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Epidemiology of basal cell carcinoma in the United Kingdom: incidence, lifestyle factors, and comorbidities

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Background: Little is known about the epidemiology of basal cell carcinoma (BCC).

Methods: Using the Clinical Practice Research Datalink, we calculated annual incidence rates. In a case–control analysis, we examined lifestyle factors and comorbidities.

Results: Incidence rose significantly between 2000 and 2011. Basal cell carcinoma risk was increased in alcohol drinkers (slightly) and immunocompromised patients, but reduced in smokers and individuals with abnormal weight.

Conclusions: Basal cell carcinoma places a growing public health burden. Lifestyle factors do not play a major role in pathogenesis, but immunosuppression is important.

Cutaneous basal cell carcinoma (BCC) represents the most common malignancy in Caucasian populations, and the incidence is rising (Lomas *et al*, 2012). Nevertheless, it is often omitted from official cancer statistics, as little is known about the true extent of the disease. Cancer registries, if at all, only include histologically confirmed tumours and do not take into account the substantial proportion of BCCs diagnosed clinically without histology (Flohil *et al*, 2012).

Basal cell carcinoma is primarily caused by heavy episodic and chronic sun exposure (Armstrong and Kricker, 2001). Predisposing factors include fair skin type, immunosuppression, and certain genetic disorders (e.g., albinism, Gorlin syndrome, xeroderma pigmentosum; Baxter *et al*, 2012). Data on the relationship between BCC, other diseases, and lifestyle factors are limited.

Using the Clinical Practice Research Datalink (CPRD), we aimed at estimating BCC incidence in the United Kingdom (UK) and at characterising affected patients regarding lifestyle factors and comorbidities.

MATERIALS AND METHODS

Data source. The CPRD is a large primary care database containing computerised longitudinal patient records for about 6% of the UK population. Available data include demographics, lifestyle factors, medical diagnoses, and prescribed drugs. Numerous studies have demonstrated the completeness and high validity of the records (Wood and Martinez, 2004; Herrett *et al*, 2010).

Study design. We calculated incidence rates (IRs) of BCC in adults between 2000 and 2011, stratified by age, sex, and year of diagnosis.

Using a case–control design, we compared alcohol consumption, smoking status, BMI, and selected comorbidities present before diagnosis between patients with incident BCC and a disease-free control group.

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Study population. We identified all patients aged 18 years or older in the CPRD with a BCC first-time diagnosis between 2000 and 2011.

Patients with less than 3 years of history in the CPRD before diagnosis as well as those with a record of albinism, Gorlin syndrome, or xeroderma pigmentosum were excluded.

For the case–control analysis, we randomly selected a group of controls (patients with no recorded BCC) matched 1:1 to BCC cases on age, sex, general practice, calendar time, and years of history in the database. The same exclusion criteria were applied to controls as to cases.

Statistical analysis. We calculated crude IRs as the number of new BCC cases during the study period divided by the total number of person-years at risk (person-years of all adult individuals at risk in the CPRD between start of the study period and end of follow-up, i.e., the day of first BCC diagnosis, death, leaving the practice, or the end of the study period, whichever came first). We also computed directly age-standardised incidence rates (ASRs, reference: European standard population, Waterhouse *et al*, 1976) and standardised rate ratios (SRRs) to compare rates between sexes and over time.

For comparison of alcohol consumption (non, current, ex; units per week), smoking status (non, current, ex; cigarettes per day), BMI (<18.5, 18.5–24.9, 25–29.9, $\geqslant 30\,kg\,m^{-2}$), and comorbidities (Table 1) between cases and controls, we conducted conditional logistic regression analyses and presented relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs).

We controlled for confounding by running a multivariate model incorporating all examined lifestyle factors and the number of general practitioner visits in the year before diagnosis (marker for medical attention). Comorbidities were not included, as they were only thought to descriptively characterise the study population.

Analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC, USA). Statistical significance was defined at the α-level of 0.05.

RESULTS

UK IRs. We identified 57 123 adults with a BCC first-time diagnosis between 2000 and 2011. The overall crude IR and ASR were 201.7 (95% CI: 200.1–203.4) and 151.8 (95% CI: 150.5–153.1) per 100 000 person-years, respectively. Basal cell carcinoma incidence sharply increased with increasing age. Although men had a higher aggregate risk than women (SRR: 1.27, 95% CI: 1.25–1.29), BCC was more common among the latter in individuals younger than 55 years (Supplementary Table 1).

Basal cell carcinoma incidence rose over time in both sexes and in all age groups except in those under 30 years, with an overall increase of 39% between 2000 and 2011 (SRR: 1.39, 95% CI: 1.33–1.45, Figure 1).

Lifestyle factors. The case–control analysis comprised 57 121 cases and the same number of matched controls (mean age 69.5 years (s.d.: 13.3 years), 51.3% males). Current alcohol drinkers had a slightly elevated BCC risk compared with non-drinkers. However, the risk only marginally increased with increasing number of alcohol units consumed per week. Smokers had a significantly reduced BCC risk compared with non-smokers. The lowest risk was observed in current heavy smokers ($\geqslant 40$ cigarettes per day), indicating a negative dose–response relationship between smoking and BCC. Individuals with a BMI outside the normal range (BMI <18.5 or $\geqslant 25$) were less likely to develop BCC than normal-weight individuals (Table 2 and Supplementary Table 2).

Comorbidities. Compared with controls, BCC cases were significantly more likely to have a medical history of rheumatoid arthritis (RA), inflammatory bowel disease (IBD), extra-cutaneous malignancies, solid organ transplantation, and various skin disorders. On the other hand, they were less likely to have been diagnosed with chronic obstructive pulmonary disease (COPD), diabetes mellitus, schizophrenia, and dementia. The prevalences of the remaining examined comorbidities were equally distributed between the two groups (Table 1).

Table 1. Distribution of comorbidities among basal cell carcinoma cases and their matched controls

	BCC cases ($n=57\,121$), *n* (%)	BCC-free controls ($n=57\,121$), *n* (%)	OR crude (95% CI)
Diseases of internal organs			
COPD	2663 (4.7)	2922 (5.1)	0.90 (0.86–0.96)
Diabetes mellitus	5009 (8.8)	5709 (10.0)	0.86 (0.83–0.90)
Hypertension	22 235 (38.9)	21 807 (38.2)	1.04 (1.01–1.06)
Gout	3660 (6.4)	3483 (6.1)	1.06 (1.01–1.11)
Rheumatoid arthritis	1571 (2.8)	1322 (2.3)	1.20 (1.11–1.29)
Inflammatory bowel disease	729 (1.3)	589 (1.0)	1.24 (1.11–1.39)
Depression	8784 (15.4)	8758 (15.3)	1.00 (0.97–1.04)
Schizophrenia	271 (0.5)	381 (0.7)	0.71 (0.61–0.83)
Dementia	672 (1.2)	945 (1.7)	0.70 (0.63–0.77)
Malignancies (excl. skin cancer)	5247 (9.2)	4015 (7.0)	1.35 (1.29–1.41)
Solid organ transplantation	205 (0.4)	41 (0.1)	5.10 (3.63–7.16)
Skin diseases			
Atopic dermatitis	3761 (6.6)	3305 (5.8)	1.16 (1.10–1.22)
Seborrhoeic dermatitis	3514 (6.2)	2686 (4.7)	1.34 (1.27–1.41)
Skin mycoses	8560 (15.0)	7263 (12.7)	1.22 (1.18–1.27)
Bacterial skin infections	3948 (6.9)	3388 (5.9)	1.18 (1.13–1.24)
Warts	5462 (9.6)	3642 (6.4)	1.58 (1.51–1.65)
Herpes infection	6923 (12.1)	6236 (10.9)	1.13 (1.09–1.17)
Psoriasis	2480 (4.3)	2319 (4.1)	1.07 (1.01–1.14)
Rosacea	2346 (4.1)	1671 (2.9)	1.43 (1.34–1.53)
Cutaneous malignant melanoma	810 (1.4)	332 (0.6)	2.46 (2.16–2.80)

Abbreviations: BCC = basal cell carcinoma; CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio.

DISCUSSION

The observed BCC incidence in the UK is considerably high, particularly in the elderly. Projecting the crude IR in the CPRD population to the total UK population aged 18 years or older, we estimate that approximately 110 000 adults developed BCC for the first time in 2011 alone. Taking into account the ageing of the UK population and the increasing IRs over the last decade, BCC places a growing burden on the National Health Service.

In accordance with three large cohort studies (Fung *et al*, 2002; Freedman *et al*, 2003; Jensen *et al*, 2012), we observed an elevated BCC risk in alcohol drinkers. Several mechanisms have been suggested to explain how alcohol may initiate and promote skin carcinogenesis. These comprise impairment of the immune system, poor nutritional status as well as photosensitising and direct mutagenic effects of acetaldehyde, the primary oxidative metabolite of ethanol (Poschl and Seitz, 2004; Saladi *et al*, 2010). Nonetheless, the detected association between alcohol intake and BCC risk was weak and there was no evidence of a clear dose–response relationship. Two US surveys reported an increased prevalence and severity of sunburns in alcohol drinkers. Thus, alcohol consumption could also be a marker for willingness to take health risks including excessive sun exposure, which then increases the risk of BCC, rather than being a causal factor for BCC itself (Warthan *et al*, 2003; Mukamal, 2006).

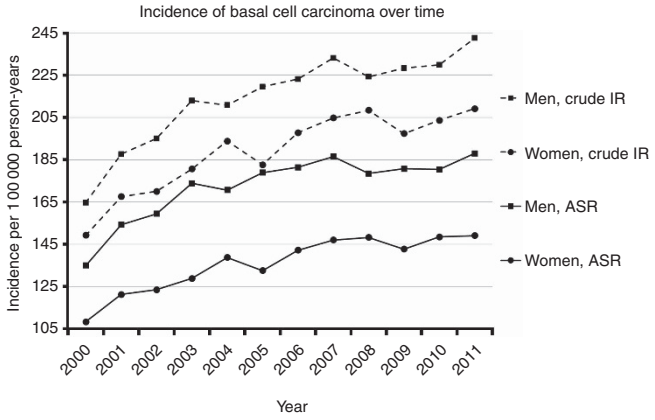

Figure 1. Sex-specific crude incidence rates (IRs) and age-standardised incidence rates (ASRs) of basal cell carcinoma first-time diagnoses in the United Kingdom from 2000 to 2011 (reference: European standard population, Waterhouse *et al*, 1976).

A meta-analysis of 11 case–control and 3 cohort studies (Leonardi-Bee *et al*, 2012) and two subsequently published individual studies (a case–control study and a study based on two cohorts) (Rollison *et al*, 2012; Song *et al*, 2012) found that smoking was not related to an increased BCC risk. Some of these studies (Freedman *et al*, 2003; Marehbian *et al*, 2007; Rees *et al*, 2007; Song *et al*, 2012) and our results even suggest a lower risk for smokers, which seems paradoxical in view of the carcinogenic effects of cigarette smoke. Aside from non-causal explanations (cigarette smoking may for example be associated with a lower socioeconomic status and fewer opportunities to go on sunny holidays), an underlying mechanism might be an attenuated cutaneous inflammatory response to ultraviolet radiation in smokers, possibly by nicotine altering prostaglandin metabolism (Mills *et al*, 1993).

The relationship between overweight and a decreased BCC risk has already been reported by others (Gilbody *et al*, 1994; van Dam *et al*, 1999; Gerstenblith *et al*, 2012; Pothiawala *et al*, 2012). It has been proposed that obese individuals engage less in physical activity, therefore spend less time outdoors, and wear less revealing clothing, which leads to reduced sun exposure of the skin. The same might be true for underweight people.

The analysis of comorbidities revealed significant associations between BCC and diseases related to iatrogenic or non-iatrogenic immunosuppression (RA, IBD, organ transplantation, malignancies, skin infections, seborrhoeic dermatitis). Besides specific photosensitising and oncogenic effects of certain immunosuppressive drugs, it is believed that impaired immune surveillance facilitates unrestricted growth of cancer-initiated cells (Athar *et al*, 2011). The increased risk of non-melanoma skin cancer in organ transplant recipients has been

Table 2. Distribution of lifestyle factors among basal cell carcinoma cases and their matched controls

	BCC cases ($n = 57\,121$), *n* (%)	BCC-free controls ($n = 57\,121$), *n* (%)	OR crude (95% CI)	OR adjusted[a] (95% CI)
Alcohol status				
Non	8592 (15.0)	9442 (16.5)	1.00 (ref.)	1.00 (ref.)
Ex	1069 (1.9)	1193 (2.1)	1.00 (0.92–1.09)	0.96 (0.87–1.05)
Current	42 640 (74.7)	40 552 (71.0)	1.18 (1.14–1.22)	1.19 (1.15–1.23)
Unknown	4820 (8.4)	5934 (10.4)	0.87 (0.82–0.91)	1.05 (0.99–1.11)
Smoking status				
Non	28 058 (49.1)	26 439 (46.3)	1.00 (ref.)	1.00 (ref.)
Ex	19 607 (34.3)	19 033 (33.3)	0.98 (0.95–1.00)	0.91 (0.89–0.94)
Current	6999 (12.3)	8359 (14.6)	0.78 (0.75–0.80)	0.77 (0.74–0.80)
Unknown	2457 (4.3)	3290 (5.8)	0.65 (0.62–0.70)	0.92 (0.86–0.99)
BMI ($kg\,m^{-2}$)				
12.0–18.4	868 (1.5)	910 (1.6)	0.86 (0.79–0.95)	0.86 (0.78–0.95)
18.5–24.9	20 522 (35.9)	18 591 (32.6)	1.00 (ref.)	1.00 (ref.)
25.0–29.9	19 849 (34.8)	19 246 (33.7)	0.93 (0.91–0.96)	0.90 (0.87–0.92)
30.0–60.0	8907 (15.6)	10 072 (17.6)	0.80 (0.78–0.83)	0.73 (0.70–0.75)
Unknown	6975 (12.2)	8302 (14.5)	0.73 (0.70–0.76)	0.89 (0.85–0.94)

Abbreviations: BCC = basal cell carcinoma; BMI = body mass index; CI = confidence interval; OR = odds ratio.
[a]Adjusted for alcohol status, smoking status, BMI, and number of general practitioner visits 1 year before BCC diagnosis.

extensively discussed in the literature, and regular dermatological examinations are an integral part of post-transplant care (Mudigonda *et al*, 2013). Evidence of a heightened susceptibility in other immunocompromised populations such as RA and IBD patients has been growing only recently, but skin cancer screening should be considered likewise in these individuals (Krathen *et al*, 2010; Long *et al*, 2011).

A plausible reason for the overrepresentation of rosacea and cutaneous malignant melanoma among BCC cases is the role of sun exposure in the pathogenesis of all three diseases, even though we cannot rule out some degree of detection and misclassification bias.

Considering the strong correlation between a history of tobacco smoking and COPD, the slightly reduced BCC risk of these patients most likely underscores the protective effect of smoking discussed above.

Similar to our observations, a few other studies also found inverse associations of non-melanoma skin cancer with diabetes mellitus, schizophrenia, and dementia. Suggested explanations include again confounding by sun exposure (possibly mediated by its role in vitamin D synthesis), detection bias, and complex biological mechanisms such as the maintenance of insulin-like growth factor-1 receptor activity (important in the response of keratinocytes to ultraviolet radiation) through exogenous insulin in diabetics (Chuang *et al*, 2005; Goldacre *et al*, 2005; White *et al*, 2013).

In conclusion, the presented IRs highlight the growing burden of BCC in the UK. Along with sun exposure, immunosuppression is an important factor in tumour pathogenesis, whereas lifestyle factors do not appear to have a major role.

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CONFLICT OF INTEREST

CS was associated with Spirig Pharma Ltd, Egerkingen, Switzerland. He is a consultant to Galderma SA, Lausanne, Switzerland.

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