumor type (Yang et al., 2017b).

There may be residual confounders within our study design, as we could not correct for other underlying comorbidities. It has been reported that statin users live unhealthier lifestyles in general and have a lower socioeconomic status than non-statin users (Arnspang et al., 2015). In addition, dermatology access is high in Iceland, and patients under frequent observation by their physician might be more likely to be on statin therapy and to see a dermatologist, leading to the detection of KC that might have otherwise gone unnoticed. We saw variable risk between different subtypes of statins and lower overall risk with atorvastatin. Atorvastatin is a longer-acting, more potent HMG-CoA reductase inhibitor than simvastatin and was only associated with

an increased risk of SCCis while simvastatin was associated with SCCis as well as invasive SCC. It could be that some property other than “statin intensity” affects KC formation or that individuals receiving atorvastatin and simvastatin have differing levels of baseline KC risk. Optimally more statins would have been included in the analysis, but we decided to focus on Iceland's most commonly prescribed statins. It has been suggested that hydrophilic statins might confer less of a risk for KC, but this is not proven. Both atorvastatin and simvastatin are lipophilic (Arnspang et al., 2015).

The relationship between statins and KC needs to be further investigated. The literature is split in the matter, and we found no dose-response relationship in our results. While there may be residual confounding within our dataset that is unaccounted for, we have identified a group of individuals who seem to be at a higher baseline risk for KC, which needs to be kept in mind when risk stratifying patients, even though it is too early to tell whether statins are truly associated with KC.

5.3.3 TNF alpha inhibitors (Study V)

The data on TNFis demonstrated an association between TNFis use and SCCis compared to the general Icelandic population. It is possible that our study was not powered to detect differences when it came to SCC and BCC risk, especially since the ≤ 3-year sub-analysis showed significantly increased risk of BCC with TNFis use (Paper V. Jonas A. Adalsteinsson, Muzumdar, Waldman, Hu, Wu, Ratner, Ungar, et al., 2021). Multiple studies have looked at the potential relationship between TNFis and cancer risk. One systematic review of eight prospective cohort studies concluded there is an increased risk of SCC with TNFis compared to the general US population (Peleva et al., 2018). Hellgren et al. reported that patients with spondyloarthritis and psoriatic arthritis on TNFis were not at increased risk for cancer (Hellgren et al., 2017). It is unclear whether TNFis directly increase the risk of KC, but increased risk of both SCC and BCC, especially in patients with psoriasis, has been shown (Raaschou, 2016) (Van Lümig et al., 2015). Wang et al. reported in 2020 that RA patients treated with TNFis were at an increased risk of developing KC. These results are important, as patients with RA usually do not have a history of phototherapy, while psoriasis patients commonly use natural UV to improve their disease, potentially increasing their baseline risk through their behavior(J. lin Wang et al., 2020). One nationwide cohort study from Sweden looked at the risk of TNFis in rheumatoid arthritis patients. They observed no increased risk of BCC with TNFis, but they did note a baseline higher risk of SCC in RA patients, with that risk increasing by 30% after exposure to TNFi therapy (Raaschou, 2016). Our study differs from this one as we included all patients on TNFis, not only those with RA.

There were a few limitations to our TNFi analysis. We were unable to correct for comorbidities, sun exposure, and other indications for TNFi use, which could be potential confounders. In addition, we were unable to adjust for exposure to phototherapy, which may have been disproportionately higher in patients exposed to TNFis. It is important to note that patients with psoriasis and psoriatic arthritis may have a higher baseline risk of cancer than the rest of the population (Vaengebjerg et al., 2020)**.** One study reported that although the overall rate of internal malignancy was the same, the incidence of KC was higher in patients with psoriasis (Marino et al., 2020). We also looked at patients taking adalimumab, etanercept, infliximab, and golimumab, which were the major TNFis prescribed in Iceland during this time frame and therefore should have been able to include the majority of the patients treated with these agents.

In conclusion, there is a considerable amount of data supporting the association of KC, especially SCC, with TNFis. The SCCis risk increase that we observed might be greater in regions with higher UV exposure. Moderate sun-protective behaviors alone might not eliminate this risk, even in the setting of low baseline UVR. The immunosuppression associated with TNFis might render the immune system less capable of mounting a T-cell response against dysplastic keratinocytes, leading to higher rates of progression into SCCis and possibly invasive SCC. Our study results also align with the hypothesis that T-cell-induced immunosuppression might play a more prominent role in SCC pathogenesis than BCC.

5.3.4 Metformin (Study VI)

Our study supports an association between metformin use and a significantly decreased risk of BCC in a low-UV environment (Paper VI. Jonas A. Adalsteinsson, Muzumdar, Waldman, Wu, et al., 2021). Metformin has been used for many decades as an oral hypoglycemic agent, being considered first-line therapy in obese type 2 diabetic patients (D et al., 2013). Its primary mechanism for use in diabetes is suppression of hepatic glucose production, thereby increasing glucose utilization by tissues, which lowers serum insulin levels (D et al., 2013). Metformin has been effective in many dermatologic conditions, including hidradenitis suppurativa and acanthosis nigricans, which are worsened by hyperinsulinemia (D et al., 2013). More recently, however, attention has shifted towards potential alternative functions of metformin, mainly its antiaging and anti-carcinogenic effects. It has been shown to have the potential to increase the lifespan of multiple model organisms and decrease carcinogenesis. There is growing evidence suggesting that it could decrease cancer risk and the risks of other age-related conditions, such as cardiovascular and neurodegenerative diseases (V et al., 2020). For metformin's anticarcinogenic effects, multiple pathways have been suggested, such as activation of AMP-kinase leading to the inhibition of mTOR, reduction of insulin growth factors, or inhibition of reactive oxygen species (Fan et al., 2015) (Kisfalvi et al., 2009) (Hosono et al., 2010) (CV et al., 2020). More recently, metformin has been shown to directly inhibit the Sonic hedgehog (Shh) signaling pathway (Niu et al., 2019; Z. Song et al., 2017), which is vital for cell growth and characterized by Shh ligand binding to the cell surface receptor Patched to initiate cell growth. Metformin inhibits Shh ligand expression, thereby reducing pathway activation, a clinically relevant finding, as demonstrated by direct inhibition of the Shh pathway in breast cancer cells and cancer stem cells (Fan et al., 2015).

Multiple studies have shown that metformin can inhibit cancer growth in humans, including cervical cancer (C et al., 2020) and breast, pancreatic and colorectal cancer (G et al., 2020) (Fan et al., 2015) (Kisfalvi et al., 2009) (Hosono et al., 2010). Studies looking at skin cancer are mainly conducted on small selected populations and have shown conflicting results. One meta-analysis, looking at six trials combining 8,541 patients, concluded that metformin was not significantly associated with decreased risk of melanoma, BCC, or SCC (MS et al., 2021). Another study that combined BCC and SCC in their analysis did show a reduced risk of a second KC in diabetic patients who were started on metformin (Ravishankar et al., 2020).

We observed a decreased risk of BCC, which was similar in all dose categories, for which there are a few potential explanations. An idiosyncratic risk lowering effect is one possibility, with metformin demonstrating beneficial effects even at low doses after a short time. Patients taking metformin are more likely to be on other medications, which could increase KC risk, such as HCTZ and statins. In the models adjusted for the use of these medications, we observed a decrease in OR. The OR did not decrease when adjusting for TNFis, which could be because this group of patients is not more likely to be on this class of medication. We also observed decreased BCC risk in all sub-analyses except for the <60 years of age category, likely due to a lack of power, but metformin's protective effect could also be less significant in younger individuals. Interestingly, we saw a possibility of increased risk of SCCis 1.40 (95% CI: 1.00-1.96) as well as SCC (1.47 (95% CI: 1.01-2.14) in the 501-1500 DDU category. This was not seen in other subcategories and in the case of SCC, was not significant after adjusting for the use of other medications (1.35 (95% CI: 0.92 -1.97).

Unfortunately, our retrospective design did not allow for the possibility of residual confounders, including a diagnosis of diabetes, diabetic risk factors, or use of another diabetic medication. Some studies have reported an increased risk of skin cancer in type 2 diabetes (H. W. Tseng et al., 2016), while others have reported decreased risk (T.-Y. Chuang et al., 2005; Reinau et al., 2014). One study from the UK concluded that patients diagnosed with type 2 diabetes were diagnosed with BCC less often (Reinau et al., 2014), prompting speculation that differences in diabetic lifestyles could protect against the development of KC (Reinau et al., 2014). This is an unlikely explanation for our study findings, as we would expect to see decreased risks of SCC and SCCis in the metformin group, especially since SCC has been reported to have an even stronger UVR association than BCC. It has been speculated that insulin-like growth factor 1 receptor in keratinocytes might play a protective role, with activation protecting the cell from UVB-induced carcinogenesis (T.-Y. Chuang et al., 2005). Again, if this were the case, we would expect to see a decrease in SCC and SCCis risk. We, therefore, think that the most likely mechanism of metformin's protective effect is through selective inhibition of the Shh pathway.

While nicotinamide and acitretin have shown effectiveness in reducing SCC and AK counts, their role in treating and preventing BCC is unclear (Kadakia et al., 2012; Snaidr et al., 2019). The main chemoprophylaxis options for BCCs currently are the Shh inhibitors. The first Shh pathway inhibitor approved by the FDA was vismodegib (Aditya & Rattan, 2013), followed by

sonidegib (Lear et al., 2018), both of which block the SMO receptor, inhibiting Shh pathway activation (Aditya & Rattan, 2013). Long-term use of these agents is limited by side effects that affect many patients, the most notable being muscle spasms, dysgeusia, and alopecia (Aditya & Rattan, 2013). Notably, there does not seem to be an increased risk of SCC after treatment of BCC with vismodegib (Bhutani et al., 2017). This is important to consider in the context of our findings that some subanalyses showed increased risks of SCCis and SCC with metformin use. Metformin's most common side effects are nausea and diarrhea, which are usually mild and can be minimized by taking the medication with meals or decreasing the dose. These side effects are present in up to 50% of patients (Siavash et al., 2017). If the association we observe in this study is true, it could be that beneficial effects concerning KC prevention may be achievable with lower doses that are less likely to cause side effects.

5.4 Strengths and weaknesses

The major strength of our study is that we used nationwide population-based data that included all patients with pathologically confirmed KC in Iceland, including high-quality data available from the ICR and the Icelandic Prescription Medicine Register held by the Icelandic Directorate of Health. Most registries only document the first diagnosed SCC without registering BCC and SCCis. We had available data on not only the first tumor but subsequent diagnoses as well. In addition, we had data on BCC as well as SCCis. This makes our dataset highly unique. We were thus able to calculate accurate incidence rates and assess cumulative risk in a very well-defined homogeneous population. The main weaknesses of the epidemiology part of this study are the lack of individualized data on sun exposure, such as sex-specific travel data, artificial tanning exposure, and underlying co-morbidities. Furthermore, we probably underestimated the true incidence of KC by a small margin, as clinicians occasionally treat lesions without doing a biopsy (Hery et al., 2010). In addition, a reservoir of undiagnosed and untreated KC is bound to be present in the Icelandic population. It is unknown what proportion of KC has an indolent course without clinical progression, and thus, it is difficult to determine whether it is possible to 'overdiagnose" KC. Three notable articles exist on the disease course of BCC without treatment. Two of them looked at BCC progression without treatment, demonstrating that about 50% of lesions did not grow and the other half grew about 10% per month (W. MR et al., 2018; Winden et al., 2021). Another study demonstrated that only about 9% of incompletely excised BCCs and 4.6% of SCCis recurred. When looking at KC with minimal transection, the overall recurrence rate of 124 KC was only 5.6% (KE et al., 2010). This suggests that observation and nonsurgical treatments can potentially play a larger role in KC management that what current standard of care suggests but this needs to be confirmed in higher quality prospective studies (Wehner, 2021). Overdiagnosis, especially in the elderly population, thus seems like a definite possibility.

While retrospective observational studies are notorious for their potential to report spurious findings, they are at the same time vital for scientific progress. The central importance of observational studies lies in our ability to generate hypotheses that can later be tested with prospective randomized control trials (Nijsten et al., 2021). When interpreting the results of our medication analysis, one must keep in mind a few things. Even when a significant result is reported, it could be due to chance. When making conclusions based on subgroup analyses, one must always consider whether the effect seen could occur by chance and whether there is sufficient biological

basis for the suggested hypothesis. Therefore, consistency across multiple studies is essential when making conclusions or developing guidelines (X et al., 2014) (Nijsten et al., 2021). One other major limitation within our design is the possibility of residual confounding, which is unavoidable with most retrospective designs. We lacked data on UVR exposure habits, tanning bed use, smoking status, and socioeconomic status. In our statin study, it is possible that statin users had higher amounts of sunlight exposure, increasing their risk of SCC and SCCis, given that one Danish study showed that statin users had less healthy lifestyle profiles compared to nonusers (RW et al., 2013). This could also be the case for our HCTZ group, although our observed associations were stronger, have a confirmed biological explanation, and were consistent with those of other studies. An optimal strategy to minimize the risk of confounding would have been to use a cohort design with a control group on a separate anti-hypertensive medication, such as an ACE-inhibitor or a beta blocker. However, we lacked power to conduct such a study. Another benefit of cohort design would have been the abiiity to translate relative risk estimates into absolute risk, making it possible to calculate the number needed to treat, or harm. This should be an essential part of future studies so that we may elucidate the true risk/benefit ratio of using these medications, and determine the true significance of their side effects. One other explanation for increased KC risk in HCTZ, statin and TNFi users could be closer physician surveillance, leading to the diagnosis of lesions that might otherwise go unnoticed.

Replication is of utmost importance in the process of establishing an association between a disease and exposure. We, therefore, emphasize the importance of further research, both retrospective, and prospective, to confirm some of our findings. If warranted, the implementation of clinical prediction models could be of benefit in the future when or if these associations become more established.

Conclusions

All of the aims put forward in this thesis were met. Our data shows a serious public health problem in a population exposed to low levels of natural UVR. We observed a rapid increase in KC in both men and women that appeared to correlate with a period of high artificial tanning use in Iceland, as well as increased travel abroad. Our multiplicity numbers suggest that KC burden in white populations might be a more serious problem than previously estimated. In addition, our results suggest that significant behavioral differences between men and women should be considered when mapping out public health interventions for skin cancer prevention. Such efforts should focus on primary prevention methods, which have higher evidence levels than secondary prevention methods for KC.

Physicians should be aware of how medications potentially influence KC risk. Our results suggest that a complicated relationship exists between medications and skin cancer pathogenesis. When patients are started on HCTZ and TNFi, they should be counseled on the potential association with increased KC risk and educated about proper sun protection. Average sun protection might not be sufficient for patients living in environments with high background UVR to nullify this risk, especially with HCTZ exposure. It is too early to tell whether statins are truly associated with KC, as residual confounding is a possibility and could explain our findings. Patients on statins could be a population that is in general at higher risk for KC, which is also important to keep in mind for patient risk stratification. Finally, metformin showed a strong relationship with decreased BCC risk. While it is too early to tell, metformin could be an option in the future for patients at high risk for BCC, or in patients with a history of multiple BCCs to slow the rate of further BCC development.

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Original publications

Paper I

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Basal cell carcinoma: an emerging epidemic in women in Iceland

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Summary

Background An epidemic of basal cell carcinoma (BCC) has led to a significant healthcare burden in white populations.
Objectives To provide an update on incidence rates and tumour burden in an unselected, geographically isolated population that is exposed to a low level of ultraviolet radiation.
Methods This was a whole-population study using a cancer registry containing records of all cases of BCC in 1981–2017. We assessed BCC incidence according to age, residence and multiplicity and assessed trends using join-point analysis. Age-standardized and age-specific incidence rates were calculated along with cumulative and lifetime risks.
Results During the study period, the age-standardized incidence rates increased from 25·7 to 59·9 for men, and from 22·2 to 83·1 for women (per 100 000). Compared with the single-tumour burden, the total tumour burden in the population was 1·72 times higher when accounting for multiplicity. At the beginning of the study period, the world-standardized rates in men and women were similar, but by the end of the study period the rates were 39% higher in women (83·1 per 100 000, 95% confidence interval 77·9–88·3) than in men (59·9 per 100 000, 95% confidence interval 55·6–64·2). This increase was most prominent in women on sites that are normally not exposed to ultraviolet radiation in Iceland: the trunk and legs.
Conclusions This is the only reported population in which the incidence of BCC is significantly higher in women than in men. The period of notable increase in BCC lesions correlates with the period of an increase in tanning beds and travel popularity. The high multiplicity rates suggest that the total tumour burden worldwide might be higher than previously thought.

What is already known about this topic?

- Basal cell carcinoma (BCC) is becoming an increasing healthcare burden worldwide, especially in white populations.
- Recent population studies have reported a rapid increase in incidence among younger individuals, especially women.

What does this study add?

- Iceland is the only reported population in which the incidence of BCC is significantly higher in women than in men, and there does not seem to be a clear relationship between latitude and BCC incidence in Europe.
- Men might be comparatively protected in the northern low-ultraviolet environment, with tanning beds and travel abroad likely playing important roles in the observed incidence increase, especially in women.
- The high multiplicity rates suggest that the total tumour burden worldwide might be higher than previously thought.

Basal cell carcinoma (BCC) is the most common cancer in white populations,[1,2] and associated healthcare costs have become an increasing burden.[2,3] Although BCCs are historically associated with male sex and increasing age, recent population studies have reported a rapid increase in incidence among younger individuals, especially women. This trend may lead to an exponential increase in the overall occurrence of BCCs.[4,5]

As BCCs are not a reportable disease in most countries, they are not included in most national cancer registry incidence reports. Because of this, the majority of data on BCC incidence come from local studies of incidence in well-defined geographical regions. Furthermore, in a large number of registries only the first case of BCC is reported, and subsequent tumours are excluded. Consequently, the true incidence and tumour burden of BCC remain unknown and are probably underestimated.[6] Based on data from the Icelandic Cancer Registry (ICR), a population-based national cancer registry,[7] it was possible to analyse incidence trends and multiplicity from 1981 to 2017 by taking advantage of the complete records of pathologically confirmed BCCs diagnosed within this time period. This registry afforded a unique opportunity to combine histological confirmation of keratinocyte cancers with tumour registry verification over an extensive time period for an entire population, while simultaneously looking at multiplicity.

BCC incidence has a strong relationship with skin colour and an inverse relationship with latitude. Reykjavik is the northernmost capital in the world, with no other capital having a lower overall background ultraviolet index (UVI). The Icelandic population therefore represents an interesting contrast to Australia's population, which has the highest reported BCC incidence rates in the world.[8] Tanning beds are a known risk factor for BCCs,[9] and use in Iceland increased tremendously from the 1980s up until 2004.[10] Studying the Icelandic population may therefore provide important information regarding the behaviour of these cancers.

Patients and methods

The ICR is a high-quality registry that contains complete records of all cases of pathologically confirmed skin cancers nationwide from 1981, with histological verification.[7] Our study cohort contained all patients diagnosed with first and subsequent BCCs in the years 1981–2017, with an associated International Classification of Diseases code and pathological diagnosis. We divided Iceland into two regions: (i) Reykjavik and the adjacent Reykjanes peninsula, and (ii) the rest of the country, which is composed mainly of small towns and rural areas. All BCCs diagnosed in individuals younger than 30 years of age were re-reviewed by a dermatopathologist accredited by the Accreditation Council for Graduate Medical Education before being included in the study.

For BCC incidence and join-point analysis, we used data from the population-based ICR. All new BCCs that occurred between January 1981 and December 2017 were included. Incidence rates of confirmed BCCs were presented for the 37-year period using world-standardized rates (WSRs)[11] expressed per 100 000 person-years, as well as cumulative risk. Cumulative risk of BCC occurrence before ages 40, 65 and 80 years (the latter defined as the lifetime risk) was calculated using age-specific rates, multiplied by the proportion of survivors and expressed as a percentage: cumulative risk = $1 - \exp(-\text{cumulative rate})$.[12]

For single and multiple BCCs, we present age-specific incidence rates. Due to the small population of Iceland (350 000 individuals), random variation was prominent. For example, the average yearly number of cases was only between one and four for sites other than the head/neck, trunk and legs (women). Therefore we used 5-year moving averages when showing changes with time, instead of looking at individual years. When calculating multiplicity, because the same tumour might be histologically diagnosed twice, all records of apparently multiple BCCs diagnosed within a 4-month period in the same person, and at the same anatomical location, were excluded. We also calculated the median interval between first and second BCCs, as well as the overall median interval between all BCCs that occurred.

Trends and join points were calculated for the three most common sites (head/neck, trunk and legs; in women) using Joinpoint version 4·6·0·0.[13] We stratified according to age ($<$ 50 years and $\geq$ 50 years) in order to be able to compare the data with those from a previous Icelandic study on melanoma.[14] Trends were assessed by calculating the annual

percentage change and the corresponding 95% confidence interval (CI).[13] Due to the large sample size in this whole population with independent observations, P-values were calculated using the c^2-test, which met all assumptions. P-values < 0·05 were considered statistically significant. Due to the chance of BCCs in the early years of the study being second or third lesions we conducted a sensitivity analysis.

Results

Sensitivity analysis showed a nonsignificant difference in multiplicity proportions. Thus, all years were included in the analysis. The final number of first diagnosed BCCs after excluding 32 cases diagnosed outside of the country was 7226. No cases diagnosed in individuals aged < 30 years were excluded after review. There were 3100 cases in men (42·9%) and 4126 (57·1%) in women. For first BCC, the average age at diagnosis for the entire study period was 67·2 years for men and 65·2 years for women (P < 0·001). Overall, 71% of all BCCs in men and 72% in women (P = 0·21) were diagnosed in the Reykjavik region. Head and neck was the most common anatomical location for both men and women (62% and 55%, respectively) (P < 0·01). Next was the trunk (29% for men and women) (P = 0·56) and then the legs (3% for men, 8% for women) (P < 0·01).

Age-standardized incidence rates – by sex

In 1981 the age-standardized incidence rates were 25·7 tumours per 100 000 for men and 22·2 per 100 000 for women (not statistically significantly different). The rates had increased approximately 2·33 times for men and 3·74 times for women by 2017 (Figure 1). After the period 1998–2002 the difference in incidence the between sexes became statistically significant, as can be seen in Figure 1 from the nonoverlapping 95% CIs. In the final 2013–2017 period, the WSR was 1·39-fold higher for women than for men (83·1 and 59·9 per 100 000, respectively). The largest increase in WSR was observed for women between 1995 and 2004, with a 1·49-fold difference (from 39·8 to 59·2). For men, the increase in WSR was more stable over time, with the WSR increasing 1·19-fold during the same period (35·5 to 42·4).

Age-standardized incidence rates – by anatomical location and geographical area

For all body sites, the WSR increased for both men and women from 1981 to 2017 (Figure 2). The higher total number of BCCs in women compared with men can be mostly accounted for by a rapid increase in truncal and leg lesions compared with head and neck lesions. In the 1981–1990 time period, 72% of BCCs were located on the head and neck in both men and women. In the 2009–2017 time period this percentage had decreased to 57% for men and 49% for women (P < 0·01), not because of a decrease in the number of cases, but because of a proportional increase in truncal and leg lesions in women.

There was a notable increase in BCC age-standardized rates for both Reykjavik and rural areas. Rates in rural areas were lower for both sexes (Figure 3). For 2009–2017, the difference in incidence between rural men (50·0 per 100 000,

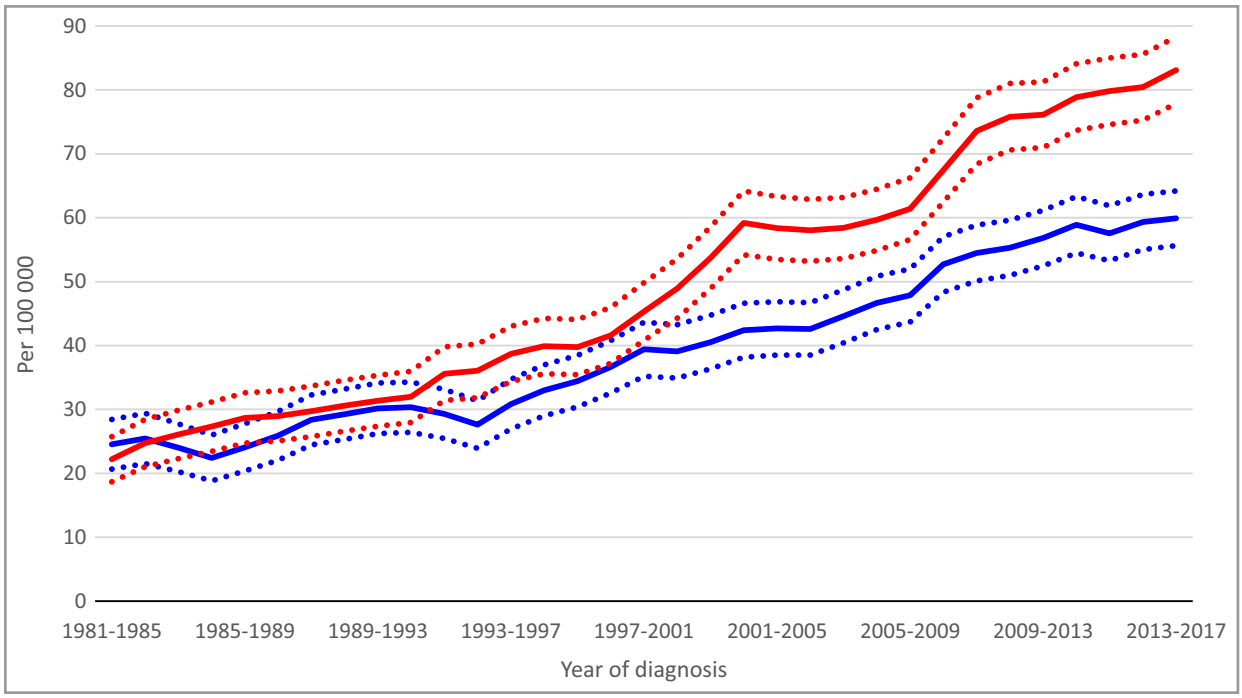

Figure 1 Histologically confirmed basal cell carcinoma in Iceland, age-standardized (world) incidence (5-year moving averages) from 1981 to 2017 for men (blue) and women (red), including 95% confidence intervals (dotted lines).

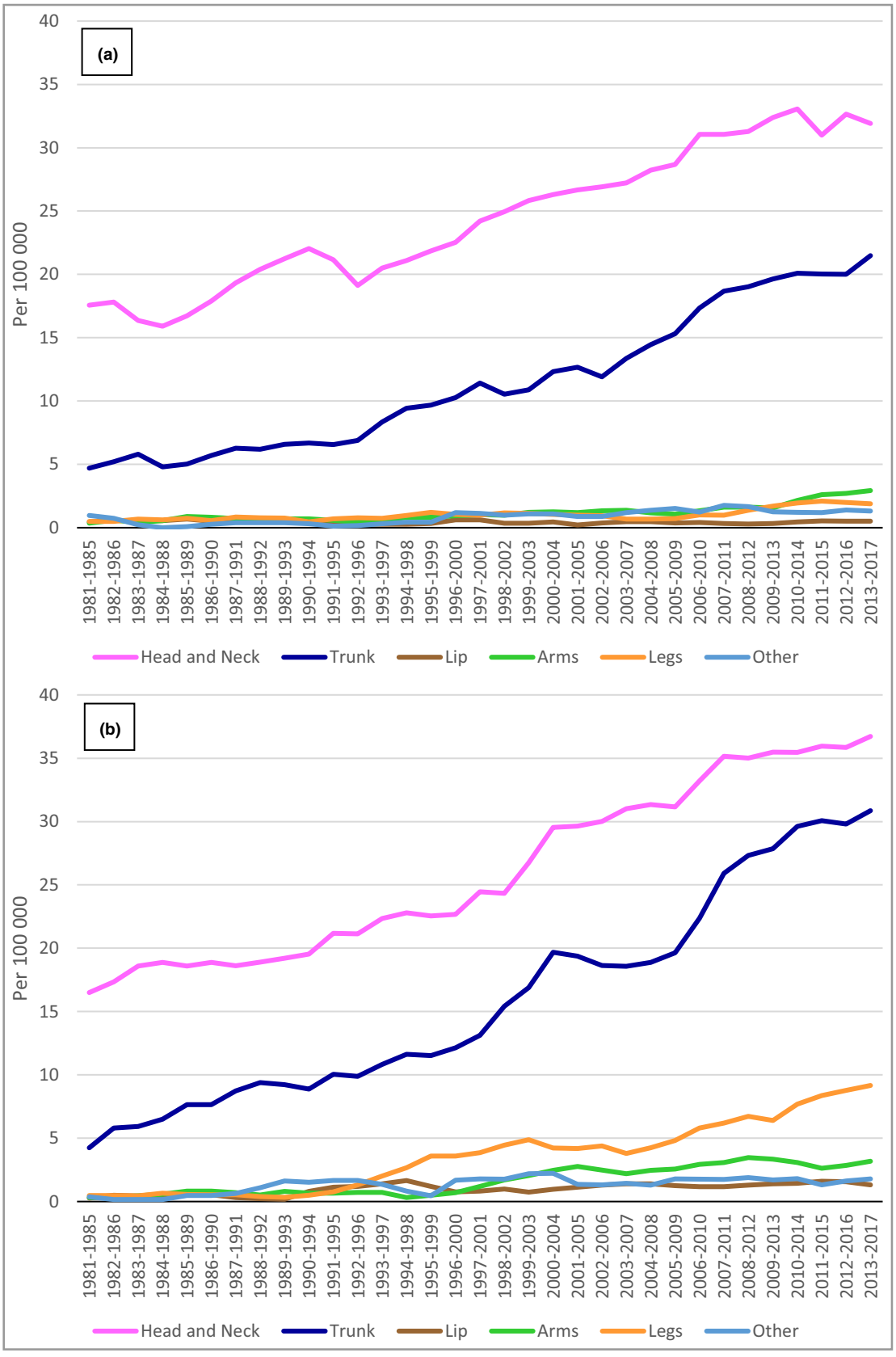

Figure 2 Trends in age-standardized (world) incidence (5-year moving averages) of basal cell carcinoma according to sex, anatomical location and time period. (a) Men and (b) women.

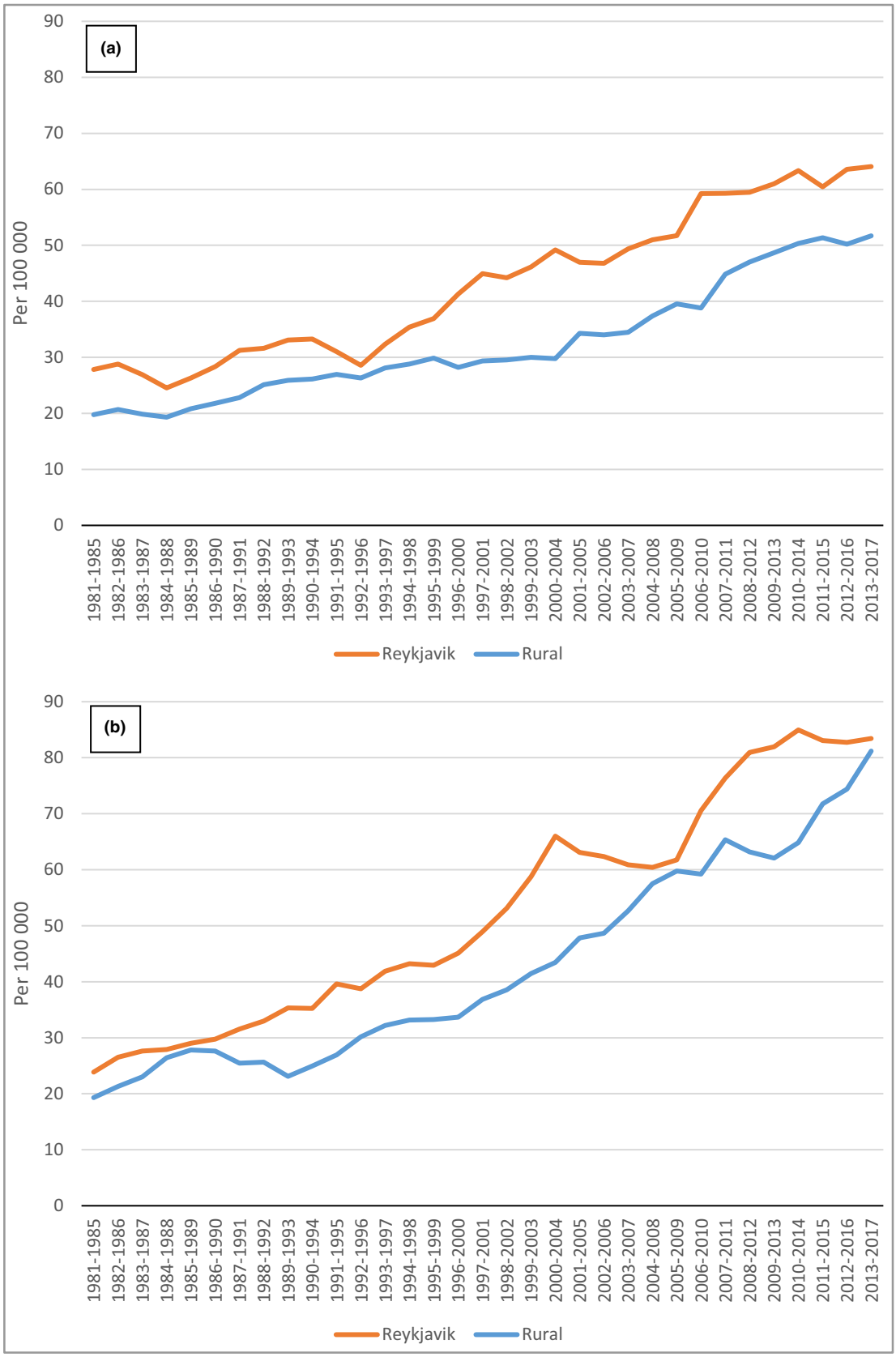

Figure 3 Trends in age-standardized (world) incidence (5-year moving averages) of basal cell carcinoma according to time period, sex and residence (Reykjavik vs. rural areas). (a) Men and (b) women.

95% CI 44·7–55·3) and Reykjavik men (62·2, 95% CI 58·2–66·2) was statistically significant. The difference between Reykjavik women (83·8, 95% CI 79·0–88·5) and rural women (72·4, 95% CI 65·7–79·2) was marginally significant.

Join-point analysis

For the whole study period the annual percentage change in incidence was 2·99% for men and 4·12% for women. Figure 4 shows slopes for BCCs of the head and neck for the groups aged < 50 years and ≥ 50 years. No join points occurred. There was a marginally significant difference between the slopes in the < 50-year group: 0·11 (95% CI 0·05–0·17) for men and 0·24 (95% CI 0·17–0·31) for women. In the ≥ 50-year group there was no significant difference between the slopes: 2·89 (95% CI 2·38–3·40) for men and 3·26 (95% CI 2·66–3·86) for women.

For lesions of the trunk in the < 50-year group (Figure 5), join points occurred for women in 1993 and men in 1988. No join points were observed in the ≥ 50-year group. As with head and neck lesions, a more prominent difference between sexes was noted for the < 50-year age category compared with age ≥ 50 years. For leg lesions, statistically significant join points occurred for women aged < 50 years in 2004 (slope increased from 0·0 to 0·36) and for women aged ≥ 50 years in 1992 (slope increased from 0·00 to 1·34). For men there was no corresponding increase in leg lesions.

Multiplicity

When accounting for multiplicity, the total number of BCCs during the entire study period was 12 432 lesions in 7226 individuals. Similar numbers of lesions on average were diagnosed in men and women (1·7 and 1·73, respectively). Overall, 92% of individuals, both men and women, had between one and three lesions. During the first period of the study (1981–1990) a slightly higher proportion of men had multiple lesions (35%) compared with women (33%; P = 0·74). During the last period (2009–2017) the multiplicity proportions had decreased to 25% for both sexes.

The median time interval between first and second BCCs was 2·2 years for women (range 0–34) and 2·1 years for men (range 0–30). The overall median interval between all BCCs that developed was 1·4 years (range 0–34) for women and 1·3 years (range 0–30) for men. This difference between sexes was not statistically significant. Table 1 demonstrates age-specific rates (ASRs) analysed by age group and sex. Overall, women had higher ASRs for both single and multiple tumours, with the exception being the ≥ 65-year single-BCC category, where men had a higher ASR.

Lifetime and cumulative risk

In the 2009–2017 time period the lifetime risk for women was 10·1%, compared with 7·3% in men (P < 0·01). This is an increase from the 1981–1990 period, when the lifetime risk was 3·2% for women and 2·8% for men (P = 0·1). The risk for women aged < 40 years saw the highest proportional increase: sixfold (from 0·1% to 0·6%), compared with threefold for men (from 0·1% to 0·3%).

Discussion

Although skin cancer used to be rare in Iceland, BCC has now become one of the cancers with the highest incidence in the Icelandic population, surpassing lung and colon cancer, but not prostate and breast cancer.[15] The country's capital, Reykjavik, has the lowest UVI of all world capitals and has on average a higher proportion of cloudy days than sunny days.[16] The WSR in Iceland is among the lowest reported (60 for men, 83 for women, per 100 000), with lower rates reported in Malta, Slovenia, Croatia and Lithuania,[6,17,18] despite Iceland's UV exposure being dramatically lower than in these countries. Thus, there does not seem to be a clear correlation between latitude and BCC incidence in Europe.[6] While the head and neck region was the most commonly affected location in this study, the incidence of leg and truncal lesions is increasing at a much faster rate. It is thus unlikely that natural background UV in Iceland is playing a significant role in this increase, as these anatomical locations are usually concealed outdoors in this population.

We noted a significantly higher BCC incidence in women than in men, as well as a greater increase in incidence, with women also being younger when diagnosed with their first BCC. A statistically significant higher incidence in women has not been observed previously, to our knowledge, in a whole-population epidemiological study.[18–25] In some areas that tend to have high overall background UV exposure, men have an incidence rate that is almost twice that of women.[26–30]

There are a few potential explanations for this observed sex difference. A 2002 survey conducted in the Reykjavik area indicated that 70% of women and 35% of men had used a tanning bed. This difference was especially pronounced in Icelandic teenagers: 50% of teenage girls had used a tanning bed in the previous year, compared with 30% of boys. It has been hypothesized that tanning bed exposure at a young age might exponentially increase BCC risk at a later age.[9,14,31] Women might also be more diligent with skin cancer screening, leading to discovery of BCCs on the legs and trunk that might otherwise have gone unnoticed. Some parts of the southern USA have considerably less access to dermatology care than Iceland, yet their BCC rates are much higher in comparison. This suggests that while increased screening might play some part in the increased incidence that has been observed, it cannot explain the whole picture.[28,30]

BCC rates in rural areas in Iceland were lower overall than in Reykjavik. This is the opposite of what is presumed to be the case in the USA and Australia, with individuals in rural areas thought to be at increased risk of developing BCCs due to occupational sun exposure.[32] The high rates observed there in rural areas in men are most likely due to chronic background occupational UV exposure.[33] In Iceland, the greater

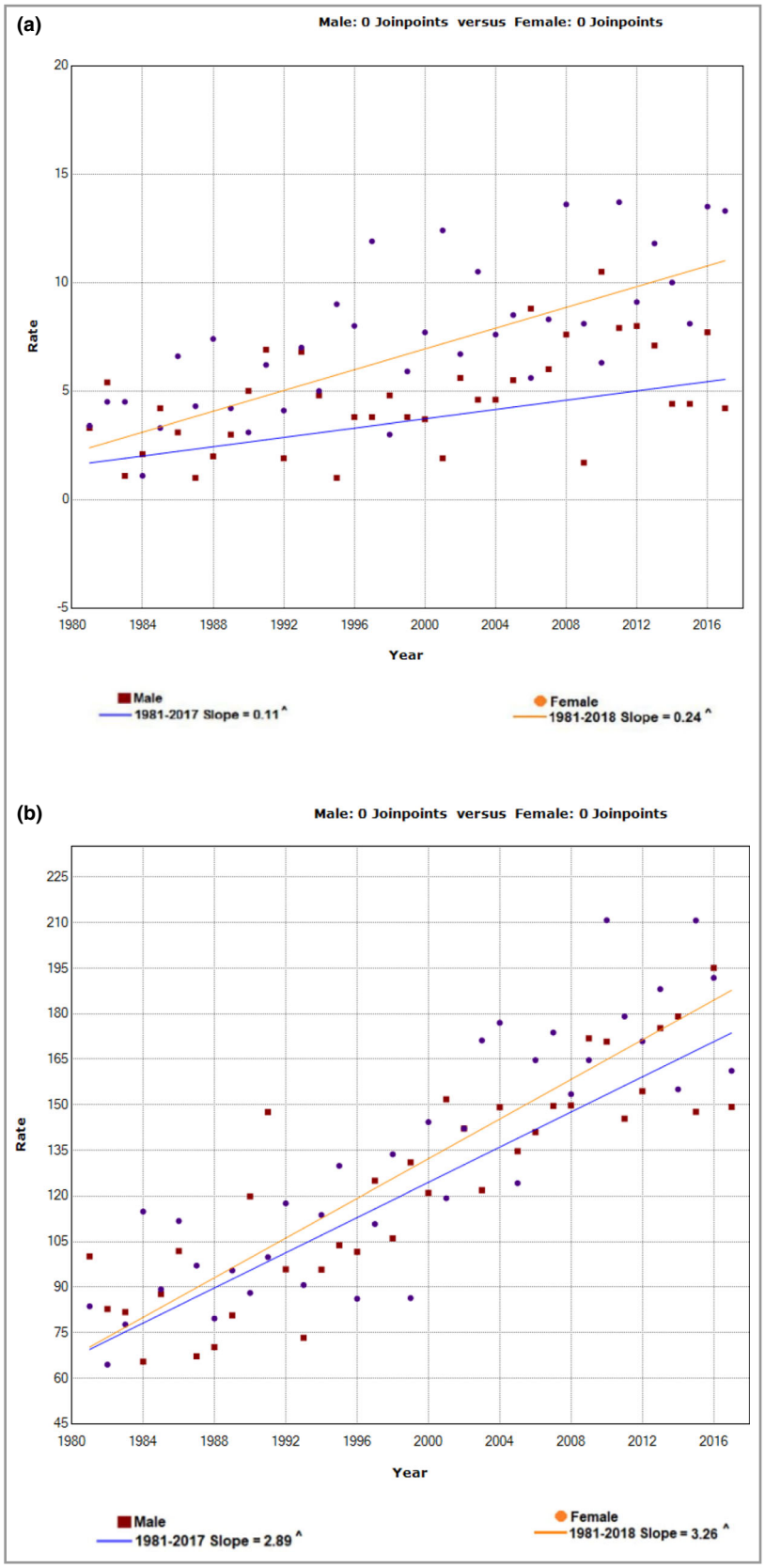

Figure 4 Join-point analysis of basal cell carcinomas of the head and neck for men (blue) and women (orange), using age-standardized rates (world) per 100 000. (a) Age < 50 years and (b) age ≥ 50 years. ^ indicates that the slope is significantly different from zero at the alpha = 0·05 level.

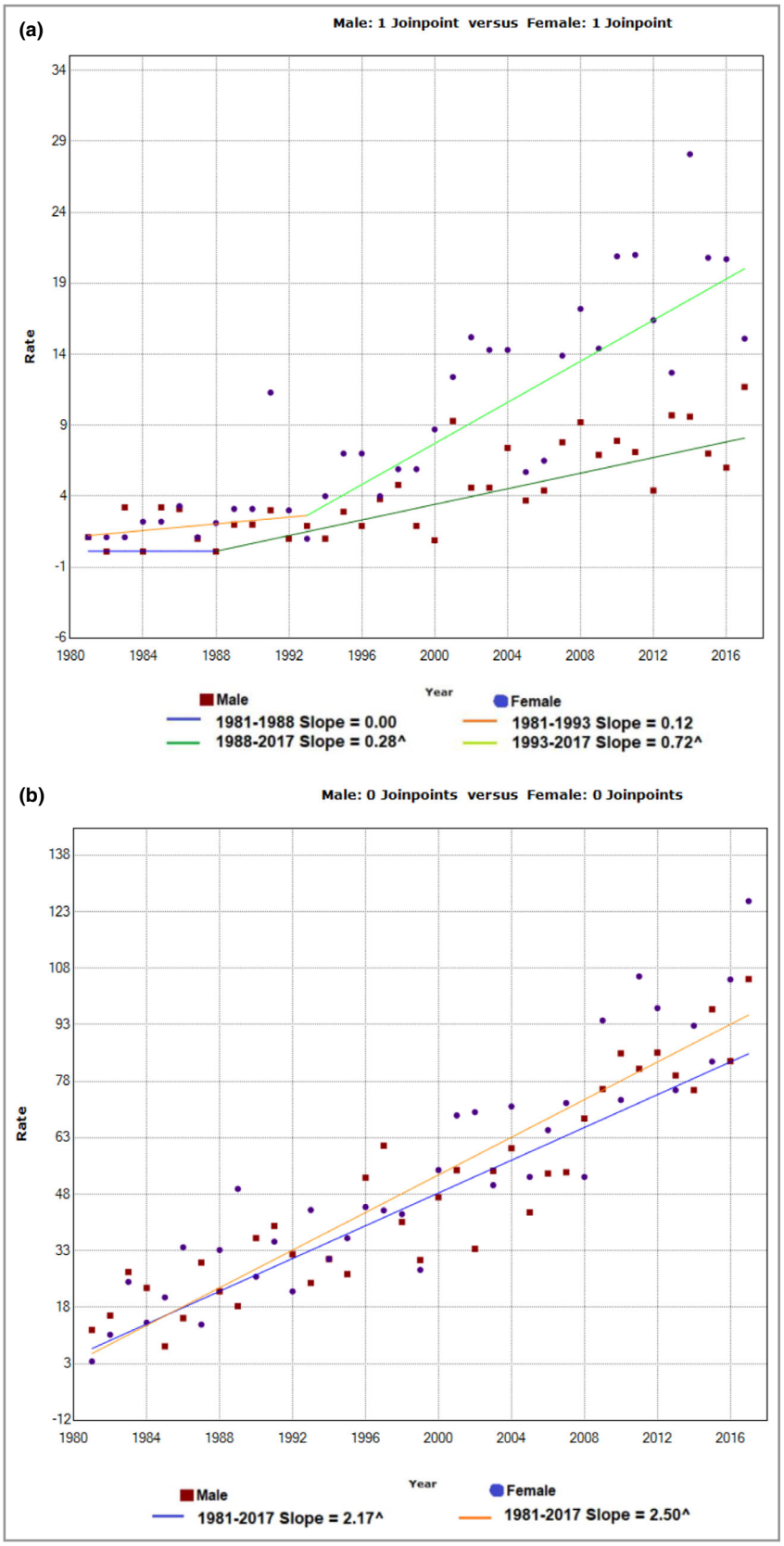

Figure 5 Join-point analysis of basal cell carcinomas of the trunk for men (blue/dark green) and women (orange/light green), using age-standardized rates (world) per 100 000. (a) Age < 50 years and (b) age ≥ 50 years. ^ indicates that the slope is significantly different from zero at the alpha = 0·05 level.

Table 1 Single and multiple basal cell carcinoma (BCC) age-specific incidence rates per 100 000 during 1981–2017, stratified by sex and age in years. The world-standardized rate (WSR) is reported for each sex in each category

	All BCCs		Single BCC		Multiple BCCs	
	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)
Male						
< 40	139	4·3 (3·6–5·0)	109	3·4 (2·7–4·0)	30	0·9 (0·6–1·3)
40–64	1049	72·5 (68·1–76·9)	712	49·2 (45·6–52·8)	337	23·3 (20·8–25·8)
≥ 65	1912	347·0 (331·5–362·6)	1352	245·4 (232·3–258·5)	560	101·6 (93·2–110·1)
WSR	3100	42·4 (40·8–43·9)	2173	29·5 (28·2–30·8)	927	12·9 (12·0–13·7)
Female						
< 40	278	8·9 (7·9–10·0)	211	6·8 (5·9–7·7)	67	2·2 (1·6–2·7)
40–64	1528	108·0 (102·6–113·4)	1024	72·4 (67·9–76·8)	504	35·6 (32·5–38·7)
≥ 65	2320	351·0 (336·7–365·3)	1604	242·7 (230·8–254·6)	716	108·3 (100·4–116·3)
WSR	4126	53·9 (42·2–55·7)	2839	36·7 (35·2–38·1)	1287	17·3 (16·3–18·3)

CI, confidence interval.

number of cloudy days and low UVI create a sun-protective environment for outdoor workers. Tanning bed use is comparable between Reykjavik and rural areas, but rural Icelanders might be less likely to see a dermatologist regularly due to low access.[14,31] Men also tend to be less diligent in their day-to-day sunscreen use.[34] Preventive efforts in Iceland and other countries with low background UVI might thus be more effective than in other countries with a high UVI and light-skinned populations. Theoretically it is easier for individuals to avoid high-risk behaviours such as tanning bed use, or to apply sunscreens in the little time spent in high UVI zones, rather than to avoid daily chronic UV exposure.

Tanning booths are an avoidable source of exposure to highly carcinogenic UV radiation, which increases the risk of both melanoma and nonmelanoma skin cancers.[35] The fact that there does not generally seem to be a relationship between latitude and BCC incidence in Europe could partly be explained by the increased use of tanning beds seen in Iceland between 1979 and 2004, as well as increased travel abroad. In 1979 there were only three sunbed salons in Reykjavik. By 1988 this number had increased to 56 facilities with 207 sunbeds.[10] The average of 2·8 tanning bed sessions per year in 2004–2007 in Iceland was around two to three times higher than in neighbouring countries, with a rapid decline in tanning bed use after the year 2004. In 2005, the number of publicly available sunbeds in the Reykjavik area had decreased to 144, and it further decreased to 97 in 2008.[10]

The significant join points noted in this study were on the trunk in men aged < 50 years in 1988 and in women aged < 50 years in 1992, and on the legs in 1992 for women aged ≥ 50 years and in 2004 for women aged < 50 years. These are anatomical locations not normally exposed to the sun in Iceland. All of these join points occurred within the height of tanning bed usage in Iceland (1979–2004). Interestingly, the join points occurred mostly in individuals aged < 50 years, but a 2001–2002 survey showed that 16% of women and 12% of men aged 20–39 years had used a solarium more than 100 times during their lifetime. In contrast, these proportions were 2% and 1% among women and men aged ≥ 50 years.[10,14,31]

Another potential reason for the increase in BCC incidence is travel abroad. The frequency of travelling abroad for Icelanders has increased considerably, from 65 941 yearly voyages to 937 315 between 1970 and 2006. Young Icelanders make fewer cumulative trips abroad but have higher cumulative tanning bed use than older Icelanders.[14] In 1988 and 1993 a join point was noted for truncal lesions for men and women < 50 years of age, but no join point was seen in individuals aged ≥ 50 years, possibly suggesting that a behavioural change might have occurred in the < 50-year group, which had less impact in the ≥ 50-year group. We lack sex-specific travel data, which could help delineate further the differences observed between sexes in this study. The reason for the sex-specific increase in leg lesions in women is unclear, but it could be a combination of tanning bed exposure, increased travel abroad and increased screening.[14]

An increase in truncal lesions in women was also reported in a 2010 study looking at melanoma in Iceland, which demonstrated a rapid increase in truncal lesions in women after 1992, and was attributed at least in part to use of tanning beds.[14] In that study, a decrease was seen in melanoma incidence after 2001, which was attributed to population-wide educational efforts against the use of tanning beds.[14] However, we do not see the same trend for BCC incidence. This might be explained by UV exposure having a more immediate effect on melanoma risk, with risk rapidly falling off 2–3 years after exposure. This might not be true for BCCs, where risk of development after UV exposure may be more prolonged.[14] It is not clear what the lag time is between UV exposure and increased risk of BCC development, but it might be as low as 2 years.[36]

To our knowledge, this is the first whole-population study investigating BCC multiplicity. A recent study exploring multiplicity rate estimates throughout Europe reported that for total

estimates of BCC incidence, the first BCC diagnosis should be multiplied by 1·3.[17] Our study indicated that the rate should be multiplied by 1·7, implying that BCCs might be an even larger healthcare burden worldwide than previously thought. The median interval between development of BCCs decreased between the third and fourth BCC diagnoses (1·3 and 1·4 years for men and women, respectively) compared with that of the first and second diagnoses (2·1 and 2·2 years, respectively), supporting that more frequent surveillance might be warranted for individuals who have developed more than two lesions. The reason for the decreased multiplicity seen with time throughout the study period is likely to be in part due to shortened follow-up for individuals diagnosed late in the study.

This study's main weaknesses are its retrospective nature and the resulting inability to analyse specific characteristics of individuals developing BCCs.

In conclusion, these data show a significant public health problem in a country with limited UV radiation. There is a notable increase in BCC lesions, especially in women, which correlates with both a period of increase in tanning bed popularity and increasing travelling abroad. The trends observed in this study imply that BCCs are an even larger problem worldwide than previously thought, with behavioural differences existing between sexes that should be taken into consideration when planning much needed educational initiatives to decrease the incidence of skin cancer.

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Paper II

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Invasive and *in situ* squamous cell carcinoma of the skin: a nationwide study in Iceland

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Summary

Background The worldwide incidence of cutaneous squamous cell carcinoma (cSCC) is increasing.
Objectives To evaluate the tumour burden of *in situ* and invasive cSCC in Iceland, where the population is exposed to limited ultraviolet radiation.
Methods This whole-population study used the Icelandic Cancer Registry, which contains records of all *in situ* and invasive cSCC cases from 1981 to 2017. Incidence of cSCC was evaluated according to age, anatomical location, residence and multiplicity, and trends were assessed using joinpoint analysis. Age-standardized rates (WSR) and age-specific incidence rates per 100 000 person-years were calculated, along with cumulative and lifetime risks.
Results Between 1981 and 2017, *in situ* cSCC WSR increased from 1·2 to 19·1 for men and from 2·0 to 22·3 for women. Invasive cSCC WSR rose from 4·6 to 14 for men and from 0·3 to 13·2 for women. The average number of *in situ* cSCC lesions was 1·71 per woman and 1·39 per man. Women developed more *in situ* cSCCs than invasive cSCCs in almost all anatomical locations, whereas men developed more invasive cSCCs, mostly on the head and neck. The rates of *in situ* cSCC were higher in Reykjavik compared with rural areas. Furthermore, women more commonly developed multiple *in situ* lesions. For lip cSCCs, invasive lesions occurred more frequently than *in situ* lesions among both sexes. Joinpoint analysis showed that *in situ* cSCC in women exhibited the most rapid incidence increase.
Conclusions cSCC has become an increasingly significant public health problem in Iceland. Tanning bed use and travelling abroad may contribute to skin cancer development. Public health efforts are needed to stem the behaviours leading to this rapid rise in cSCC.

What is already known about this topic?

- Cutaneous squamous cell carcinoma (cSCC) incidence is on the rise worldwide, posing a significant public health threat, especially in light-skinned populations.

What does this study add?

- Icelandic women were more likely to develop *in situ* cSCC, and men were more likely to develop invasive cSCC of the head and neck.

- Women with *in situ* cSCCs were also at a higher risk of developing more than one cSCC compared with men.
- cSCC is becoming a significant public health problem in a country with low background ultraviolet radiation. This finding may be due, in part, to increased tanning bed exposure and travel abroad.

Cutaneous squamous cell carcinoma (cSCC) is the second most common human cancer after basal cell carcinoma (BCC),[1–3] and has the potential to metastasize and cause significant morbidity.[4] cSCC occurs in both *in situ* and invasive forms, but it is unclear whether *in situ* cSCC is a true precursor to invasive cSCC.[5,6] Most national cancer registries register only the first diagnosed invasive cSCC, and most do not register *in situ* disease.[5,6] While the incidence of cSCC is rising worldwide, the epidemiological relationship between *in situ* and invasive cSCC remains unclear.

We recently described rapid increases in the incidence of BCC in Iceland and noted that the total worldwide tumour burden might be higher than previously estimated.[7] However, the incidence and tumour burden of invasive and *in situ* cSCC in the Icelandic population is unknown. Using the unique database constructed by the Icelandic Cancer Registry (ICR), which contains complete records of pathologically confirmed cSCCs diagnosed within this time period, it was possible to analyse incidence trends and multiplicity between 1981 and 2017. The population of Iceland is homogeneous and is exposed to low levels of ambient ultraviolet (UV) radiation.[8,9] Therefore, studying population trends in this country may provide important information regarding the incidence of *in situ* and invasive cSCC and the relationship between these two forms of carcinoma.

Patients and methods

The ICR is a high-quality registry, containing complete case records of all pathologically confirmed skin cancers nationwide since 1981.[10] All patients diagnosed with first and subsequent invasive and *in situ* cSCCs between 1981 and 2017, with an associated International Classification of Diseases code and pathological diagnosis, were included in this study. A dermatopathologist (A.K.K.) accredited by the Accreditation Council for Graduate Medical Education reviewed all cases diagnosed in individuals < 30 years of age before study inclusion.

Using the population-based ICR, age-standardized incidence rates per 100 000 person-years using the world standard (WSR) were calculated. Median age with interquartile range (IQR) was also calculated. Joinpoint analysis was performed. All new cSCCs occurring between January 1981 and December 2017 were included. We divided Iceland into the following two regions: (i) Reykjavik and the adjacent Reykjanes peninsula, and (ii) the rest of the country, mainly comprising small towns and rural areas. Cumulative cSCC risk before age 40 years, 65 years and 80 years (defined as the lifetime risk) was calculated using age-specific rates, multiplied by the proportion of survivors and expressed as a percentage [cumulative risk = 1 − exp (− cumulative rate)].[11]

Age-specific incidence rates were calculated, for single and multiple *in situ* and invasive cSCCs. Owing to the small population of Iceland (350 000 individuals), random variation was frequently observed. Therefore, 5-year moving averages were used to evaluate age-related changes rather than individual years. Multiplicity was also calculated for *in situ* and invasive cSCCs. Notably, to avoid data duplication, all cSCCs diagnosed within 4 months after the first diagnosis were excluded if they occurred in the same anatomical location as the primary tumour.

Trends and joinpoints were calculated for *in situ* and invasive cSCC separately using Joinpoint version 4.8.0.1 (National Cancer Institute, Bethesda, MD USA).[12] Joinpoints were also calculated for the most commonly affected anatomical sites [head/neck, trunk, and legs (in women only)]. Trends were assessed by calculating the average annual percentage change (AAPC) and the corresponding 95% confidence intervals (CIs).[12] χ^2-tests were used to compare proportions, and t-tests were used to compare the mean number of diagnoses; all statistical assumptions were met. Statistical tests were two-sided. P-values < 0·05 were considered statistically significant.

Results

Between 1981 and 2017, there were 1534 first diagnosed *in situ* cSCCs and 1471 invasive cSCCs. No cases were excluded from analysis. During this period, the first diagnosed *in situ* cSCC WSR increased from 1·2 to 19·1 in men and from 2·0 to 22·3 in women; the first diagnosed invasive cSCC WSR increased from 4·6 to 14 in men, and from 0·3 to 13·2 in women (per 100 000 person-years). There were 560 first diagnosed *in situ* cSCCs in men (36·5%) and 974 in women (63·5%) (male/female ratio = 0·57), with 70% of cases in men and 75% of cases in women diagnosed in the Reykjavik area (P = 0·035). There were 769 first diagnosed invasive cSCCs in men (52·3%) and 702 in women (47·7%) (male/female ratio = 1·1). Overall, 67% of cases in men and 70% of cases in women were diagnosed in the Reykjavik area (P = 0·22). The median age at diagnosis was similar in men and women for *in situ* cSCC [76 years (IQR 15) vs. 75 years (IQR 18), P > 0·05] and invasive cSCC [77 years (IQR 15) vs. 78 years (IQR 16), P > 0·05]. The median age at diagnosis

for *in situ* cSCC was lower than the median age at diagnosis for invasive cSCC for both male patients ($P < 0{\cdot}01$) and female patients ($P < 0{\cdot}01$).

The frequencies of *in situ* and invasive cSCC arising at different anatomical locations in both sexes are summarized in Table 1. The head and neck was the most common location for both invasive cSCC (74% in male patients, 53% in female patients; $P < 0{\cdot}01$) and *in situ* cSCC (54% in male patients, 45% in female patients; $P < 0{\cdot}01$). Women were found to have invasive (14%) and *in situ* (20%) leg lesions more frequently than men (2% and 6%, respectively; $P < 0{\cdot}01$). Lip lesions were more likely to be invasive than *in situ*. Invasive lip lesions accounted for 6% of invasive cSCCs in men and 4% in women with 1% of *in situ* lesions occurring on the lip in both men and women ($P < 0{\cdot}01$).

Age-standardized and specific incidence rates stratified by sex

The *in situ* cSCC WSR consistently increased over time for both sexes, from 1·2 to 11·6 in men and from 2·7 to 18·9 in women per 100 000 person-years (Figure 1). Women had a higher *in situ* cSCC WSR compared with men from 1981 onwards, but the sex differences did not become statistically significant until 1999–2003.

For invasive cSCC, a different trend was noted. Men had a higher WSR throughout most of the study period, but the sex difference was statistically significant only within the 1993–1997 time period, when the WSR increased from 4·3 to 13·2 in men and from 2·3 to 11·0 in women. Men currently have a similar incidence of invasive cSCC and *in situ* cSCC [13·2 (11·8–14·6) and 11·6 (10·2–12·9), $P > 0{\cdot}05$], whereas women have a higher WSR of *in situ* cSCC than invasive cSCC [18·9 (17·1–20·6) and 11·0 (9·7–12·2), $P < 0{\cdot}05$].

Figure 2 summarizes age-specific incidence rates of invasive cSCC and *in situ* cSCC for both sexes.

Age-standardized incidence rates stratified by anatomical location

Figure 3 summarizes *in situ* cSCC incidence trends. The most common location of *in situ* cSCC in men and women was the

Table 1 Frequency of *in situ* cutaneous squamous cell carcinoma (cSCC) and invasive cSCC among men and women for different anatomic locations for the study period (1981–2017) (upper part of the table). Trends in age-standardized (world) incidence (10-year averages) of *in situ* and invasive cSCC from 1981 to 2017 according to sex, geographical area and time period per 100 000 person-years (lower part of the table)

In situ cSCC frequency			
Anatomical location, n (%)	Men (n = 560)	Women (n = 974)	P-values[a]
Lip	5 (1)	9 (1)	0·95
Head/neck	304 (54)	438 (45)	< 0·01
Trunk	122 (22)	194 (20)	0·38
Arms	79 (14)	120 (12)	0·31
Legs	32 (6)	195 (20)	< 0·01
Other and unknown	18 (3)	18 (2)	0·09
Invasive cSCC frequency			
Anatomical location, n (%)	Men (n = 769)	Women (n = 702)	P-values
Lip	44 (6)	27 (4)	0·11
Head/neck	566 (74)	372 (53)	< 0·01
Trunk	63 (8)	100 (14)	< 0·01
Arms	71 (9)	87 (12)	0·06
Legs	18 (2)	98 (14)	< 0·01
Other and unknown	7 (1)	18 (3)	0·01
In situ cSCC incidence (95% confidence interval)			
	Men		Women
Time period	Reykjavik–Reykjanes	Outside capital area	Reykjavik–Reykjanes	Outside capital area
1981–1990	1·3 (0·5–2·1)	1·0 (0·3–1·6)	3·2 (2·1–4·3)	1·7 (0·7–2·8)
1991–1999	4·1 (2·8–5·4)	3·6 (2·1–5·1)	5·0 (4·2–5·8)	3·2 (2·1–4·3)
2000–2008	7·5 (5·9–9·0)	6·2 (4·4–8·0)	12·9 (10·9–14·8)	8·8 (6·4–11·2)
2009–2017	13·3 (11·6–15·1)	8·0 (6·1–9·8)	20·5 (18·4–22·7)	15·2 (12·4–18·0)
Invasive cSCC incidence				
1981–1990	3·8 (2·5–5·0)	5·0 (3·2–6·9)	2·7 (1·7–3·7)	1·4 (0·7–2·1)
1991–1999	6·0 (4·5–7·5)	5·9 (4·0–7·7)	3·6 (2·5–4·7)	3·6 (2·1–5·1)
2000–2008	9·3 (7·6–10·9)	9·7 (7·4–12·1)	8·5 (6·1–10·8)	8·4 (6·1–10·8)
2009–2017	14·5 (12·7–16·3)	10·9 (8·7–13·2)	11·5 (9·9–13·0)	9·9 (7·7–12·1)

[a]Calculated using the χ^2-test.

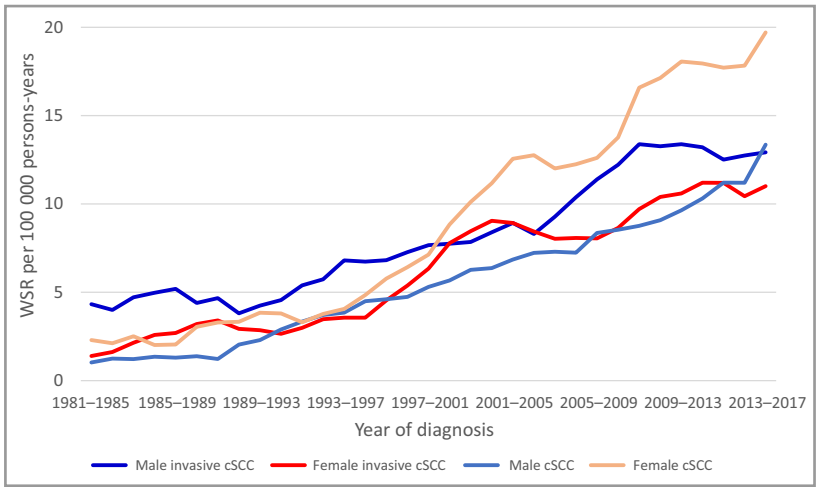

Figure 1 The age-standardized incidence rate using the world global standard population (WSR) per 100 000 person-years of histologically confirmed *in situ* and invasive cutaneous squamous cell carcinoma (cSCC) in Iceland for men and women from 1981 to 2017 (5-year averages).

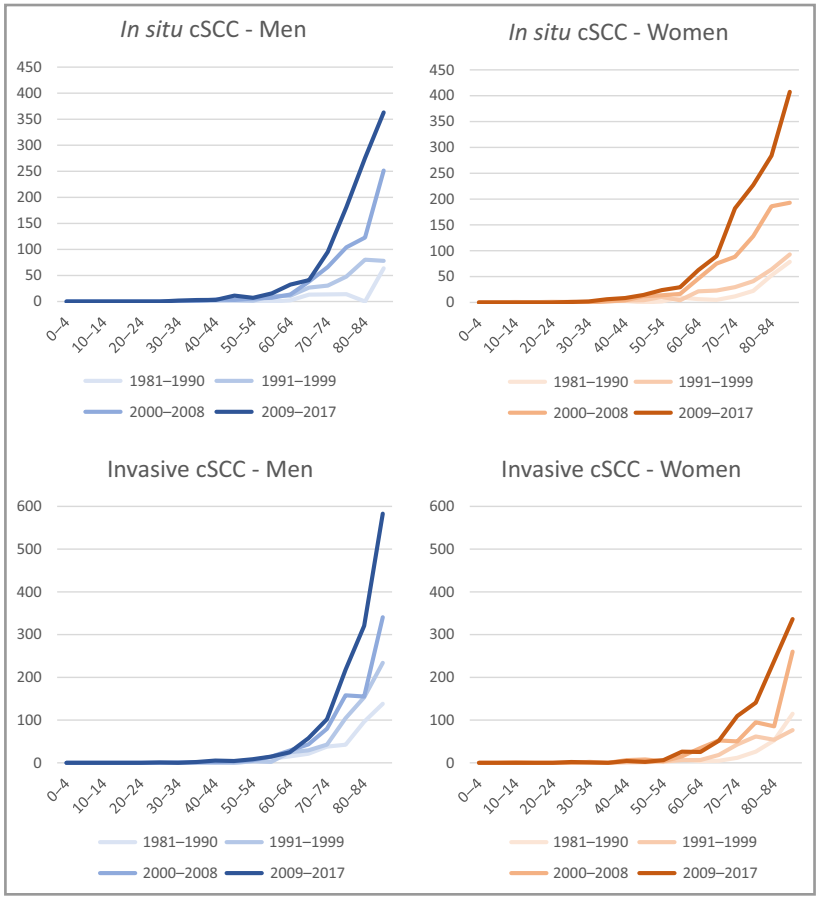

Figure 2 Age-specific incidence rates per 100 000 person-years for men and women for both *in situ* and invasive cutaneous squamous cell carcinoma (cSCC). Age-specific incidence rates are indicated on the y-axes and the x-axes indicate age ranges.

head and neck. The proportion of head/neck lesions increased from 47% to 56% in men and decreased from 57% to 43% in women, mainly because of increased truncal, leg and arm lesions.

Figure 4 summarizes incidence trends for invasive cSCC, which resemble those of *in situ* cSCC. The head and neck was the most commonly affected location in men and women. However, the proportional increase of invasive cSCC on the

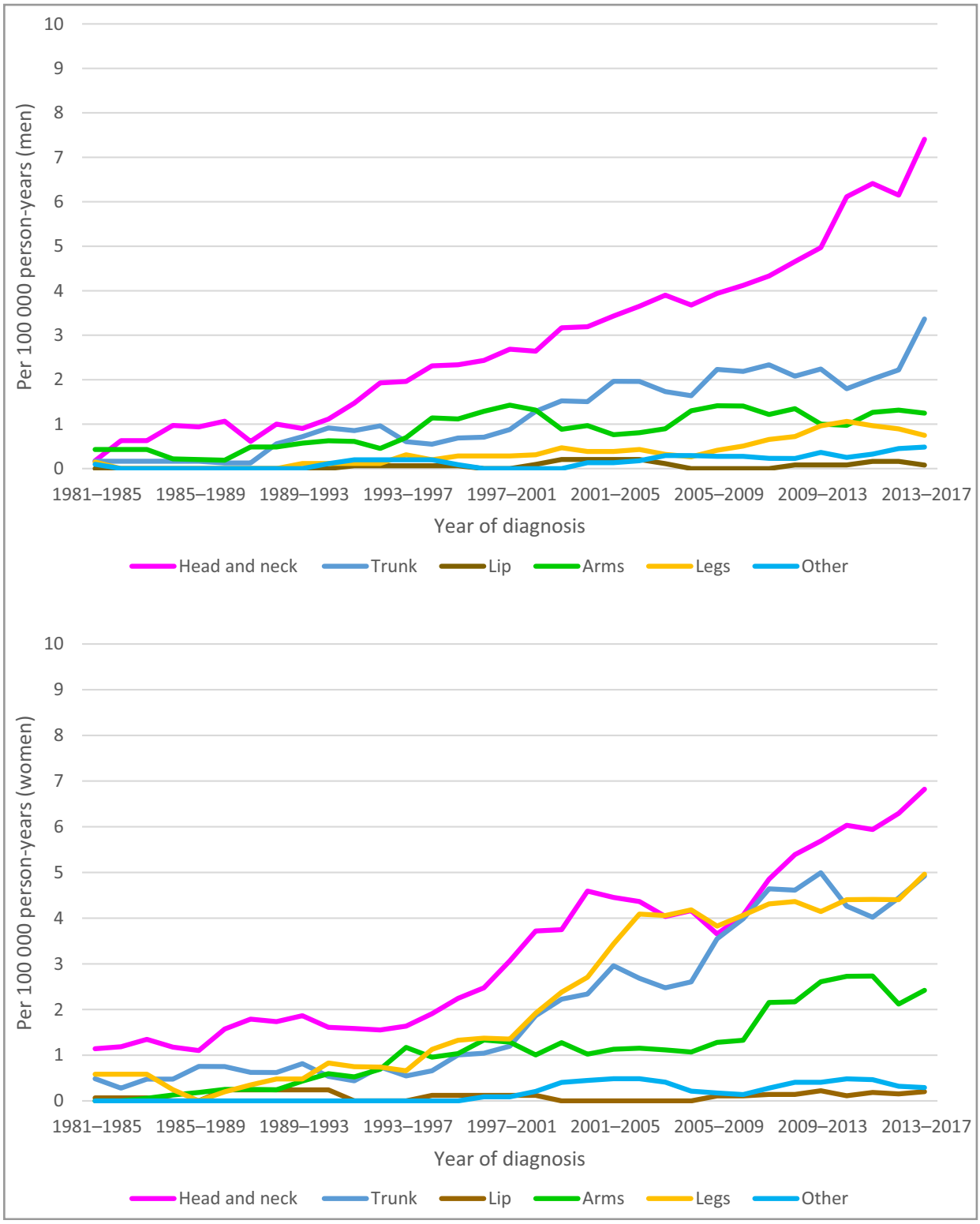

Figure 3 Trends in age-standardized (world) incidence (5-year moving averages) of *in situ* squamous cell carcinoma from 1981 to 2017 according to sex, anatomical location and time period. Trends for men are shown in the upper panel and trends for women are shown in the lower panel.

head and neck in men was much lower than that of *in situ* cSCC. Head and neck lesions accounted for 83% of all lesions in the 1981–1985 period, decreasing to 74% by the end of the study. In contrast, the proportion of *in situ* cSCC occurring on the head and neck in men increased over the same period. In women, the proportion of invasive cSCC occurring on the

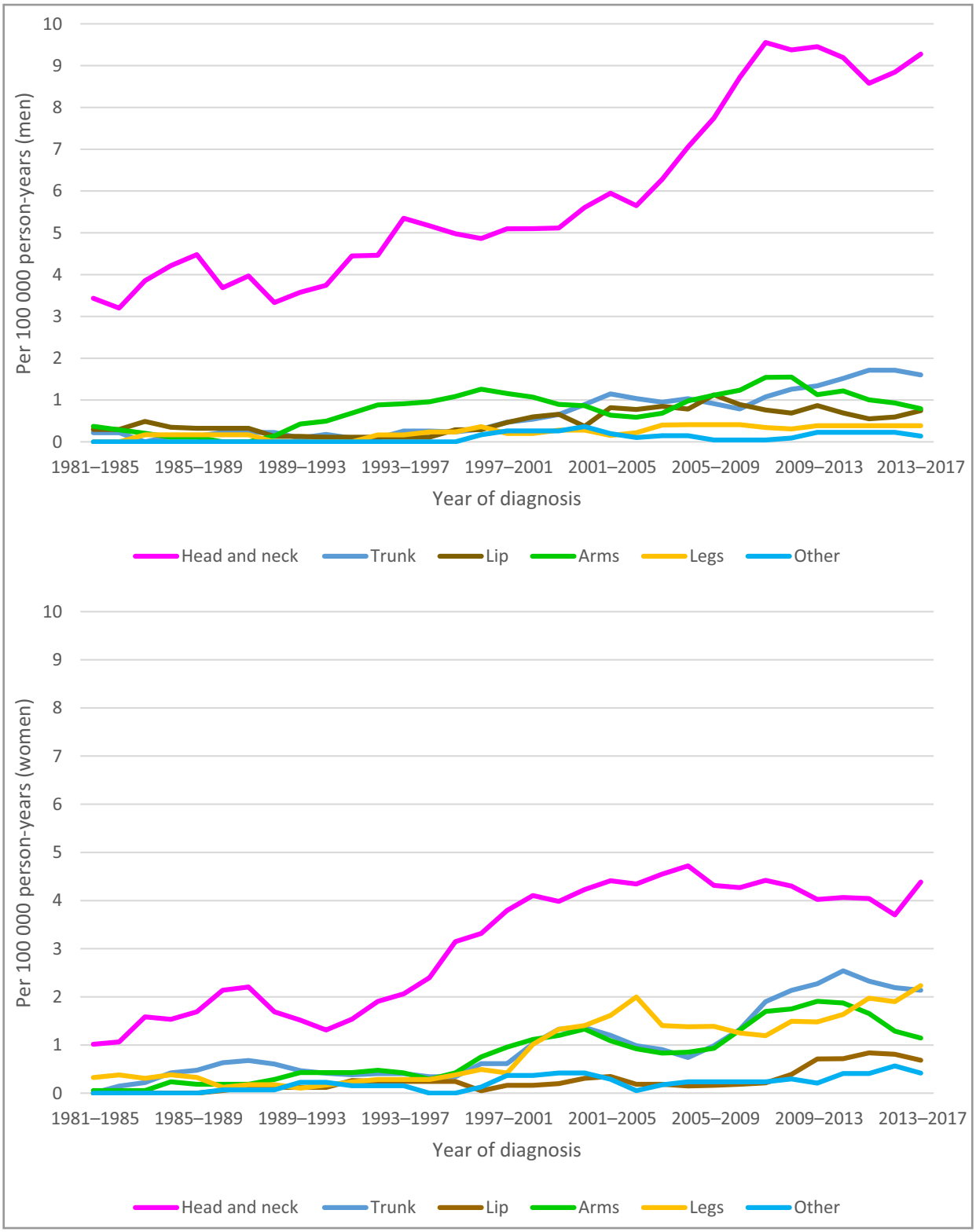

Figure 4 Trends in age-standardized (world) incidence (5-year moving averages) of invasive squamous cell carcinoma from 1981 to 2017 according to sex, anatomical location and time period. Trends for men are shown in the upper panel and trends for women are shown in the lower panel.

head and neck also decreased (from 67% in 1981–1985 to 46% in 2013–2017).

Age-standardized incidence rates stratified by geographical area

The *in situ* cSCC WSR increased steadily in both geographical areas for men and women (Table 1). Although the increase was slightly higher overall in Reykjavik, this difference was generally insignificant. However, by the end of the study period, the *in situ* cSCC WSR was higher in Reykjavik than in rural areas for men and women (Table 1).

Joinpoint analysis

For the study period the AAPC was 7·1% (95% CI 5·9–8·4) for *in situ* cSCC in male patients, 7·0% (95% CI 5·8–8·2) for *in situ* cSCC in female patients, 3·8% (95% CI 3·1–4·6) for invasive cSCC in male patients and 5·2% (95% CI 4·0–6·4) for invasive cSCC in female patients. Throughout the study period, we saw a higher increase in the incidence of *in situ* cSCC compared with invasive cSCC.

Figure 5 summarizes the joinpoint analysis for all sites, and specifically for the head and neck for *in situ* cSCC and invasive cSCC. When examining *in situ* cSCC, joinpoints occurred in 1987 for men and 1995 in women. After the joinpoints, the slope was 0·76 (95% CI 0·60–0·93) for women and 0·41 (95% CI 0·36–0·47) for men, which was a statistically significant difference. For invasive cSCC, a joinpoint occurred in 1994 for women, changing the slope from 0·15 (95% CI 0·03–0·28) to 0·44 (95% CI 0·32–0·55). The slope for men was 0·31 (95% CI 0·26–0·37) throughout the study period. For *in situ* cSCC, joinpoints occurred in 1991 for men and 1994 for women, but the slopes were similar [0·25 (95% CI 0·18–0·31) and 0·29 (95% CI 0·22–0·36), respectively]. For invasive cSCC, no joinpoints occurred, and the slope was steeper for men (0·21, 95% CI 0·17–0·26) than for women (0·15, 95% CI 0·12–0·17).

Figure 6 summarizes joinpoint analysis for the trunk for both *in situ* cSCC and invasive cSCC, and for the legs for *in situ* cSCC only. For *in situ* cSCC, joinpoints occurred in 1994, 2009 and 2012 for men, and in 1997 for women. Notably, the 2009 and 2012 joinpoints for men occurred because of a single year in which the incidence was low. For invasive cSCC, joinpoints occurred in 1998 for men and in 2006 for women. The postjoinpoint slopes were 0·08 (95% CI 0·05–0·11) for men, and 0·26 (95% CI 0·12–0·40) for women, which was a statistically significant difference. The incidence of *in situ* leg lesions was stable throughout the study period for men. However, a joinpoint occurred for women in 1997, after which a steep increase in leg lesions was noted.

Multiplicity

The total number of *in situ* cSCCs during the study period was 2443 lesions in 1534 individuals. The median interval between the first and second *in situ* cSCC was 1·5 years for men and 1·3 years for women. The median interval between the first and second invasive cSCC was 2·3 years for men and 1·6 years for women. Women had on average a significantly greater number of *in situ* lesions than men [1·71 (range 1–20) compared with 1·39 (range 1–15) ($P < 0·01$)]. Overall, 19% of men and 29% of women had at least two lesions ($P < 0·01$). The total number of invasive cSCCs during the study period was 2144 lesions in 1471 individuals. Women and men had a similar number of lesions on average [1·49 (range 1–29) and 1·43 (range 1–13), respectively ($P = 0·45$)]. Overall, 22% of men and 18% of women had at least two lesions ($P = 0·09$). Women had a significantly higher number of *in situ* lesions on average compared with invasive lesions ($P < 0·01$), while men had a similar average number of *in situ* and invasive lesions ($P = 0·24$).

Table 2 presents age-specific incidence rates stratified by age group and sex. Women had higher *in situ* cSCC age-specific rates for single and multiple lesions in all age groups. Invasive cSCC age-specific rates were similar for both sexes for ages < 65 years, whereas for those aged ≥ 65 years, men had significantly higher age-specific rates when it came to developing single or multiple invasive cSCCs.

Cumulative and lifetime risk

The lifetime invasive cSCC risk in the 2009–2017 period was similar for men (1·7%, 95% CI 1·5–1·9) and women (1·6%, 95% CI 1·4–1·8). The *in situ* cSCC lifetime risk for women (2·8%, 95% CI 2·6–3·0) was significantly higher than for men (1·6%, 95% CI 1·4–1·8). The *in situ* cSCC lifetime risk for women has increased 9·3-fold since 1981–1990, when it was 0·3%. The cumulative invasive cSCC risk was 0·3% for both men and women aged < 65 years. The cumulative *in situ* cSCC risk was 0·7% for women aged < 65 years and was 0·4% for men aged < 65 years, which was an increase from 0·1% for women and 0·0% for men and during the 1981–1990 time period.

Discussion

This is the first whole-population study to report the multiplicity for *in situ* cSCC. A recent study from the Netherlands examined nationwide incidence trends of invasive cSCC and found that age-standardized incidence rates of a first cSCC increased threefold for men and fivefold for women.[13] In our study, the rates of invasive cSCC increased threefold for men but 44-fold for women. This large increase of WSR in women is mostly due to a low WSR of 0·3 at the beginning of the study period. Thus, cSCC went from being a relatively rare disease in women in Iceland to being one of the most common cancers. In addition, similar to the Netherlands study, the multiplicity seen in our cohort suggests that cSCC burden worldwide is likely to be largely underestimated, not only for invasive cSCC, but also for *in situ* disease.[13]

The principal weaknesses of this study are its retrospective nature and the resulting inability to analyse specific

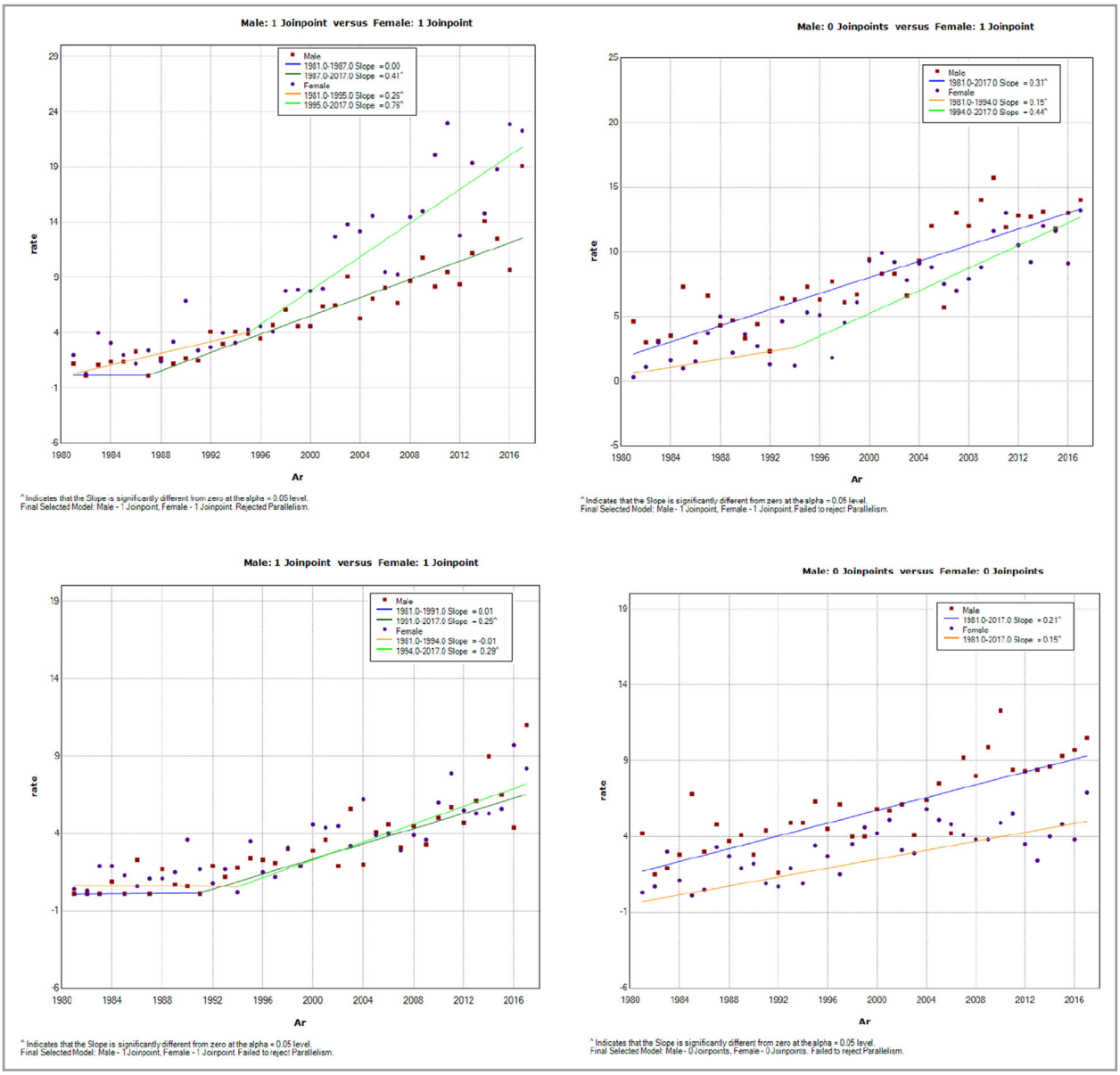

Figure 5 Joinpoint analysis for men and women. All anatomical sites for *in situ* cutaneous squamous cell carcinoma (cSCC) (upper left) and invasive cSCC (upper right). Head and neck cancer incidence for *in situ* cSCC (lower left) and invasive cSCC (lower right), using age-standardized rates (world) per 100 000 person-years.

characteristics of individuals developing *in situ* and invasive cSCCs. In addition, by using pathologically confirmed cases we probably underestimated the true incidence of BCC and *in situ* cSCC, which are sometimes treated by clinicians without doing a biopsy.

The most critical findings of this study include the following: (i) there was a sharp rise in cSCC in a country with low natural UV,[14] (ii) this rise was particularly prominent in women, who were more likely to develop *in situ* cSCC, whereas men were more likely to develop invasive cSCC, (iii) most invasive and *in situ* lesions occurring in men were located on the head and neck, whereas lesions occurring in women were more generalized (including lesions occurring on the arms and legs), signifying possible important behavioural differences between sexes, (iv) lip lesions were more likely to be invasive than *in situ* for both men and women, (v) women with *in situ* cSCC were significantly more likely to have multiple *in situ* tumours than men and (vi) the total tumour burden is probably substantially underestimated for both invasive and *in situ* cSCC worldwide.

A lower average age of diagnosis for *in situ* cSCC, compared with invasive cSCC, was noted in this dataset for men and women. Although it may be difficult to prove, the difference of 1·9 years in men and 2·7 years in women could suggest that, on average, the interval between *in situ* cSCC formation and the development of invasive disease could be 2–3 years. *In situ* cSCC incidence was higher than that of invasive cSCC

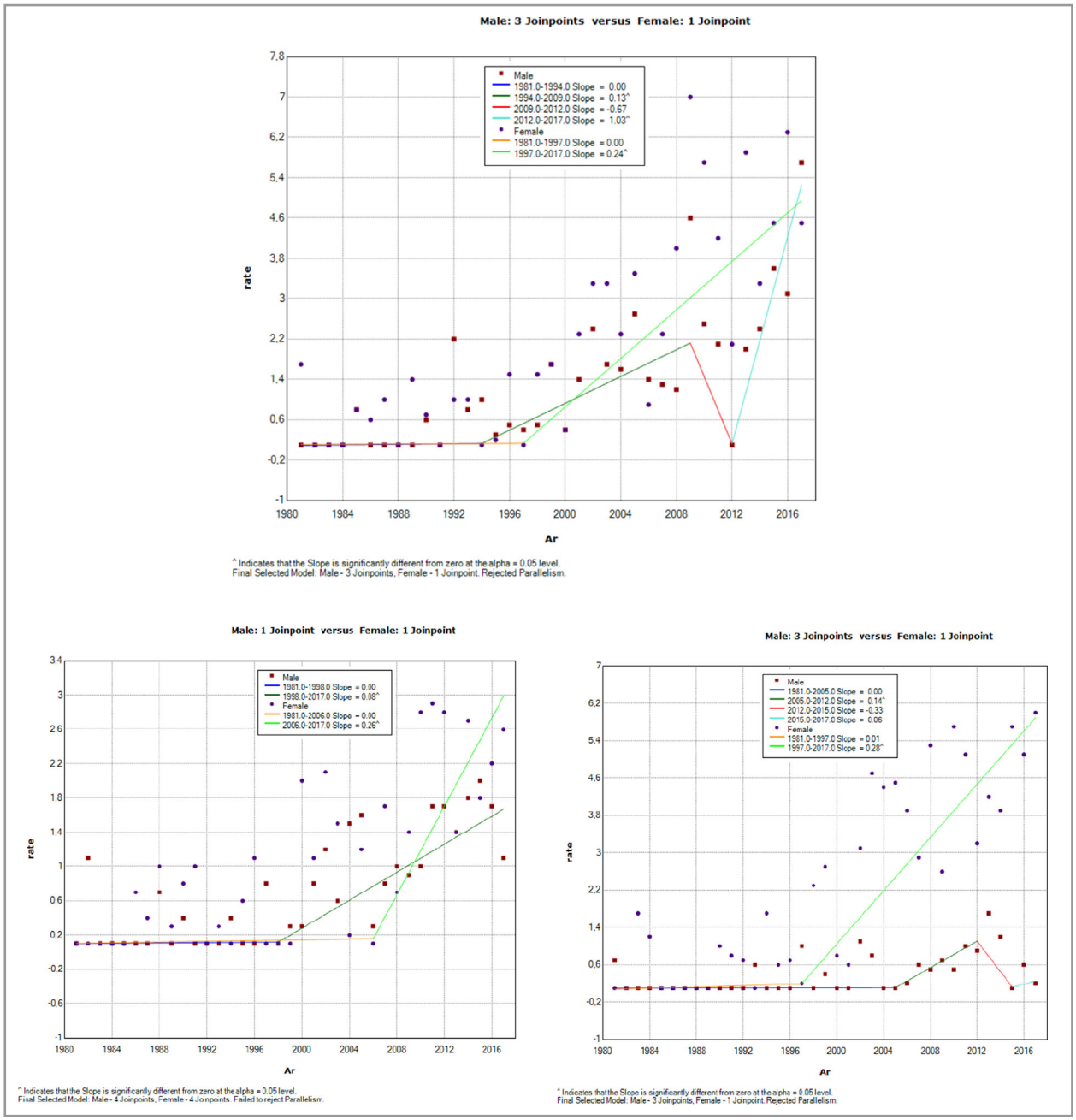

Figure 6 Joinpoint analysis in men and women. Truncal *in situ* cutaneous squamous cell carcinoma (cSCC) (upper panel), truncal invasive cSCC (bottom left) and *in situ* lesions of the legs (bottom right) using age-standardized rates (world) per 100 000 person-years.

for almost all anatomical locations in the 2013–2017 time period, with the two following exceptions: invasive lip SCC in both sexes and invasive head and neck cSCC in men. Assuming that *in situ* and invasive lesions exist on a histological spectrum, these findings suggest either a significant delay in diagnosing lip cSCC, or that the invasive growth phase of lip cSCC occurs more rapidly than that of other cSCCs. The findings regarding invasive head and neck lesions may be explained by the fact that men may simply seek medical care later than women, delaying diagnosis, or be more prone to developing aggressive cSCCs than women.[15,16] Women may also have a lower incidence of cSCC of the scalp owing to greater hair coverage, which could confer protection. It is unclear why *in situ* cSCC WSR in Reykjavik was higher compared with rural areas, but it could be a result of higher rates of travel and tanning bed use among those living in Reykjavik, in addition to having higher levels of access to dermatological treatment.

The most striking epidemiological trend noted was that the increase in incidence of *in situ* and invasive cSCC was more rapid for women than for men. Joinpoint analysis supported this finding, showing the steepest slope of 0·76 for *in situ* cSCC

Table 2 Single and multiple *in situ* and invasive cutaneous squamous cell carcinoma (cSCC) age-specific incidence rates per 100 000 person-years during the study period (1981–2017), stratified by sex and age. Age-standardized (world) incidence rate is reported for each sex in each category

	All *in situ* cSCCs		Single cSCC (*in situ*)		Multiple *in situ* cSCCs	
	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)
Men						
Age, years						
< 40	7	0·1 (0·0–0·3)	6	0·1 (0·0–0·2)	1	0·0 (0·0–0·1)
40–64	100	6·9 (5·6–8·3)	77	5·4 (4·2–6·6)	23	1·6 (0·9–2·2)
≥ 65	453	69·5 (62·8–76·2)	373	56·9 (50·9–62·9)	80	12·6 (9·7–15·5)
Incidence	560	6·7 (6·1–7·3)	456	5·4 (4·9–5·9)	104	1·3 (1·0–1·6)
Women						
Age, years						
< 40	21	0·5 (0·3–0·8)	18	0·5 (0·2–0·7)	3	0·1 (0·0–0·2)
40–64	214	15·0 (13·0–17·1)	155	10·8 (9·1–12·5)	59	4·2 (3·1–5·3)
≥ 65	739	91·0 (83·8–98·2)	519	62·3 (56·4–68·1)	220	28·7 (24·6–32·9)
Incidence	974	10·5 (9·8–11·2)	692	7·4 (6·8–8·0)	282	3·1 (2·7–3·5)
	All invasive cSCCs		Single invasive cSCCs		Multiple invasive cSCCs	
	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)
Men						
Age, years						
< 40	6	0·1 (0·0–0·3)	5	0·1 (0·0–0·2)	1	0·0 (0·0–0·1)
40–64	114	7·9 (6·4–9·3)	91	6·3 (5·0–7·6)	23	1·6 (0·9–2·2)
≥ 65	649	98·0 (90·2–105·8)	507	76·8 (69·9–83·8)	142	21·2 (17·6–24·8)
Incidence	769	8·9 (8·3–9·6)	603	7·0 (6·4–7·6)	166	1·9 (1·6–2·2)
Women						
< 40	7	0·2 (0·0–0·3)	6	0·2 (0·0–0·3)	1	0·0 (0·0–0·1)
40–64	118	8·2 (6·7–9·6)	91	6·3 (5·0–7·6)	27	1·9 (1·2–2·6)
≥ 65	577	67·6 (61·6–73·7)	1604	56·0 (50·5–61·5)	99	11·6 (9·1–14·1)
Incidence	702	6·9 (6·3–7·5)	575	5·6 (5·1–6·1)	127	1·3 (1·0–1·6)

CI, confidence interval.

in female patients after 1995, suggesting behavioural changes in the 1980s or early 1990s, which was a similar trend to that seen in BCC incidence in Iceland,[7] with a sharper rise for women than for men.

Men usually have much higher nonmelanoma skin cancer incidence rates compared with women, especially in areas with high ambient UV, where age-standardized rates are up to twice as high for men as for women.[17,18] Therefore, the comparable age-standardized rates of invasive cSCC seen in this dataset are unusual.

Although the head and neck region seems to be the most cSCC-prone region for men, a more generalized distribution was reported for women, which was similar to that observed in our BCC study where a more generalized distribution was reported for female patients.[7] Interestingly, *in situ* cSCCs seem to be sharply rising in women, while invasive cSCC does not appear to be following suit. If *in situ* cSCCs are merely precursor lesions, a similar trend would be expected, with invasive lesions appearing a few years after a sharp increase in *in situ* lesions; however, this did not occur in our cohort.

In Figure 2, we can see how the age at diagnosis of first cSCC seems to be decreasing for women. This could signify that increased high-risk UV exposure is more likely to occur in younger women compared with younger men.

We considered the most likely explanations for the increasing incidence and sex differences reported in our findings. These possible explanations include the following: (i) increased tanning bed use among women,[7,19] leading to lesions in nonsun-exposed areas; (ii) significant work-related outdoor UV exposure, which is more common in men, who tend to be less diligent with sunscreen,[20] and therefore develop more head and neck lesions; (iii) increased travel to sunny climates for both men and women,[21] which further increases the risk of keratinocyte carcinoma, (iv) increased surveillance, particularly in women and younger individuals, which may lead to higher detection rates of *in situ* lesions that may have otherwise remained undiagnosed and (v) men aged > 65 years may be less likely to see a dermatologist, leading to higher incidence rates of more serious invasive disease. This was the case for melanoma in Iceland, where men aged > 50 years more often presented with deeper lesions compared with women or younger men.[22]

Iceland has low natural background UV, and its residents usually cover their skin for most of the year, with exposure mainly affecting the head and neck.[14] Tanning bed usage surged in the 1980s and 1990s, with women and teenage girls more likely to have used tanning beds.[21,23] This time course correlates with most of the joinpoints observed in this

study, in addition to the increase in leg lesions occurring in women. Travel abroad has increased among Icelanders, but sex-specific travel data that could explain the differences observed between men and women is not available.[21] Iceland's low-UV environment might be relatively protective for men, who more often work outdoors,[24] whereas women are more likely to engage in high-risk UV behaviours, such as using tanning booths and wearing lighter clothing, which might partially explain why the invasive cSCC WSR for men and women is similar.[25] While the use of tanning beds could explain the increased incidence of *in situ* and invasive cSCC lesions in women, this does not explain why invasive cSCCs in men are almost exclusively on the head and neck. It could be that travel abroad and detection bias from increased skin cancer screening play a larger role in the observed risk of developing skin cancer for women, whereas chronic outdoor exposure is more relevant for men.

With Iceland's ageing population, cSCC has become a significant public health issue. Initiating population-based educational efforts to prevent high-risk behaviours is essential to bring about a decrease in skin cancer rates and to effect significant and long-lasting change in a population whose risk level was hitherto unrecognized.

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Paper III

Adalsteinsson, J.A., Muzumdar S., Waldman, R., Hu, C., Wu, R., Ratner, D., Ungar, J., Silverberg, J.I., Olafsdottir, G., Kristjansson, A.K., Tryggvadottir, L., Jonasson J.G. Association between Hydrochlorothiazide and the Risk of In-Situ and Invasive Squamous Cell Skin Carcinoma and Basal Cell Carcinoma: A Population-Based Case-Control Study. Journal of the American Association of Dermatology. March 2021. DOI: 10.1016/j.jaad.2020.08.025.

Association between hydrochlorothiazide and the risk of in situ and invasive squamous cell skin carcinoma and basal cell carcinoma: A population-based case-control study

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Background: Population-based studies analyzing hydrochlorothiazide's (HCTZ's) effect on keratinocyte carcinoma, and particularly invasive squamous cell carcinoma (SCC), are lacking.

Objectives: To characterize the association between HCTZ use and invasive SCC, SCC in situ (SCCis), and basal cell carcinoma (BCC).

Methods: This population-based case-control study included all 6880 patients diagnosed with first-time BCC, SCCis, and invasive SCC between 2003 and 2017 in Iceland and 69,620 population controls. Conditional logistic regression analyses were used to calculate multivariate odds ratios (ORs) for keratinocyte carcinoma associated with HCTZ use.

Results: A cumulative HCTZ dose above 37,500 mg was associated with increased risk of invasive SCC (OR, 1.69; 95% confidence interval [CI], 1.04-2.74). Users of HCTZ also had an increased risk of SCCis (OR, 1.24; 95% CI, 1.01-1.52) and BCC (OR, 1.14; 95% CI, 1.02-1.29).

Limitations: Limitations include this study's retrospective nature with the resulting inability to adjust for ultraviolet exposure, Fitzpatrick skin type, and comorbidities.

Conclusions: High cumulative exposure to HCTZ is associated with the development of keratinocyte carcinoma and, most importantly, invasive SCC. Sun protective behaviors alone may not eliminate the carcinogenic potential of HCTZ. (J Am Acad Dermatol 2021;84:669-75.)

Key words: basal cell carcinoma; epidemiology; hydrochlorothiazide; keratinocyte carcinoma; squamous cell carcinoma.

There is increasing evidence suggesting an association between hydrochlorothiazide (HCTZ) exposure and the development of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).[1,2] Whether HCTZ has a causal effect on the development of keratinocyte carcinoma

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is of great interest because HCTZ is one of the most commonly prescribed antihypertensives in Europe and North America.[2,3] HCTZ is a known photosensitizer and is thought to contribute to the development of keratinocyte carcinoma by causing the production of free radicals and reactive oxygen species upon exposure to ultraviolet (UV) radiation.[2] The effect of HCTZ in low-UV environments is unknown, and the identification of strong epidemiologic data supporting a causal association between HCTZ use and keratinocyte carcinoma development would help guide initial antihypertensive management in patients at high risk of developing keratinocyte carcinoma.

To date, 3 population-based case-control studies and several smaller case-control and cohort studies have evaluated the association between HCTZ and keratinocyte carcinoma.[1,4-12] However, the results from these studies were conflicting. As a result, no clear clinical recommendations have been developed based on their findings.[13] Previous studies were limited by small sample size, inconsistent definitions of exposure (HCTZ alone, HCTZ in combination with other medications, or all thiazide diuretics), and different outcome measures (SCC, BCC, or keratinocyte carcinoma).

We present a population-based study analyzing the association between keratinocyte carcinoma and HCTZ in Iceland. This study covering the entire Icelandic population is a unique addition to previous studies because (1) Iceland's population is homogenous[14,15]; (2) Reykjavik, Iceland's capital, is the northernmost capital in the world, with very low levels of daily ambient UV radiation[16]; (3) Iceland is a small country with minimal variation in daily ambient UV exposure[17]; and (4) the Icelandic Cancer Registry (ICR) separately classifies squamous cell carcinoma in situ (SCCis) from invasive SCC, allowing this study to be the first to assess HCTZ's relationship with each of these prognostically distinct entities[18]; (5) The Icelandic Prescription Medicine Register is a population-based registry that records all outpatient prescriptions and can be directly linked to the ICR.[19]

CAPSULE SUMMARY

- High cumulative hydrochlorothiazide (HCTZ) exposure is associated with an increased risk of keratinocyte carcinoma and, particularly, invasive squamous cell carcinoma.
- Patients on long-term HCTZ treatment should be counseled about the risk of developing keratinocyte carcinoma. Because average sun protection alone may not eliminate HCTZ's carcinogenic potential, practitioners may consider switching patients to other first-line antihypertensives.

METHODS

This is a population-based case-control study. The group of cases consisted of all individuals diagnosed for the first time with SCCis, invasive SCC, and BCC of the skin with histologic confirmation in Iceland between 2003 and 2017. For each case, 10 unaffected population control individuals, matched by year of birth and sex, were randomly selected from the National Register of Iceland.

Two nationwide databases were used to extract data about keratinocyte carcinoma diagnosis and prescription drug use in Iceland. The ICR records all cases of skin cancer diagnosed with histologic verification.[18] The Icelandic Prescription Medicine Register is run by the Directorate of Health and records all electronic outpatient prescriptions since 2002.[19] Demographic data, including Charleston Comorbidity Index, ethnicity, smoking status, and socioeconomic status, were not available for analysis. By record linkage using the unique personal identification number, all HCTZ prescriptions for case patients and control individuals were identified from the Icelandic Prescription Medicine Register.

The index date was defined as the date of keratinocyte carcinoma diagnosis. Patients were considered exposed to HCTZ if they had filled 1 or more HCTZ prescriptions at least 2 years before the index date. Prescriptions of HCTZ filled less than 2 years before the index date were disregarded to account for possible lag time of HCTZ affecting the risk of developing keratinocyte carcinoma. We chose to implement a 2-year lag time because it has been shown in other similar studies that increased lag time is associated with increasing SCC risk.[4] Prescriptions filled less than 2 years before diagnosis were unlikely to have affected the risk of keratinocyte carcinoma because photosensitization is a chronic process that takes multiple years.[20] For all patients, cumulative exposure to HCTZ was recorded in daily dose units (DDU) and milligrams. A DDU is the average daily maintenance dose of a drug when used for its primary indication.[21] Patients taking azathioprine, mycophenolate mofetil, and cyclosporine were subsequently excluded as these immunosuppressive medications dramatically increase the risk of keratinocyte carcinoma.[20]

Conditional logistic regression analyses were performed to determine multivariate odds ratios (ORs) with 95% confidence intervals (CI) for the

Abbreviations used:

BCC:	basal cell carcinoma
CI:	confidence interval
DDU:	daily dose unit
HCTZ:	hydrochlorothiazide
ICR:	Icelandic Cancer Registry
OR:	odds ratio
SCC:	squamous cell carcinoma
SCCis:	squamous cell carcinoma in-situ
UV:	ultraviolet

association between HCTZ use and the likelihood of BCC, invasive SCC, and SCCis. ORs were adjusted for the use of tetracyclines and topical and oral retinoids because these are photosensitizing medications that independently increase the risk of keratinocyte carcinoma.[20] Invasive SCC, SCCis, and BCC were evaluated separately in all analyses, with never users of HCTZ serving as the control for all cases. Trend analysis was used to assess for a dose-response relationship for each tumor subtype. *P* values of the tests were calculated by using weighted linear regression, which regressed ORs based on the median dosage for each HCTZ dose category (1-500, 501-1500, and >1500 DDU). The inverse variance of the log-effect size was used as weight.[22] A *P* value of less than .05 was considered statistically significant. The study protocol was approved by the Icelandic National Bioethics Committee (VSNb2018030013).

RESULTS

Altogether, 1013 patients with invasive SCC, 1167 with SCCis, and 4700 with BCC were identified and were age- and sex-matched with 10,367; 11,961; and 47,292 control individuals, respectively. Patient characteristics are described in Table I. Male patients constituted 42%, 36%, and 51% of patients with BCC, SCCis, and invasive SCC, respectively.

The relationship between HCTZ exposure and keratinocyte carcinoma risk is reported in Table II and Fig 1. Of individuals with invasive SCC, 8.9% were users of HCTZ as compared to 8.6% of control individuals. At low and moderate doses of HCTZ, there was no difference in invasive SCC risk between HCTZ users and control individuals. Cumulative HCTZ doses greater than 1500 DDU (37,500 mg) were associated with an increased risk of invasive SCC (OR, 1.69; 95% CI, 1.04-2.74).

Similarly, 10.0% of individuals diagnosed with SCCis were users of HCTZ as compared to 8.2% of control individuals. Users of HCTZ showed a significant increase in SCCis risk as compared to control individuals (OR, 1.24; 95% CI, 1.01-1.52).

Additionally, 7.4% of individuals diagnosed with BCC were users of HCTZ compared to 6.5% of control individuals. HCTZ use was associated with an increased risk of developing BCC (OR, 1.14; 95% CI, 1.02-1.29). The dose-response relationship was statistically significant for BCC ($P = .02$) but not for SCCis ($P = .64$) or for invasive SCC ($P = .1$) (Fig 1).

Subgroup analysis was performed (Table III). HCTZ use was associated with a significant increase in risk of SCCis in male patients and people aged 50 years and older (OR, 1.45; 95% CI, 1.03-2.04 and OR, 1.23; 95% CI, 1.00-1.52, respectively). Similarly, HCTZ use was associated with a significant increase in BCC risk in people aged 50 years and older (OR, 1.15; 95% CI, 1.02-1.30).

DISCUSSION

This population-based Icelandic study, which includes more than 1000 patients with invasive SCC, 1100 patients with SCCis, and 4700 patients with BCC, supports an association between HCTZ use and all 3 types of keratinocyte carcinoma studied herein. This study is well suited to show an association between HCTZ use and keratinocyte carcinoma because of Iceland's unique demographics, low average daily ambient UV exposure, and stringent recording of keratinocyte carcinoma cases.

The Icelandic population is exceptionally homogenous with minimal variance in Fitzpatrick skin type among Icelanders.[15] Close to 100% of Icelanders are white.[14] In contrast, Denmark, where a similar population-based cohort study was performed, is more genetically heterogeneous.[15] Because Fitzpatrick skin type is a major determinant of skin cancer risk at the population level, Iceland's homogeneity strongly contributes to the study's internal validity. Although South Korea, where a population-based cohort study was also performed, is also ethnically homogenous, the incidence of keratinocyte carcinoma in South Koreans is approximately 24 to 40 times lower than the incidence of keratinocyte carcinoma in Iceland, due in large part to ethnic differences between the populations.[12]

Additionally, our data suggest that relatively low levels of average daily UV exposure are sufficient to observe an association between HCTZ exposure and keratinocyte carcinoma development. As mentioned previously, Reykjavik, Iceland's capital, is the northernmost capital in the world.[16] The average daily UV exposure in Iceland is 957 J/m^2, which is roughly half of Denmark's exposure (1691 J/m^2), and one third that of South Korea and the United States (2535 J/m^2

Table I. Characteristics of patients with BCC, SCCis, and invasive SCC and age- and sex-matched control individuals

	BCC		SCCis		Invasive SCC	
Characteristics	Case patients (n = 4700)	Control individuals (n = 47,292)	Case patients (n = 1167)	Control individuals (n = 11,961)	Case patients (n = 1013)	Control individuals (n = 10,376)
Age, y, median (IQR)	69 (56-79)	69 (56-79)	77 (67-84)	77 (67-84)	79 (71-85)	79 (70-85)
Male sex, n (%)	1988 (42.3)	20,022 (42.3)	425 (36.4)	4368 (36.5)	521 (51.4)	5309 (51.2)
Use of HCTZ, n (%)						
Never use	4354 (92.6)	44,226 (93.5)	1051 (90.1)	10982 (91.8)	923 (91.1)	9473 (91.4)
Ever use	346 (7.4)	3066 (6.5)	116 (10.0)	979 (8.2)	90 (8.9)	894 (8.6)

BCC, Basal cell carcinoma; *HCTZ*, hydrochlorothiazide; *IQR*, interquartile range; *SCC*, squamous cell carcinoma; *SCCis*, in situ squamous cell carcinoma.

Table II. Association between HCTZ use and risk of BCC, SCCis, and invasive SCC

Subgroup	Case patients	Control individuals	OR (95% CI)	Adjusted OR (95% CI)*
BCC				
Never use, n	4354	44,226	1.00	1.00
Ever use	346	3066	1.15 (1.02-1.30)	1.14 (1.02-1.29)
Cumulative dosage, n				
1-500 DDU (25-12,500 mg)	210	1981	1.08 (0.93-1.25)	1.07 (0.93-1.24)
501-1500 DDU (12,525-37,500 mg)	87	734	1.22 (0.97-1.53)	1.21 (0.97-1.52)
>1500 DDU (>37,500 mg)	49	351	1.43 (1.06-1.94)	1.42 (1.05-1.92)
BCC continuous trend test	*P* = .02			
SCCis				
Never use, n	1051	10,982	1.00	1.00
Ever use, n	116	979	1.24 (1.01-1.53)	1.24 (1.01-1.52)
Cumulative dosage, n				
1-500 DDU (25-12,500 mg)	68	639	1.12 (0.86-1.45)	1.11 (0.86-1.45)
501-1500 DDU (12,525-37,500 mg)	32	215	1.55 (1.06-2.26)	1.55 (1.06-2.26)
>1500 DDU (>37,500 mg)	16	125	1.34 (0.79-2.28)	1.35 (0.79-2.29)
SCCis continuous trend test	*P* = .64			
Invasive SCC				
Never use, n	923	9473	1.00	1.00
Ever use, n	90	894	1.03 (0.82-1.30)	1.02 (0.81-1.29)
Cumulative dosage, n				
1-500 DDU (25-12,500 mg)	49	568	0.88 (0.65-1.20)	0.87 (0.64-1.18)
501-1500 DDU (12,525-37,500 mg)	21	205	1.05 (0.67-1.66)	1.05 (0.66-1.66)
>1500 DDU (>37,500 mg)	20	121	1.67 (1.03-2.71)	1.69 (1.04-2.74)
Invasive SCC continuous trend test	*P* = .1			

BCC, Basal cell carcinoma; *CI*, confidence interval; *DDU*, daily dose unit; *HCTZ*, hydrochlorothiazide; *OR*, odds ratio; *SCC*, squamous cell carcinoma; *SCCis*, in situ squamous cell carcinoma.
*Model adjusted for the use of the following photosensitizing medications: tetracyclines, oral retinoids, and topical retinoids.

and 2736 J/m^2).[23] Furthermore, because of Iceland's small size of 39,769 square miles and approximately 3° range of latitude from its northernmost to southernmost tips, average daily ambient UV exposure is relatively consistent throughout the country.[24] Tanning bed use is commonplace in Iceland, with 70% of women and 35% of men having used a tanning bed.[16] Foreign travel is also common and has been increasing in recent years.[16] It is likely that these 2 factors play an important part in the UV exposure of this population.

SCCis and invasive SCC

To our knowledge, this study is the first to analyze the association between HCTZ and the risk of invasive SCC and SCCis separately. This is important because invasive SCC has a more aggressive disease course compared to SCCis. Our study was able to distinguish between these entities because the ICR records these histopathologic diagnoses separately.[18] We identified independent associations between invasive SCC and SCCis with HCTZ use. Only patients with the highest exposures

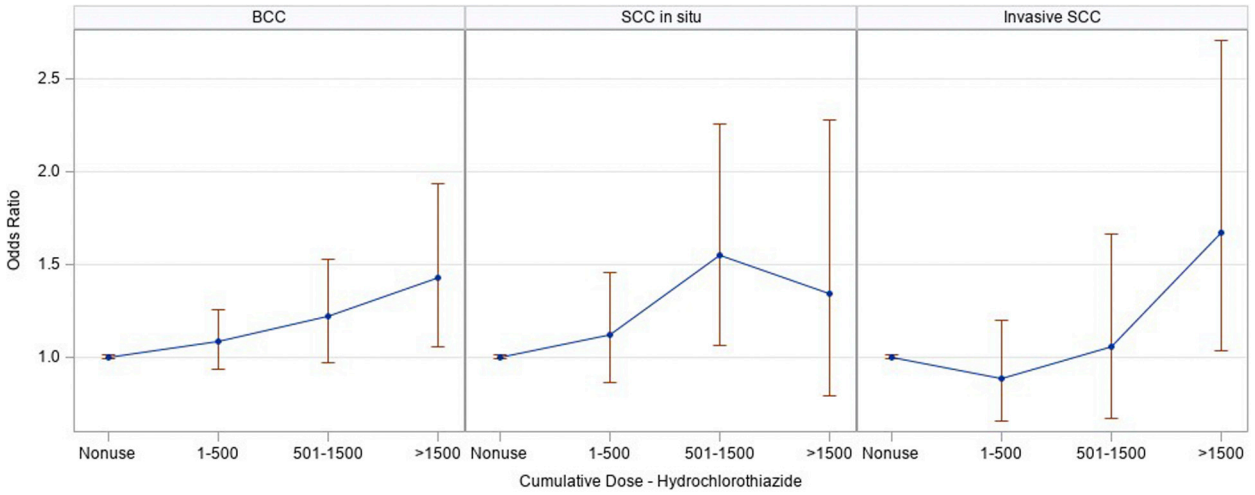

Fig 1. Dose-response relationships between cumulative HCTZ dosage and risk of BCC, SCCis, and invasive SCC. A continuous trend test resulted in *P* values of .02, .64, and .1, respectively.

Table III. Associations of HCTZ use and keratinocyte carcinoma by subgroup

Subgroup	Case patients, n (exposed/unexposed)	Control individuals, n (exposed/unexposed)	OR (95% CI)	Adjusted OR (95% CI)
BCC				
Male	136/1852	1226/18,796	1.13 (0.94-1.37)	1.12 (0.93-1.36)
Female	210/2502	1840/25,430	1.16 (1.00-1.36)	1.16 (0.99-1.35)
<50 y	7/740	73/7445	0.97 (0.44-2.12)	0.72 (0.61-0.86)
≥50 y	339/3614	2993/36,781	1.16 (1.03-1.30)	1.15 (1.02-1.30)
SCCis				
Male	44/381	328/4040	1.45 (1.04-2.04)	1.45 (1.03-2.04)
Female	72/670	651/6942	1.14 (0.88-1.48)	1.13 (0.87-1.47)
<50 y	1/63	4/671	2.65 (0.27-26.29)	2.21 (0.21-22.94)
≥50 y	115/988	975/10,311	1.24 (1.00-1.52)	1.23 (1.00-1.52)
Invasive SCC				
Male	39/482	389/4920	1.01 (0.71-1.43)	1.01 (0.71-1.43)
Female	51/441	505/4553	1.05 (0.77-1.43)	1.03 (0.75-1.41)
<50 y	0/35	0/380	—	—
≥50 y	90/888	894/9093	1.03 (0.82-1.30)	1.021 (0.810-1.29)

BCC, Basal cell carcinoma; *CI*, confidence interval; *HCTZ*, hydrochlorothiazide; *OR*, odds ratio; *SCC*, squamous cell carcinoma; *SCCis*, in situ squamous cell carcinoma.

to HCTZ (cumulative dose of >1500 DDU or 37,500 mg) showed a statistically significant association with invasive SCC, and a significant dose-response relationship was not detected. When stratified into subgroups by age and sex, HCTZ use was not significantly associated with invasive SCC, likely because the study was not sufficiently powered to detect these associations.

Interestingly, although the overall association between SCCis and HCTZ use was stronger than the association between invasive SCC and HCTZ, there was no association seen between the highest cumulative dosages of HCTZ (cumulative dose of >1500 DDU or >37,500 mg) and SCCis; however, both ever use and use of 500t o 1500 DDU of HCTZ were associated with SCCis development. It is possible that the study was not powered to identify associations of SCCis with different doses of HCTZ or that the observed relationship between ever use of HCTZ and SCCis was, in fact, spurious. When stratified by age and sex, HCTZ use was significantly associated with SCCis in male patients and individuals aged 50 years and older.

Previous studies evaluating the association of SCC with HCTZ use did not distinguish between cases of invasive SCC and SCCis, as noted earlier. The majority of these studies found a significantly increased risk of SCC with HCTZ use.[2] The 2 population-based studies found a significant dose-dependent increase in the risk

of cutaneous SCC and SCC of the lip in the Danish population.[1,4]

BCC

An association between BCC development and HCTZ use has been less consistently shown in previous research than the relationship between SCC and HCTZ,[2] possibly because BCCs have been shown to have longer promoter periods than SCC.[25] As a result of this longer promoter period, previous case-control studies evaluating the relationship of keratinocyte carcinoma with other exposures (eg, sunscreen) have frequently had more difficulty demonstrating an association with BCC than with SCC.

We found a significantly increased risk of BCC with HCTZ use with a clear dose-response relationship. The association was shown for ever users of HCTZ. When further stratified by cumulative dose, statistical significance was observed only at cumulative doses above 1500 DDU. These results may be explained by the fact that significantly longer periods of HCTZ use are required to observe an increased risk of BCC, as has been documented with other known causal exposures, or may suggest that this study was not powered to evaluate these smaller subgroups. Similarly, when divided into subgroups by age and sex, only people aged 50 years and older had a significant increase in BCC risk with HCTZ use.

Only 1 other population-based study, of the Danish population, evaluated the risk of BCC with HCTZ use.[1] The investigators identified a dose-dependent increase in BCC risk with use of HCTZ. Similarly, a cohort study from the United States showed a significant association between thiazides and increased BCC risk.[5] Two case-control studies from Denmark, a case-control multicenter study from Europe, and a cohort study from the Netherlands trended toward an association between BCC and thiazide use but did not reach statistical significance.[6,8,10,11] Of note, a recent meta-analysis that included all of the aforementioned studies found a marginal association between BCC development and HCTZ exposure.[2]

Strengths and limitations

An important strength of the study is the population-based design using record linkage of high-quality nationwide health registries. This design eliminates the drawbacks typical for most case-control studies, that is, a nonrepresentative control group and information bias. In addition, using the unique personal identification number for record linkage ensures accurate linkage and virtually no loss to follow-up. This study has several key limitations affecting its internal and external validity. The relationship between HCTZ and skin cancer raises the possibility of hypertension or other antihypertensive medications being possible confounders. Optimally, we would have included a control group on a separate antihypertensive medication, such as a beta-blocker or an angiotensin-converting enzyme inhibitor. However, we lacked sufficient power to assess this. Internal validity is primarily affected by the inherent limitations of the ICR. For example, the registry does not record potential confounders such as patient comorbidities, UV exposure habits, tanning bed use, smoking status, or socioeconomic status.[18] Finally, one possible explanation for the increased risk in HCTZ users could be the fact that they are under closer surveillance and, thus, are more frequently diagnosed with skin cancer, and this was impossible to correct for in this study.

CONCLUSION AND CLINICAL IMPLICATIONS

Our findings strengthen the argument that HCTZ exposure is associated with the development of SCCis, SCC, and BCC. This risk, at least for BCC and invasive SCC, was shown to be most pronounced in individuals with prolonged exposure to HCTZ. Importantly, a similar risk has not been observed with other Eighth Joint National Committee first-line antihypertensive medications, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers,[1,13] suggesting that a patient's individual skin cancer risk should be accounted for when choosing a first-line hypertensive. When HCTZ is initiated, patients should be counseled about the potential association of its use with keratinocyte carcinoma and, therefore, encouraged to practice sun protection. Because an association between keratinocyte carcinoma and HCTZ has now been documented in Iceland's low-UV environment, it is important to recognize that average sun protection behaviors may not necessarily eliminate the carcinogenic potential of HCTZ. Although additional studies are required to show that discontinuation of HCTZ decreases the risk of subsequent keratinocyte carcinoma development, the risk/benefit ratio of using HCTZ in patients at risk for keratinocyte carcinoma development needs to be carefully considered.

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Paper IV

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CONCISE COMMUNICATIONS

Statins are associated with increased risk of squamous cell carcinoma of the skin: a whole-population study from Iceland

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Abstract

Statins have been associated with an increased risk of keratinocyte carcinoma but data are limited and conflicting. Statins are hypothesized to contribute to KC through immunomodulation. A whole-population case–control study of the Icelandic population was conducted using the Icelandic Cancer Registry and Icelandic Prescription Medicine Register. These are high-quality registers which include all cancer diagnoses, as well as every prescription in the country. Cases included all first-time histologically confirmed diagnoses of (BCC), in situ squamous cell carcinoma (SCCis) and invasive SCC between 2003 and 2017. Each case was paired with 10 age- and sex-matched controls. Multivariate conditional logistic regression analysis was performed. Four thousand seven hundred patients with BCC, 1167 patients with SCCis and 1013 patients with invasive SCC were identified and paired with 47,292, 11,961 and 10,367 controls, respectively. Overall statin use was associated with an increased risk of invasive SCC and SCCis but not BCC (adjusted OR [95% CI]: 1.29 [1.11–1.50]; 1.43 [1.24–1.64]; 1.03 [0.95–1.12], respectively). Subgroup analysis demonstrated that statins were significantly associated with invasive SCC and SCCis in patients over 60, but not in those under 60. Atorvastatin was only associated with an increased risk of SCCis; whereas, simvastatin was associated with an increased risk of both invasive SCC and SCCis. This whole-population study of Iceland demonstrates that statin exposure is associated with increased risk of SCC, but not BCC, in a low UV environment. The reasons are unclear, but our results may suggest that individuals receiving atorvastatin and simvastatin have differing levels of baseline keratinocyte cancer risk or that properties of a statin other than 'statin intensity' affect association with SCC.

Keywords Statins · Atorvastatin · Simvastatin · Nonmelanoma skin cancer · Basal cell carcinoma · Squamous cell carcinoma

Statins have been associated with an increased risk of keratinocyte carcinoma (KC), but data are limited and conflicting [1]. Population-wide data are especially lacking, with most studies combining basal cell carcinoma (BCC) and

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Table 1 Demographics of patients with basal cell carcinoma, in situ squamous cell carcinoma and invasive squamous cell carcinoma and age- and sex-matched controls

Characteristic	BCC		SCCis		Invasive SCC	
	Case ($n=4700$)	Control ($n=47,292$)	Case ($n=1167$)	Control ($n=11,961$)	Case	Control
Age: median (IQR)	69 (56–79)	69 (56–79)	77 (67–84)	77 (67–84)	79 (71–85)	79 (70–85)
Male sex	1988 (42.30%)	20,022 (42.34%)	425 (36.42%)	4368 (36.52%)	521 (51.43%)	5309 (51.21%)
Use of statin	1093 (23.26%)	10,661 (22.54%)	405 (34.70%)	3350 (28.01%)	365 (36.03%)	3185 (30.72%)

BCC basal cell carcinoma, *SCCis* in situ squamous cell carcinoma, *SCC* squamous cell carcinoma, *IQR* interquartile range

squamous cell carcinoma (SCC) into a suboptimal unified analysis [2, 3]. Due to this lack of quality data, we decided to analyze this relationship in Iceland, which has very low background UV environment in a genetically homogenous population, providing an interesting environment to study the possible relationship between KC and statin use [4, 5].

A whole-population case–control study of the Icelandic population was conducted using the Icelandic Cancer Registry and Icelandic Prescription Medicine Register. These are high-quality registers which include all cancer diagnoses, as well as every prescription in the country [6, 7]. Cases included all first-time histologically confirmed diagnoses of (BCC), in situ squamous cell carcinoma (SCCis) and invasive SCC between 2003 and 2017. Patients using mycophenolate mofetil, azathioprine and cyclosporine were excluded. Statin prescriptions initiated less than 2 years before the index date were disregarded to account for possible lag time. Each case was paired with 10 age- and sex-matched controls. Patients who filled at least one statin (simvastatin or atorvastatin) prescription prior to their first KC diagnosis were considered exposed. Multivariate conditional logistic regression analysis was performed to assess the association between statin exposure and BCC, SCCis and invasive SCC. Odds ratios (ORs) and 95% confidence intervals (CIs) were adjusted for age, sex and the use of hydrochlorothiazide and photosensitizing medications (retinoids; tetracyclines).

Four thousand seven hundred patients with BCC, 1167 patients with SCCis and 1013 patients with invasive SCC were identified and paired with 47,292, 11,961 and 10,367 controls, respectively (Table 1). Overall statin use was associated with an increased risk of invasive SCC and SCCis but not BCC (adjusted OR [95% CI]: 1.29 [1.11–1.50]; 1.43 [1.24–1.64]; 1.03 [0.95–1.12], respectively). Subgroup analysis demonstrated that statins were significantly associated with invasive SCC and SCCis in patients over 60, but not in those under 60 (Table 2).

This whole-population study of Iceland demonstrates that statin exposure is associated with increased risk of SCC, but not BCC, in a low UV environment. One other population wide study from Denmark has analyzed the impact of statins on SCC and BCC in a separate manner. In their study, no increased risk of invasive SCC was found but they did not analyze SCCis risk [2, 3]. Similarly, an analysis of the Nurses' Health Study and Health Professionals' Follow-up

Table 2 Association between statin exposure and risk of basal cell carcinoma, in situ squamous cell carcinoma and invasive squamous cell carcinoma with subgroup analysis

	Cases (exposed/unexposed)	Controls (exposed/unexposed)	OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)**
BCC	1093/3607	10,661/36,631	1.05 (0.97–1.14)	1.05 (0.97–1.13)	1.03 (0.95–1.12)
Cumulative dose					
1–500 DDU	315	3000	1.07 (0.95–1.22)	1.07 (0.94–1.21)	1.06 (0.93–1.20)
501–1500 DDU	363	3448	1.08 (0.96–1.21)	1.07 (0.95–1.20)	1.06 (0.94–1.19)
> 1500 DDU	415	4213	1.01 (0.90–1.13)	1.00 (0.89–1.13)	0.99 (0.88–1.11)
Subgroup					
Male	588/1400	5696/14,326	1.07 (0.96–1.20)	1.07 (0.95–1.19)	1.05 (0.94–1.18)
Female	505/2207	4965/22,305	1.03 (0.92–1.16)	1.03 (0.92–1.15)	1.01 (0.91–1.13)
< 60 years old	61/1364	680/13,703	0.90 (0.69–1.19)	0.89 (0.67–1.17)	0.87 (0.66–1.14)
≥ 60 years old	1032/2243	9981/22,928	1.07 (0.98–1.16)	1.06 (0.98–1.15)	1.05 (0.98–1.14)
Simvastatin	574/3607	5527/36,631	1.07 (0.97–1.18)	1.06 (0.96–1.17)	1.05 (0.95–1.16)
Atorvastatin	220/3607	2081/36,631	1.07 (0.92–1.24)	1.06 (0.91–1.23)	1.05 (0.91–1.23)
SCCis	405/762	3,350/8,611	1.45 (1.26–1.67)	1.44 (1.25–1.66)	1.43 (1.24–1.64)
Cumulative dose					
1–500 DDU	97	864	1.33 (1.05–1.67)	1.32 (1.05–1.65)	1.31 (1.05–1.65)
501–1500 DDU	126	1091	1.37 (1.12–1.69)	1.36 (1.11–1.67)	1.35 (1.09–1.66)
> 1500 DDU	182	1395	1.63 (1.34–1.97)	1.61 (1.33–1.96)	1.59 (1.32–1.93)
Subgroup					
Male	170/255	1505/2863	1.33 (1.07–1.67)	1.31 (1.05–1.64)	1.30 (1.04–1.63)
Female	235/507	1845/5748	1.53 (1.28–1.83)	1.53 (1.27–1.83)	1.51 (1.26–1.81)
< 60 years old	9/133	74/1466	1.55 (0.72–3.30)	1.50 (0.70–3.23)	1.47 (0.68–3.15)
≥ 60 years old	396/629	3276/7145	1.45 (1.25–1.67)	1.44 (1.25–1.66)	1.43 (1.24–1.65)
Simvastatin	226/762	1760/8611	1.50 (1.26–1.78)	1.49 (1.25–1.76)	1.47 (1.23–1.74)
Atorvastatin	68/762	569/8611	1.35 (1.02–1.78)	1.34 (1.01–1.77)	1.34 (1.01–1.77)
Invasive SCC	365/648	3,185/7,182	1.31 (1.13–1.51)	1.31 (1.13–1.51)	1.29 (1.11–1.50)
Cumulative dose					
1–500 DDU	86	759	1.28 (1.00–1.63)	1.28 (1.00–1.63)	1.27 (1.00–1.62)
501–1500 DDU	125	1038	1.36 (1.10–1.68)	1.36 (1.10–1.68)	1.35 (1.09–1.67)
> 1500 DDU	154	1388	1.28 (1.04–1.57)	1.28 (1.04–1.57)	1.26 (1.02–1.54)
Subgroup					
Male	215/306	1936/3373	1.25 (1.02–1.52)	1.25 (1.02–1.52)	1.24 (1.01–1.51)
Female	150/342	1249/3809	1.38 (1.11–1.73)	1.38 (1.11–1.73)	1.37 (1.10–1.71)
< 60 years old	Jul-88	59/969	1.19 (0.49–2.88)	1.28 (0.53–3.10)	1.24 (0.51–3.02)
≥ 60 years old	358/560	3,126/6,213	1.31 (1.12–1.52)	1.30 (1.12–1.52)	1.29 (1.11–1.50)
Simvastatin	203/648	1679/7182	1.37 (1.15–1.64)	1.37 (1.15–1.65)	1.35 (1.13–1.62)
Atorvastatin	68 /648	577 /7182	1.28 (0.97–1.69)	1.28 (0.97–1.69)	1.27 (0.96–1.68)

BCC basal cell carcinoma, *SCCis* in situ squamous cell carcinoma, *SCC* squamous cell carcinoma, *DDU* daily dose units, *OR* odds ratio, *CI* confidence interval

*Adjusted for hydrochlorothiazide

**Adjusted for hydrochlorothiazide and photosensitizing medications

Study found no significant association between statins and SCC, but did not assess SCCis risk [8]. It is unclear why this is but the differences observed could be due to numerous reasons. First, as discussed below, we see different risk increases between different subtypes of statins (with lower risk observed with atorvastatin). Statin intake could differ between these populations. The age composition might also differ, as the risk increase we observed was not significant for individuals < 60. Dermatology access is high in Iceland, and patients who are under frequent observation by their physician might both be more likely to take a statin, and also more likely to see a dermatologist for screening This could be leading to the discovery of SCCs that might otherwise not have been diagnosed.

Statins are hypothesized to contribute to KC through immunomodulation [1]. They increase regulatory T cell concentration which may impair host effector T cell surveillance-promoting carcinogenesis [1]. While atorvastatin is a longer-acting, more potent inhibitor of HMG-CoA reductase than simvastatin [1], atorvastatin was only associated with an increased risk of SCCis; whereas, simvastatin was associated with an increased risk of both invasive SCC and SCCis. This may suggest that individuals receiving atorvastatin and simvastatin have differing levels of baseline KC risk or that properties of a statin other than 'statin intensity' affect association with SCC.

Limitations of this study include the inability to adjust for patient comorbidities, potential confounding medications, Fitzpatrick skin type, smoking, ultraviolet exposure and patient socioeconomic status. Our results, thus, cannot confirm causation. While the reason for the observed association is unclear, our results suggest that there is reason to conduct larger prospective studies looking at statin exposure and KC risk. We emphasize that moving forward, the risk might be different between different subtypes of statins, and thus, they should be analyzed in a separate manner.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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Paper V

Adalsteinsson, J.A., Muzumdar S., Waldman, R., Hu, C., Wu, R., Ratner, D., Ungar, J., Silverberg, J.I., Olafsdottir, G., Kristjansson, A.K., Tryggvadottir, L., Jonasson J.G. Anti-Tumor Necrosis Factor Therapy is Associated with Increased In-Situ Squamous Cell Carcinoma of the Skin: A Population-Based Case-Control Study. Journal of the American Association of Dermatology. June 2021. DOI: 10.1016/j.jaad.2020.11.029.

nail unit, including the hyponychium, in pediatric patients with longitudinal melanonychia. We propose that hyponychial LBP is a distinctive dermoscopic feature observed in pediatric longitudinal melanonychia and that its presence supports the clinical impression of NMN in pediatric patients.

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Conflicts of interest

None disclosed.

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Anti–tumor necrosis factor therapy is associated with increased in situ squamous cell carcinoma of the skin: A population-based case-control study

To the Editor: Tumor necrosis factor inhibitors (TNFis) have been associated with an increased risk of keratinocyte carcinoma in patients with rheumatoid arthritis and psoriasis, but population-wide data are lacking.[1-3] A population-based case-control study was performed to analyze the association between TNFis and keratinocyte carcinoma using the Icelandic Cancer Registry and the Icelandic Prescription Medicine Register.[4,5] All patients with an initial, histologically confirmed diagnosis of invasive squamous cell carcinoma (SCC), SCC in situ (SCCis), or basal cell carcinoma (BCC) were included as cases and were identified using an *International Classification of Diseases, 10th revision* code between 2003 and 2017. Patients taking cyclosporine, azathioprine, or mycophenolate mofetil were excluded. Risk-set sampling was used to pair each case with 10 age- and sex-matched control subjects. Patients were considered exposed to TNFi if they filled ≥1 prescription for adalimumab, etanercept, infliximab, or golimumab before their first diagnosis of keratinocyte carcinoma. Multivariable conditional logistic regression was performed and adjusted for age, sex, and the use of photosensitizing medications (tetracyclines or oral and topical retinoids) and hydrochlorothiazide. Adjusted odds ratio (aORs) and 95% confidence intervals (CIs) were estimated.

Four thousand seven hundred patients with BCC, 1013 with invasive SCC, and 1167 with SCCis and 47,293, 10,367, and 11,961 control subjects, respectively, were identified (Table I). TNFi exposure was associated with an increased risk of SCCis (aOR 3.13 [95% CI 1.15-8.55]; Table II) but not invasive SCC. Overall TNFi exposure was not associated with risk of BCC (aOR 1.68 [95% CI 0.91-3.11]).

This population-based study shows a significantly increased risk of SCCis, but not invasive SCC, among TNFi users compared with the general Icelandic population. While other studies found an association between TNFi and SCC,[2,3] they did not separate invasive SCC and SCCis in their analyses. It is possible that our study was not powered to detect differences in invasive SCC and BCC risk. Iceland has a low level of background ultraviolet light exposure in a population that is almost exclusively white. The SCCis risk increase with TNFi exposure could be even greater in regions with higher exposure to ultraviolet light. This study differs from the Swedish population-based study of TNFi and keratinocyte carcinoma in that it includes all patients taking TNFis, whereas the Swedish study only studied patients with rheumatoid arthritis.[2] Previous studies have not shown an increased risk of BCC with TNFi use.[2,3]

Study limitations include the inability to adjust for sun exposure, patient comorbidities, and indication for TNFi use. Similarly, we were unable to adjust for exposure to phototherapy, which may have been

Table I. Summary of patients with SCC, SCCis, and BCC and age- and sex-matched control subjects

	Invasive SCC		SCCis		BCC	
Characteristic	Case, n = 1013	Control, n = 10,367	Case, n = 1167	Control, n = 11,961	Case, n = 4700	Control, n = 47,293
Age, median (IQR)	79 (71-85)	79 (70-85)	77 (67-84)	77 (67-84)	69 (56-79)	69 (56-79)
Male sex, n (%)	521 (51.43)	5309 (51.21)	425 (36.42)	4368 (36.52)	1988 (42.30)	20,023 (42.34)
Use of PM, n (%)	403 (39.78)	3597 (34.70)	483 (41.39)	4430 (37.04)	1735 (36.91)	15,810 (33.43)
Use of HCTZ, n (%)	90 (8.88)	894 (8.62)	116 (9.94)	979 (8.18)	346 (7.36)	3065 (6.48)
Use of TNFi, n (%)	3 (0.30)	16 (0.15)	5 (0.43)	19 (0.16)	12 (0.26)	70 (0.15)

BCC, Basal cell carcinoma; *HCTZ*, hydrochlorothiazide; *IQR*, interquartile range; *PM*, photosensitizing medications, including tetracyclines and retinoids; *SCC*, squamous cell carcinoma; *SCCis*, SCC in situ; *TNFi*, tumor necrosis factor alpha inhibitor.

Table II. Association between TNFi exposure and incidence of BCC and SCC with subgroup analysis

	Cases exposed/unexposed	Control subjects exposed/unexposed	Adjusted OR (95% CI)*
Invasive SCC	3/1010	16/10,351	1.80 (0.51-6.34)
Male	1/520	7/5302	1.37 (0.16-11.66)
Female	2/490	9/5049	2.10 (0.44-10.09)
<50 y	1/34	0/380	N/A
≥50 y	2/976	16/9971	1.19 (0.27-5.31)
SCCis	5/1162	19/11,942	3.13 (1.15-8.55)
Male	1/424	3/4365	5.02 (0.45-55.69)
Female	4/738	16/7577	2.84 (0.93-8.63)
<50 y	0/64	2/673	N/A
≥50 y	5/1098	17/11,269	3.37 (1.22-9.28)
BCC	12/4688	70/47,223	1.68 (0.91-3.11)
Male	4/1984	21/20,002	1.82 (0.62-5.36)
Female	8/2704	49/27,221	1.62 (0.76-3.42)
<50 y	1/746	9/7509	1.00 (0.12-8.13)
≥50 y	11/3942	61/39,714	1.78 (0.93-3.38)

BCC, Basal cell carcinoma; *CI*, confidence interval; *N/A*, not available; *OR*, odds ratio; *SCC*, squamous cell carcinoma; *SCCis*, SCC in situ; *TNFi*, tumor necrosis factor alpha inhibitor.
*Odds ratio adjusted for use of oral and topical retinoids, tetracyclines, and hydrochlorothiazide.

disproportionately higher in individuals exposed to TNFi. In addition, only patients taking adalimumab, etanercept, infliximab, and golimumab were evaluated because these were the only TNFis prescribed significantly in Iceland during this timeframe.

In conclusion, this population-based study suggests that individuals receiving TNFis are at an elevated risk of developing SCCis in a low ultraviolet light environment. Sun protective behaviors alone might not eliminate this risk. TNFi-induced immunosuppression might play a larger role in the pathogenesis of SCCis compared with BCC.

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Conflicts of interest

None disclosed.

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The chronic use of multiple photosensitizing drugs is associated with Breslow thickness in female melanoma patients: A bicentric retrospective study

To the Editor: Pharmacopoeia encompasses a wide spectrum of molecules known to have a photosensitizing effect.[1] Both experimental and epidemiologic studies suggest that photosensitizing drugs, especially antihypertensive agents, may influence the incidence of skin cancer.[2,3] The objective of our study was to investigate a possible association between the intake of photosensitizing drugs and Breslow thickness (BT) among melanoma patients. The study was retrospectively performed at inpatient wards of melanoma units from 2 different hospitals: IDI-IRCCS in Rome and University Hospital Sant'Orsola-Malpighi in Bologna, Italy. A total of 554 patients with cutaneous melanoma met the inclusion criteria and were enrolled in the study. Data on socio-demographic variables, histologic variables, skin phototype, and sun exposure and clinical variables, including the presence of chronic diseases, the regular use of drugs, and the body mass index (BMI), were collected. To investigate a possible association between photosensitizing drug use and BT, the Cumulative Logit Model was used. Sex, age, center, ulceration, mitotic rate, anatomic site of the lesion, BMI, the presence of chronic diseases, skin phototype, and sun exposure were considered potential confounders. Statistically significant variables were included in the final multivariate model. The likelihood-ratio test was used to test for interactions. Because the non−drug users may differ from the users on uncontrolled confounders, we also included in the model an indication of drug use. To test if the effect of photosensitizing drug exposure would increase systematically with the level of BT (dose-response), we included the intensity of photosensitizing drugs use as an ordinal variable in the logit model and tested for any trends (Wald test). The statistical software used was package STATA, release 15 (StataCorp LLC, College Station, TX).

Table I shows the demographic, clinical, and histologic characteristics of the subjects as well as drug use and association with BT together with a univariate analysis.

In the multivariate model, after adjusting for age, center, BMI, skin phototype, and sun exposure, women taking 2 or more photosensitizing drugs had 3 times an increased risk of a thicker melanoma compared with non−drug users (odds ratio [OR], 3.77; 95% confidence interval [CI], 1.36-10.4, *P*-trend = .003). This result seemed to be caused by the calcium channel blockers (OR, 3.32; 95% CI, 1.00-11.0; $P = .049$). However, no association was found among men (OR, 1.0; 95% CI, 0.40-2.55) (Table II). This finding may be explained by the gender differences in the cancer biology, genetic background, pharmacokinetics, and immune response or by differences in the behavior toward sun exposure and healthcare.[4] The mean BT in men was 1.3 mm (standard deviation, 1.6) and 1.0 mm (standard deviation, 1.5) in women ($P = .071$).

The limitations of this study include the low number of participants, its retrospective nature, and the possible recall bias.

Further studies with a larger sample size are necessary. Because of population aging and an increased life expectancy, there is a high prevalence of the so-called polypharmacy to treat chronic diseases. The effects of the drugs on photosensitization can be subclinical and go unnoticed. Long-term surveillance may be indicated together with photoprotection as an effective form of cancer prevention in patients receiving multiple drugs.[5]

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Paper VI

Adalsteinsson, J.A., Muzumdar S., Waldman, R., Hu, C., Wu, R., Ratner, D., Feng, H., Ungar, J., Silverberg, J.I., Olafsdottir, G., Kristjansson, A.K., Tryggvadottir, L., Jonasson J.G. Metformin is associated with decreased risk of basal cell carcinoma: A whole-population case-control study from Iceland. Journal of the American Association of Dermatology. February 2021. DOI: 10.1016/j.jaad.2021.02.042.

ORIGINAL ARTICLE

Metformin is associated with decreased risk of basal cell carcinoma: A whole-population case-control study from Iceland

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Background: Metformin has anticarcinogenic properties and is also known to inhibit the sonic hedgehog pathway, but population-based studies analyzing the potential protective effect for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are needed.

Objectives: To delineate the association between metformin use and invasive SCC, SCC in situ (SCCis), and BCC.

Methods: A population-based case-control study design was employed using all 6880 patients diagnosed in Iceland between 2003-2017 with first-time BCC, SCCis, or invasive SCC, and 69,620 population controls. Multivariate odds ratios (ORs) were calculated using conditional logistic regression.

Results: Metformin was associated with a lower risk of developing BCC (OR, 0.71; 95% confidence interval [CI], 0.61-0.83), even at low doses. No increased risk of developing SCC was observed. SCCis risk was mildly elevated in the 501-1500 daily dose unit category (OR, 1.40; 95% CI, 1.00-1.96).

Limitations: This study was retrospective in nature with the inability to adjust for ultraviolet exposure, Fitzpatrick skin type, and comorbidities.

Conclusion: Metformin is associated with decreased risk of BCC development, even at low doses. Metformin might have potential as a chemoprotective agent for patients at high risk of BCC, although this will need confirmation in future studies. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2021.02.042.)

Key words: basal cell carcinoma; keratinocyte carcinoma; metformin; squamous cell carcinoma; squamous cell carcinoma in situ.

INTRODUCTION

There is growing evidence to suggest that metformin may decrease the risk of several human malignancies, including those of the liver, pancreas, colon, and breast.[1] Metformin is thought to inhibit carcinogenesis through a number of mechanisms, including (1) inhibition of the mammalian target of rapamycin; (2) inhibition of

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protein synthesis and the cell cycle; (3) activation of p53 and p21, leading to cell apoptosis and autophagy; (4) activation of the immune system; (5) destruction of cancer stem cells; (6) inhibition of angiogenesis; and (7) reduction in blood lipid and insulin levels.[2] In addition to general anticarcinogenic effects, metformin has also been shown to directly inhibit the sonic hedgehog (Shh) pathway, a key pathway in basal cell carcinoma (BCC) pathogenesis.[3,4] This pathway is the target of vismodegib and sonidegib, which are highly effective for BCC prevention, but their broad use for BCC prophylaxis is limited due to numerous side effects.[5,6]

CAPSULE SUMMARY

- Metformin is known for its antiaging and anticarcinogenic effects.
- Metformin is associated with decreased risk of basal cell carcinoma and could have future potential as a chemoprotective agent in patients at increased risk for basal cell carcinoma.

The relationship between metformin and keratinocyte carcinoma has not been well-characterized but is of importance considering that metformin is a commonly prescribed medication.[7] To date, only 1 population-wide study from Taiwan has analyzed the impact of metformin on the development of keratinocyte carcinoma.[8] This retrospective cohort study found a significantly decreased risk of first-time keratinocyte carcinoma with metformin use, especially at higher cumulative doses, but it did not differentiate between BCC and squamous cell carcinoma (SCC).[8] Additionally, the Taiwanese population has a low baseline risk for keratinocyte carcinoma.[8] Another smaller retrospective cohort study of the Veterans Affairs population found no significant association between metformin and the development of a second keratinocyte carcinoma, but it was limited by the fact that BCC and SCC were not analyzed separately.[9]

Herein, we conducted a whole-population case-control study in the Icelandic population to better delineate the relationship between metformin and the development of BCC, in situ SCC (SCCis), and SCC. Iceland is unique compared with previously studied populations as it (1) has a largely White and genetically homogenous population[10]; (2) has a low level of ambient ultraviolet (UV) exposure given its high latitude[11]; (3) has minimal countrywide variation in UV exposure due to its small size; (4) keeps thorough records of skin cancer diagnoses with histologic verification in the Icelandic Cancer Registry (ICR)[12]; and (5) documents all electronic outpatient prescriptions in the Prescription Medicine Register.[13]

METHODS

A whole-population case-control study of the Icelandic population was performed using the ICR and Icelandic Prescription Medicine Register. The ICR records all keratinocyte carcinoma diagnoses with histologic verification.[12] The Prescription Medicine Register has documented all electronic outpatient prescriptions in Iceland since 2002.[13] All first-time diagnoses of SCCis, SCC, or BCC in the ICR between 2003 and 2017 were included as cases. Each case was matched with 10 randomly selected unaffected age- and gender-matched population controls. Unique personal identification numbers were used to identify all metformin prescriptions among cases and controls.

Individuals were considered exposed to metformin if they had filled at least 1 prescription of metformin more than 2 years before their diagnosis of keratinocyte carcinoma. To account for possible lag time, all medication prescriptions within 2 years of diagnosis were disregarded. Analyses were conducted using grams and daily dose units (DDUs) of metformin. A DDU of metformin, or its average daily maintenance dose when used for its primary indication, is 2 grams.[14]

Azathioprine, mycophenolate mofetil, and cyclosporine have been shown to increase the risk of keratinocyte carcinoma, thus individuals on these medications were excluded.[15] Multivariate odds ratios (ORs) were calculated with 95% confidence intervals (CIs) using conditional logistic regression analyses for the association between metformin and the risk of first-time SCCis, invasive SCC, and BCC. Analyses were adjusted for photosensitizing medications (tetracyclines and oral and topical retinoids), hydrochlorothiazide, statins, and tumor necrosis alpha inhibitors because these medications have been associated with increased risk of skin cancer.[15-18] Analyses were performed separately for SCCis, invasive SCC, and BCC with never-users of metformin serving as controls.

Cumulative dose-response analyses were conducted for each subtype of keratinocyte carcinoma using trend analysis. Weighted linear regression was used to calculate ORs based on the median dose of metformin for each category (1-500, 501-1500, and >1500 DDUs). For all analyses, $P < .05$ was considered statistically significant.

Abbreviations used:

BCC: basal cell carcinoma
DDU: daily dose unit
ICR: The Icelandic Cancer Registry
OR: odds ratio
SCC: squamous cell carcinoma
SCCis: squamous cell carcinoma in situ
Shh: sonic hedgehog
T2DM: type 2 diabetes mellitus

RESULTS

During this study, 4700 individuals with BCC, 1167 with SCCis, and 1013 with invasive SCC were identified and matched with 47,293, 11,961, and 10,367 controls, respectively (Table I).

The relationship between metformin use and keratinocyte carcinoma risk is summarized in Table II. Of the individuals with BCC, 4.0% were exposed to metformin, as compared to 5.3% of controls. Lower risk of BCC was significantly associated with metformin use as compared to nonuse (adjusted OR, 0.71; 95% CI, 0.61-0.83).

Additionally, 7.5% of individuals with SCCis and 6.2% of controls were exposed to metformin. Metformin use was not significantly associated with SCCis (adjusted OR, 1.06; 95% CI, 0.84-0.35).

Similarly, 7.2% of individuals with invasive SCC and 6.6% of controls were exposed to metformin. Metformin use was not significantly associated with invasive SCC (adjusted OR, 1.01; 95% CI, 0.78-1.30). Dose-response relationships were not statistically significant for BCC, SCCis, or invasive SCC (P = .87, .94, and .88, respectively).

Subgroup analysis was conducted and shown in Table III. Metformin use was associated with a lower risk of BCC in both males and females (adjusted OR, 0.71; 95% CI, 0.57-0.88 and adjusted OR, 0.72; 95% CI, 0.57-0.90, respectively). Similarly, individuals older than 60 years had a decreased risk of BCC with metformin exposure (adjusted OR, 0.69; 95% CI, 0.59-0.82).

DISCUSSION

This population-based study shows an association between decreased risk of BCC and metformin use in a low-UV environment. By using a nested case-control design and linking nationwide health registries, the risks of having a nonrepresentative control group or information bias were eliminated. These are drawbacks typical for most case-control studies. The Icelandic unique personal identification numbers provided high-quality record linkage and ensured that virtually no loss to follow-up occurred during the study's 15-year span. Fitzpatrick skin type is a risk factor for skin cancer development at a population level. The majority of the Icelandic population is White,[14] which contributes to the study's internal validity. Although background UV is low in Iceland, it is important to note that tanning bed use and foreign travel are commonplace.[16] These 2 factors likely play a relatively recent and important role in the exposure of this population to UV radiation.

Metformin is an oral medication used mostly for type 2 diabetes mellitus (T2DM). It has been shown to have potential when it comes to inhibiting cancer cell proliferation in animal models and, to a limited extent, has been linked with a lower risk of certain types of cancer in humans, such as breast, pancreatic, and colon cancer.[19-21] Metformin's main antitumor properties are thought to be due to AMP-kinase inhibition, leading to the inhibition of the mammalian target of rapamycin.[19] In addition, metformin can directly inhibit the Shh signaling pathway,[3,4] which is an important pathway for cell growth in BCC. Specifically, it has been shown that metformin inhibits expression of the Shh ligand, thereby reducing activation of this pathway, a finding that is clinically relevant, as demonstrated by direct inhibition of the Shh pathway in breast cancer cells and cancer stem cells.[19]

Decreased BCC risk seen with metformin administration was similar for all dose categories. It is unclear why this is. It could be that we have a

Table I. Characteristics of individuals with BCC, SCCis, and SCC and age- and gender-matched controls

	BCC		In-situ SCC		SCC	
Characteristic	Case (n = 4700)	Control (n = 47,293)	Case (n = 1167)	Control (n = 11,961)	Case (n = 1013)	Control (n = 10,367)
Age, Median (IQR)	69 (56-79)	69 (56-79)	77 (67-84)	77 (67-84)	79 (71-85)	79 (70-85)
Gender						
Male	1988 (42.30%)	20,023 (42.34%)	425 (36.42%)	4368 (36.52%)	521 (51.43%)	5309 (51.21%)
Female	2712 (57.70%)	27,270 (57.66%)	742 (63.58%)	7593 (63.48%)	492 (48.57%)	5058 (48.79%)
Metformin Use						
Ever	189 (4.02%)	2500 (5.29%)	87 (7.46%)	740 (6.19%)	73 (7.21%)	687 (6.63%)
Never	4511 (95.98%)	44,793 (94.71%)	1080 (92.54%)	11,221 (93.81%)	940 (92.79%)	9680 (93.37%)

BCC, Basal cell carcinoma; *IQR,* interquartile range; *SCC,* squamous cell carcinoma; *SCCis,* squamous cell carcinoma in situ.

Table II. Association between metformin and BCC, SCCis, and SCC

	Cases	Controls	OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡	Adjusted OR (95% CI)§	Adjusted OR (95% CI)‖
BCC								
Never use	4511	44,793	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	189	2500	0.75 (0.64-0.87)	0.74 (0.63-0.86)	0.73 (0.63-0.85)	0.71 (0.61-0.83)	0.71 (0.61-0.83)	0.72 (0.61-0.85)
Cumulative dose								
1-500 DDUs	79	1041	0.75 (0.60-0.95)	0.75 (0.59-0.94)	0.74 (0.58-0.93)	0.72 (0.57-0.91)	0.72 (0.57-0.91)	0.76 (0.59-0.97)
501-1500 DDUs	60	816	0.73 (0.56-0.95)	0.72 (0.54-0.93)	0.71 (0.54-0.93)	0.69 (0.53-0.90)	0.69 (0.53-0.90)	0.69 (0.53-0.90)
>1500 DDUs	50	643	0.77 (0.57-1.03)	0.76 (0.57-1.01)	0.75 (0.56-1.00)	0.73 (0.54-0.98)	0.73 (0.54-0.98)	0.73 (0.54-0.97)
Continuous trend test		$P = .87$						
In situ SCC								
Never use	1080	11,221	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	87	740	1.22 (0.97-1.54)	1.20 (0.95-1.52)	1.20 (0.95-1.51)	1.06 (0.84-1.35)	1.06 (0.84-1.35)	1.05 (0.82-1.34)
Cumulative dose								
1-500 DDUs	25	281	0.92 (0.61-1.40)	0.91 (0.60-1.38)	0.91 (0.60-1.37)	0.83 (0.55-1.27)	0.84 (0.55-1.27)	0.74 (0.46-1.21)
501-1500 DDUs	43	273	1.64 (1.18-2.27)	1.61 (1.16-2.24)	1.59 (1.15-2.22)	1.40 (1.00-1.96)	1.40 (1.00-1.96)	1.38 (0.99-1.93)
>1500 DDUs	19	186	1.06 (0.65-1.71)	1.05 (0.65-1.69)	1.05 (0.65-1.71)	0.91 (0.56-1.48)	0.90 (0.56-1.47)	0.91 (0.56-1.49)
Continuous trend test		$P = .94$						
SCC								
Never use	940	9680	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	73	687	1.10 (0.85-1.42)	1.10 (0.85-1.42)	1.09 (0.85-1.41)	1.01 (0.78-1.30)	1.01 (0.78-1.30)	1.05 (0.80-1.37)
Cumulative dose								
1-500 DDUs	24	267	0.93 (0.61-1.42)	0.93 (0.60-1.42)	0.92 (0.60-1.40)	0.86 (0.56-1.32)	0.86 (0.56-1.32)	0.95 (0.60-1.51)
501-1500 DDUs	33	234	1.47 (1.01-2.14)	1.47 (1.01-2.14)	1.47 (1.01-2.14)	1.35 (0.92-1.97)	1.35 (0.92-1.97)	1.35 (0.92-1.97)
>1500 DDUs	16	186	0.89 (0.53-1.50)	0.89 (0.53-1.50)	0.89 (0.53-1.50)	0.79 (0.47-1.34)	0.79 (0.47-1.34)	0.79 (0.47-1.34)
Continuous trend test		$P = .88$						

BCC, Basal cell carcinoma; *CI,* confidence interval; *DDU,* daily dose units; *OR,* odds ratio; *SCC,* squamous cell carcinoma; *SCCis,* squamous cell carcinoma in situ.
1-500 DDUs equivalent to 2-1000 g; 501-1500 DDUs equivalent to 1002-3000g; >1500 DDUs equivalent to >3000 g.
*Adjusted for hydrochlorothiazide.
†Adjusted for hydrochlorothiazide and photosensitizing medications.
‡Adjusted for hydrochlorothiazide, photosensitizing medications, and statins.
§Adjusted for hydrochlorothiazide, photosensitizing medications, statins, and tumor necrosis alpha inhibitors.
‖Excludes patients on voriconazole and those with <2 filled metformin prescriptions; adjusted for hydrochlorothiazide, photosensitizing medications, statins, and tumor necrosis alpha inhibitors.

Table III. Subgroup analysis by age and gender

Subgroup	Case patients (exposed/unexposed)	Controls (exposed/unexposed)	OR (95% CI)	Adjusted OR (95% CI)*
BCC				
Male	100/1888	1314/18,709	0.75 (0.61-0.93)	0.71 (0.57-0.88)
Female	89/2623	1186/26,084	0.75 (0.60-0.93)	0.72 (0.57-0.90)
<60 years	27/1398	309/14,074	0.88 (0.59-1.31)	0.86 (0.57-1.30)
≥60 years	162/3113	2191/30,719	0.73 (0.62-0.86)	0.69 (0.59-0.82)
In situ SCC				
Male	39/386	345/4023	1.18 (0.83-1.68)	1.06 (0.74-1.52)
Female	48/694	395/7198	1.25 (0.92-1.71)	1.06 (0.77-1.47)
<60 years	4/138	32/1508	1.34 (0.46-3.88)	1.04 (0.34-3.21)
≥60 years	83/942	708/9713	1.21 (0.96-1.54)	1.06 (0.83-1.36)
SCC				
Male	50/471	435/4874	1.12 (0.88-1.64)	1.12 (0.81-1.54)
Female	23/469	252/4806	0.94 (0.61-1.46)	0.83 (0.53-1.30)
<60 years	2/93	23/1005	1.17 (0.27-5.177)	1.10 (0.23-5.35)
≥60 years	71/847	664/8675	1.10 (0.85-1.42)	1.01 (0.77-1.31)

BCC, Basal cell carcinoma; *CI,* confidence interval; *OR,* odds ratio; *SCC,* squamous cell carcinoma.
*Adjusted for hydrochlorothiazide, photosensitizing medications, statins, and tumor-necrosis alpha inhibitors.

confounder that is unaccounted for in the analysis. It could also be that metformin's BCC risk-lowering effect is immediate, with only a low dose being needed to see a clinical benefit. Notably, the OR continued to decrease when adjusted for hydrochlorothiazide and statins, but not TNF-alpha inhibitors, which have been associated with increased risk of keratinocyte cancer in this population. This decreased risk of BCC was seen in all subanalyses, except for the younger than 60 years category. This might signify that metformin has less of a protective effect in younger individuals, but we might also have lacked power in this category. Looking at SCCis, we saw no decrease in risk; on the contrary, for the 501-1500 DDU dose category, we observed an adjusted OR of 1.40 (95% CI, 1.00-1.96), showing a possible increased risk of SCCis. This was not seen in any of the subanalyses or the other dose categories. A decrease or increase in risk was not observed for SCC formation with metformin exposure. However, similar to what we saw with SCCis, there was a significantly higher risk of SCC in the 501-1500 DDU category (OR, 1.47; 95% CI, 1.01-2.14), but this was not significant after adjusting for the use of other medication (OR, 1.35; 95% CI, 0.92-.97).

This study has several important limitations. We did not have information on patient comorbidities (eg, T2DM), photodynamic therapy utilization, tanning bed use, UV exposure habits, smoking status, socioeconomic status, or all potential confounding medications patients were taking.[18] The relationship between metformin and lower BCC risk raises the possibility of diabetes or other diabetic medication being possible confounders. It is unclear whether T2DM truly affects the risk of keratinocyte carcinoma, with some studies reporting an increased risk of skin cancer[22] and others reporting a decreased risk.[23,24] A study based in the United Kingdom observed that patients diagnosed with BCC had T2DM less often.[23] They speculated that differences in lifestyle of diabetic patients might account for the association they observed.[23] This reason is unlikely to explain this study's findings, as decreased risk of SCC in addition to BCC would be expected. In addition, it has been reported that there might be a possible protective role of insulin-like growth factor 1 receptor in keratinocytes, with activation protecting keratinocytes from UVB-induced carcinogenesis.[24] However, if this were the case, a decreased risk of SCC in addition to BCC would be expected. Thus, we speculate that metformin's selective inhibition of the Shh pathway is the main mechanism that decreased the observed risk of BCC in exposed Icelanders. It might be that T2DM increases the overall risk of SCC, as some studies have shown[22] with metformin selectively decreasing the risk of BCC rather than SCC. Optimally, a control group taking a separate diabetic medication, such as insulin, should have been included in this study. However, we lacked sufficient power to assess this variable.

BCC chemoprophylaxis options are lacking. Nicotinamide and acitretin have shown effectiveness in reducing SCC and actinic keratoses counts, but the benefit for BCC prophylaxis is less clear.[25,26] Vismodegib was the first Shh pathway inhibitor to gain Food and Drug Administration approval for the treatment of BCC,[5] followed by sonidegib.[6] These agents work as antagonists to the smoothened receptor, directly inhibiting activation of the Shh pathway.[5] However, their use is limited by side

effects, which affect most patients, such as muscle spasms, alopecia, and dysgeusia.[5] Metformin's most common side effects are diarrhea and nausea, which are present in up to 50% of patients. These effects are usually mild and can be minimized by taking metformin at mealtimes or by lowering the dose.[27] As mentioned earlier, our results suggest that metformin's BCC risk reduction might be idiosyncratic, with only small doses required to be effective, thereby lowering the risk of side effects. Limiting the potential of Shh inhibitors is the possibility of increased SCC risk.[28] This might also be the case with metformin, as we saw a borderline significant increase of in situ SCC risk with moderate doses. This observed risk increase might be due to an inability to adjust for all possible confounders, such as organ transplant status and all potential immunosuppressive medication.

While this study does not imply causation, it does suggest an association between metformin use and lower rates of first-time BCC. Furthermore, randomized prospective trials are required to fully understand the effect metformin has on BCC and SCC risk.

Conflicts of interest

None disclosed.

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