Nationwide Incidence of Metastatic Cutaneous Squamous Cell Carcinoma in England

Venables, Zoë C.; Autier, Philippe; Nijsten, Tamar; Wong, Kwok F.; Langan, Sinéad M.; Rous, Brian

Published in:
JAMA Dermatology

DOI:
10.1001/jamadermatol.2018.4219

Publication date:
2018

Document Version
Peer reviewed version

Title

Nationwide incidence of metastatic cutaneous squamous cell carcinoma in England

Authors

Corresponding author: Zoë C Venables, MBChB, Public Health England National Cancer Registration and Analysis Service, Public Health England, Wellington House, London, SE1 8UG zoe.venables@phe.gov.uk, 07765258297

Philippe Autier, PhD, philippe.autier@i-pri.org, International Prevention Research Institute, Lyon, France.

Tamar Nijsten, PhD, t.nijsten@erasmusmc.nl, Erasmus MC, University Medical Center, Department of Dermatology P.O. Box 2040. Rotterdam Netherlands 3000 CA

Kwok F Wong, PhD, Kwok.Wong@phe.gov.uk, National Cancer Registration and Analysis Service, Public Health England, National Cancer Registration and Analysis Service, Public Health England, Wellington House, London

Sinéad M Langan, PhD, Sinead.Langan@LSHTM.ac.uk, London School of Hygiene and Tropical Medicine

Brian Rous, MD, Brian.Rous@phe.gov.uk, National Cancer Registration and Analysis Service, Public Health England, National Cancer Registration and Analysis Service, Public Health England, Wellington House, London

John Broggio, BsC, John.Broggio@phe.gov.uk, National Cancer Registration and Analysis Service, Public Health England, National Cancer Registration and Analysis Service, Public Health England, Wellington House, London

Catherine Harwood, PhD, catherine.harwood@bartshealth.nhs.uk, Blizard institute, Barts and the London School of Medicine and Dentistry

Katherine Henson, PhD, Katherine.Henson@phe.gov.uk, National Cancer Registration and Analysis Service, Public Health England, National Cancer Registration and Analysis Service, Public Health England, Wellington House, London

Charlotte M. Proby, FRCP, C.Proby@dundee.ac.uk, School of Medicine, University of Dundee, Scotland.

Jem Rashbass, MBBS , Jem.Rashbass@phe.gov.uk, National Cancer Registration and Analysis Service, Public Health England, National Cancer Registration and Analysis Service, Public Health England, Wellington House, London

Irene M Leigh, CBE, I.M.Leigh@dundee.ac.uk, Barts and The London School of Medicine and Dentistry

Date of revision: 7/9/18Abstract word count: 302/350

Word Count: 3107/3000

Figures/Tables 6/5 (see below)

References 24

Figure 1. Flowchart of patient cohorts from the National Cancer Registration and Analysis Service, England 2013-2015. – NB this figure could be removed as over the figure/tables limit but we believe it aids understanding of the data.

Figure 2 Risk of occurrence of metastatic cSCC in patients diagnosed with primary cSCC 2013-2015. a. by sex c. by immunosuppression prior to primary diagnosis in b. men and c. women

Table 1. Patient demographics of first registered cSCC and metastatic cSCC in England 2013-2015 – univariate analysis.

Table 2 Summary of metastatic cSCC chronology

Table 3 Site specific risk of cSCC metastasis

Table 4 Risk of metastasis and risk of death in cSCC patients 2013-2015

Key points 88/100

Question: What is the national incidence of cutaneous and metastatic cutaneous squamous cell carcinoma in England?

Findings: In this national population-based study, the age-standardised rates for the first registered cutaneous SCC in England from 2013 through 2015 were 77.3 per 100,000 person-years (95% CI, 76.6-78.0) in males and 34.1 per 100,000 person-years (95% CI, 33.7-34.5) in females. After maximum follow-up of 36 months, 1.1% of women and 2.4% of men with a cutaneous SCC developed metastatic cutaneous SCC.

Meaning: These data are essential for informing future healthcare planning and evaluating skin cancer prevention policies.

Abstract:

Importance

Cutaneous squamous cell carcinoma (cSCC) is the commonest skin cancer with metastatic potential yet epidemiological data are poor. Changes to the National Cancer Registration and Analysis Service (NCRAS) in England have allowed more accurate data analysis of primary and metastatic cSCC since 2013.

Objective

We propose to assess the national incidence of cSCC and metastatic cSCC (mcSCC) in England 2013-2015.

Design

A cohort of patients with cSCC and mcSCC in England between 2013 and 2015 were identified

Setting

This is a national population based study

Participants

Patients were identified using diagnostic codes derived from pathology reports in NCRAS.

Main outcomes and measures

Incidence rates across sex and risk factors for cSCC were derived from these data. Risk of occurrence of mcSCC among the cSCC population was assessed with Cox regression analysis to determine predictors of mcSCC.

Results

Age standardised rate for the first registered cSCC in England between 2013 and 2015 were 77.3 per 100,000 person-years (PY) (95% confidence interval (CI) 76.6-78.0) in males and 34.1 per 100,000 PY (CI) 33.7-34.5) in females. Increased incidence of cSCC was associated with older age, male sex, white ethnicity and lower deprivation quintiles. After a maximum follow-up of 36 months, 1.1% of women and 2.4% of men with a primary cSCC developed mcSCC. Significant increases in the risk of metastasis with adjusted hazard rates of approximately 2.0 were observed in patients who were over 70 years, male, immunosuppressed and in higher deprivation quintiles. Primary cSCC located on the ear and lip were at highest risk of metastasis.

Conclusion and Relevance

This study presents the first ever national study of the incidence of mcSCC. With limited healthcare resources and an ageing population, accurate epidemiological data are essential for informing future healthcare planning, identification of high-risk patients and evaluating skin cancer prevention policies.

103

Introduction

Keratinocyte cancers include basal cell carcinoma and cutaneous squamous cell carcinoma (cSCC), they are the most common cancer in people of European ancestry: cSCCs represent only 20% of all keratinocyte cancers,[1] but owing to the risk of metastatic cSCC (mcSCC), cSCC represents the most common cause of mortality due to keratinocyte cancers.[2]

Epidemiological data on keratinocyte cancers have historically been of poor quality. Most cancer registries do not register keratinocyte cancers owing to their high volume and the complexity of accurately registering multiple tumors per patient.[3-5] Hence, estimates of cSCC incidence often rely upon population surveys or medical claims data.[6-9] Despite this lack of data, evidence suggests that incidence rates of cSCC are increasing rapidly worldwide in light-skinned populations.[5]

Regarding mcSCC, epidemiological data are rare, generally restricted to studies including at best several hundred patients with cSCC or small series of high-risk patients such as organ transplant recipients.[10, 11] The absence of nationwide good quality registration of cSCC and mcSCC hampers the planning and evaluation of prevention, staging, as well as the assessment of treatment cost-efficiency.[6] Moreover, therapeutic options for mcSCC are limited with minimal progress being made.

Changes in cancer registration processes in England in 2013, including the introduction of nationalised and automated cSCC registration, has enabled the creation of a population-based nationwide dataset specific for cSCC and mcSCC that is unique in the world.[2, 5, 7, 12, 13] The objective of this study was to report incidence for cSCC and mcSCC in England from the National Cancer Registration and Analysis Service (NCRAS) data.

Methods:

Study design, setting and participants

Cutaneous SCC

Data for this cohort of patients with cSCC and mcSCC in England were provided by the NCRAS (January 1, 2013, through December 31, 2015). National Health Service pathology laboratories are required and all private pathology laboratories in England are recommended to submit all pathology reports of cancer to the NCRAS. These pathology reports are enhanced with information from the Patient Administration System and Cancer Outcomes and Services Dataset to create a cancer record. No ethical approval or informed consent for this study was required; data are collected and reported by cancer registries using the statutory power provided by section 251 of the National Health Service Act 2006.[14]

Cutaneous SCCs were identified using the ICD-10 (International Classification of Diseases) topographical code C44 and ICD-02 morphology codes 8050-8052, 8070-8078, 8082- 8084 and ICD-02 behaviour code 3 (malignant). In-situ cSCC, Bowen's disease, mucosal and genital cSCC were excluded. The date of the pathology sample was interpreted as the date of diagnosis. Prior to 2013, cSCC registry data collection is less complete and was therefore not used.

Patients with nodal or distant mcSCC between 2013 and 2015 were identified from the above mentioned group of 93,890 patients diagnosed with a cSCC in 2013-2015 based on the following selection criteria:

1. Searching for keywords - review of all patients where the pathology reports included words such as metastatic, metastasis, FNA, fine needle, dissection, parotid, core biopsy, node biopsy, trucut©, needle aspirate, lymph node.
2. COSD staging data – review of all patients where American Joint Committee on Cancer 7 staging reported as N>0 or M>0.[11]
3. HES (Hospital Episode Statistics) operation code data - review of all patients who have hospital operation codes for undergoing lymph node biopsies and dissections operations during 2013-2015 (Office of Population Censuses and Surveys Classification of Interventions and Procedures Edition 4 codes 'T8' or 'Y20'),
4. Mortality data from the Office for National Statistics – review of all patients reported to have died from non-melanoma skin cancers - during 2013-2015

In addition, a review was done of 1,859 patients' pathology reports where ICD-10 codes C07 (malignant parotid neoplasm), C08 (malignant salivary glands neoplasm), C76-80 (Malignant neoplasms of ill-defined, secondary and unspecified sites) or ICD-02 behaviour code 6 (metastatic) were used to identify possible mcSCC. This resulted in 1,566 confirmed cases of mcSCC following review of 6,168 patient's registry data.

All mcSCC were histologically confirmed based upon the information provided in the pathology report (clinical and pathology information), topography, lymphatic drainage of primary and lack of presence of other potential primary cancers, with the exception of one patient who had radiologically confirmed mcSCC documented on the pathology report. All mcSCC cases were reviewed by a dermatologist +/- consultant pathologist. Where there were multiple potential primary cSCCs, the primary site was chosen based upon clinical judgement using the above information as well as the time from primary to metastasis. Only nodal and distant metastases were included in the study due to the complexity in confirming 'in transit' metastases vs recurrence of primary. mcSCCs of unknown origin or potentially from other primary sources were excluded, as were patients who developed a recurrence of mcSCC between 2013-2015 where metastasis was originally diagnosed prior to 2013. Where the primary tumour pathology report was missing (n=64/1,566), the date and site was assumed based upon clinical information provided on the

pathology report from the metastasis, historically registered tumours at NCRAS (with pathology reports no longer available) and operation codes from HES with diagnosis ICD-10 code C44. Following this, the presumed primary pathology date was not available for only 1% patients (n=19/1566).

Variables

Patient demographics including age, sex and ethnicity were analysed from NCRAS. Deprivation quintiles were calculated using the patients' Lower Super Output Area at diagnosis linked to the Index of Multiple Deprivation (IMD) 2015. The IMD 2015 is based upon socially similar (assessed through housing type) geographical units of on average 1500 residents in England. There are 32844 units in England. For each unit, an index is calculated based upon the following: income; employment; education, skills and training; health deprivation and disability; crime; barriers to housing and services and living environment.[15]

Ethnicity was self-reported and coded in PAS. To assess for immunosuppression, registry data and HES were analysed for diagnosis or operation codes relating to haematological malignancy, HIV or solid organ transplantation prior to the date of primary tumour diagnosis.

Sensitivity Analysis

To assess the sensitivity of identifying mcSCC, 1,260 randomly selected patients with primary cSCC from 2013 to 2015 were randomly selected from an Excel spreadsheet (version 2010; Microsoft Corp) using the random number generator. Review of the patient's pathology reports by a dermatologist (Z.C.V.) found no further mcSCC.

Statistical analysis:

Data were analysed from March 1, 2017, through March 1, 2018. The NCRAS data were extracted using an SQL Developer environment (version 4.1.5.21; Oracle). We used Stata software (version 14; Stata Corp) was used for statistical analyses.

Age standardised incidence rates were computed using the 2013 European Standard Population and reported per 100,000 person-years (PY).

The time to metastasis was defined as the interval between the date of 1st cSCC diagnosis during 2013-2015 to the date of diagnosis of metastasis (with a minimum of 1 day). The survival of mcSCC patients began from the date of metastasis diagnosis.

The cumulative risk of mcSCC occurrence and mortality during the 2013-2015 study period was determined using Kaplan-Meier method. Metastatic cSCC in which the tumor identified as the primary source occurred prior to 2013 was excluded from risk of occurrence and Cox proportional hazards regression analysis models. In these models, patient's follow-up started from the date of the first cSCC during the 2013-

2015 study period and ended when they died or were lost to or unavailable for follow-up. Patients were followed up until December 31, 2016, for vital status and December 31, 2015, for metastasis risk. Total number of patients with cSCC lost to follow-up were 5,665 (6.0%) which represents patients who have left the country or for whom vital status could not be confirmed on NHS digital files at the end of follow-up.

Risk factors included in multivariate analysis included age, sex, site of the primary tumor, deprivation quintile, and immunosuppression. For the risk of death, the presence of mcSCC was considered in two complementary ways: one model with a binomial variable for absence or presence of mcSCC, and one model with the absence of mcSCC and, when a mcSCC was present, the likely primary cSCC from which the mcSCC arose. Results were expressed as hazard ratios (HR) with Confidence Intervals (CI) for time to outcomes. Bi-directional p-values less than 0.05 and 95% confidence intervals of HRs not including 1.0 were deemed statistically significant.

Results

Cutaneous SCC

In 2013 through 2015, 93 890 patients living in England were diagnosed with a cSCC. Of these, 76 977 (82%) had a first registered primary cSCC (62.7% male and 37.3%

243 female; median age, 80 years, [interquartile range (IQR) 72-86 years] representing
244 age-standardized rates of 77.3 per 100,000 PY in males and 34.1 per 100,000 PY in
245 females, (eFigure in the supplement). The remaining 16 913 (18%) patients with
246 cSCC had a diagnosis of first primary cSCC before 2013 and at least one subsequent
247 cSCC from 2013 through 2015.

248 The median age of onset for the first primary cSCC was 78 and 80 years in men and
249 women, respectively (**Table 1**). Primary cSCCs occurred predominantly in patients
250 aged 70 years and over (78.8%) and those from white ethnic groups (89%). The
251 incidence of first primary cSCC significantly increased from the most (10.6%) to the
252 least (26.7%) deprived quintiles of the population. Compared with women, men had

253 cSCC considerably more frequently on the ears (15.8% vs 1.3%) and scalp and neck
254 (24% vs 5.8%). In contrast, cSCCs were more numerous on the lower limbs of women
255 (21.5% vs 4.9%).

256

257 <u>Metastatic cSCC</u>

258 In 2013 through 2015, a total of 1,566 patients living in England had a first diagnosis
259 of mcSCC. The median age at diagnosis was 80 years (IQR, 72-86 years) in male
260 patients and 84 (IQR, 75-88 years) in females, (Table 1). Of the 1,566 patients with a
261 first mcSCC, the primary cSCC was diagnosed before 2013 for 471 (30.1%) patients
262 and in 2013 through 2015 for 1,076 (68.7%) patients (**Table 2**). When the cSCC was

diagnosed in 2013 through 2015, the origin of the mcSCC was the first registered primary cSCC in 836 patients and a non-first primary cSCC for 240 patients. For 19 patients with mcSCC (1.2%), the date of primary cSCC diagnosis was unknown. Most mcSCCs (1335 [85.2%]) were diagnosed within 2 years of the primary cSCC. In a minority (102 [6.5%]), the detection of mcSCC preceded or was made at the time of the diagnosis of the primary cSCC. The site of mcSCC was the head and neck lymph nodes or parotid for 1152 patients with mcSCC (73.6%). After excluding mcSCC in which the presumed primary source of mcSCC occurred before 2013, the cumulative risk of occurrence of mcSCC was 2.1%, (1.1% in women and 2.4% in men) in 2013 through 2015 after a median follow-up of 15.2 months (range 0-36 months) (**Figure**).

The male to female ratio of mcSCC site distribution was consistent with the ratio found for the site distribution of cSCCs except for the eyelid (1.3 and 6.3, respectively), a result that could be due to the small number of mcSCCs associated with that site. In both sexes, the rates of mcSCC were highest for cSCC diagnosed on the ear (crude risk, 1.67 and 2.05, respectively) and the lip (crude risk, 1.67 and 2.05, respectively), plus the eyelid in men (crude risk, 1.89). The mcSCC rates were greater in men for all body sites except for the scalp, neck and ears, where rates were similar in both sexes, suggesting that the likelihood of mcSCC from cSCC diagnosed on these sites are the same in both sexes. (**Table 3**) There was no association between deprivation and the site from which mcSCC arose (data not shown). Overall, the rate

283 of mcSCC per 1000 cSCC patients was 13.9 in men, and 7.0 in women, giving a risk
284 1.98 (95% CI: 1.72-2.29) times greater in men than in women.

285 The risk of mcSCC was highest in patients who were aged 80 to 89 years (HR, 1.23;
286 95% CI, 1.07-1.43) and 90 years or older (HR, 1.35; 95% CI, 1.09-1.66), male (HR, 1.79;
287 95% CI, 1.52-2.10), and within the highest level of deprivation (HR, 1.64; 95% CI,
288 1.35-2.0), who had cSCC on lip (HR, 1.85; 95% CI, 1.29-2.63), eyelid (HR, 1.54; 95% CI,
289 1.0-2.38), and ear (HR, 1.70; 95% CI, 1.42-2.03), and with immunosuppression (HR,
290 1.99; 95% CI, 1.64-2.42) (**Table 4**). Restricting the analyses to the 76 977 patients with
291 first primary cSCC obtained did not change conclusions.

292

293 Survival of cSCC

294 Until end of 2016, 13 453 deaths from all causes were observed among the 76 977
295 patients diagnosed with a first primary cSCC in 2013 through 2015. The 3-year
296 survival was 65% among men and 68% among women. In the 836 patients who
297 subsequently developed a mcSCC, the 3-year survival was 46% in men and 29% in
298 women. Comparatively, expected 3-year survival of an 80 year old England in 2013
299 through 2015 would be 76% in men and 82% in women.[16]

300 Multivariate Cox proportional hazards regression analyses examined the influence
301 of factors on the risk of mcSCC and of death from all causes among the 93 890
302 patients with cSCC (**Table 4**).

The risk of short-term death from all causes was highest in age bands 80 to 89 years (HR, 2.51; 95% CI, 2.39-2.64), and 90 years or older (HR, 5.62; 95% CI, 5.32-5.93), those with a diagnosis of mcSCC (HR, 2.44; 95% CI, 2.21-2.67), and those with the highest level of deprivation (HR, 1.40; 95% CI, 1.31-1.49). The occurrence of mcSCC and a history of immunosuppression were associated with a 2-fold short-term increase in risk of death (HR, 2.14; 95% CI, 2.01-2.28) (**Table 4**). Again, restricting the analyses to the 76 977 patients with first primary cSCC obtained did not change conclusions.

Discussion

To our knowledge, this study has resulted in the first national incidence report of mcSCC in light-skinned populations owing to the modernisation of national English cancer registration data collection and the largest ever cohort of mcSCC studied. A UK Translational Research Network in Dermatology electronic DELPHI exercise to assess the research needs of health care professionals in the UK,[17] identified cSCC as a research priority because of the limited research progress over the years. These observational data form the basis for evaluating prevention and early detection efforts, planning health care activities, and determining the characteristics of cSCC patients more likely to develop mcSCC.

Study strengths

The main strength of this study relates to the use of a novel data source consolidating national databases since 2013. Before 2013, cancer registration was done at regional level. Moreover, the national database became automated for all KC, which allows more complete data collection. Indeed, the manual registration of all cancers meant that KCs were often neglected because these cancers were not a priority for registration data. In addition, the national automated registry has greatly facilitated the retrieval of pathology reports, which led to exhaustive identification of patients with mcSCC.

Cutaneous SCC

The age-standardized rate of first primary cSCC was 55.7 per 100,000 PY in 2013 through 2015. In the systematic review of Lomas et al., ASR of cSCC in England for the period 2000-2006 ranged from 18.4 to 33.0 per 100,000 PY. If the substantial differences in incidence were due to increases over time, then an annual increase of about 7% would be assumed.[5] Improvements in data collection and registration may account for some of the difference in incidence rates.

cSCC primary sites differ between men and women, presumably due to varying exposure to UV radiation provided as a result of male pattern baldness and cultural preferences i.e. shorter hair for men and women wearing dresses/skirts. This results in men being more likely to develop cSCC on the ear and scalp, and women more likely on lower limb. However the commonest site in men and women for cSCC remain the face.

Similar to previous studies, we show that cSCC are significantly associated with lower deprivation quintiles.[18] This is likely to be in part the result of the expense of foreign travel and therefore higher cumulative UV exposure in the generations affected.

Metastatic cSCC

During a median follow up of 15.2 months, 1.1% of females and 2.4% males developed mcSCC (2.1% overall). This is in line with previous observations in a single centre study (4% during median of 43 months) and a small UK population based study (1.6% during median follow up of 79 months).[10] The lower incidence in the population based study may be due to lower capture rates emphasizing the importance of a national cancer registry.

When including all patients diagnosed with mcSCC 2013-2015 (i.e. including primary tumours prior to 2013), we found that 93% of cSCC which metastasized did so within 3 years of the primary cSCC diagnosis, as shown in previous studies.[19]

In contrast to cSCC incidence, the risk of mcSCC and death is highest in the most deprived quintile. This survival 'deprivation gap'[18] where, despite the tumours being more common in the least deprived patients, mortality is highest in the most deprived quintiles, possibly reflecting healthcare and education inequalities.

The propensity of cSCC to metastasize is greater in men than in women for all anatomical sites, except the ear, scalp, neck and upper limb. Lip and ear lesions have frequently been found to be higher risk tumours in previous studies.[19-21] It is unclear whether lip lesions may result from additional risk factors other than cumulative UV radiation such as smoking, alcohol intake or human papillomavirus infection which could account for its more aggressive behaviour.[22] The apparent gender contrast in metastatic rate that we have found may warrant further investigation.

Implications on future policy and practice

Increasing cSCC incidence is presumed to result from an ageing population and increased cumulative UV radiation exposure resulting from easier access to travel abroad and tanning trends. Due to their frequency, the healthcare burden of cSCC is substantial, with high risk patients requiring at least 2-5 years clinical follow-up after treatment and patients often developing multiple tumours.[23] With poor 3-year

survival once cSCC has metastasized, earlier identification of these high risk patients and improved treatment options become clear priorities.

Limitations

Our study was limited to three years and did not identify patients with multiple cSCC in 2013-2015. The 5-year risk of a subsequent cSCC is estimated to be 37%.[24] Previous studies have shown that when counting all KCs as opposed to the first registered tumour, an additional 30-50% tumours are counted.[25,26] Identification of patients living in England with more than one primary cSCC in 2013-2015 would have required the review of medical files for nearly 100,000 patients. With more complete registration of KC from 2013 onwards, the number of first cSCC may be overestimated, where patients may have had previous cSCC not previously registered.

Primary cSCC affecting perianal sites have a different pathophysiology, with human papillomavirus infection thought to be a pivotal cause rather than cumulative UV radiation.[27] Unfortunately we were unable to identify perianal tumours from the laboratory coding which categorises perianal tumours as 'truncal', however this should represent a minority of truncal cSCC.[27]

The estimation of mcSCC occurrences may be underestimated. There is no ICD-10 code specific to mcSCC. Hence, analysis of several different data sources as well as

clinical interpretation of pathology reports was required. Clinical information was limited to that written on the pathology report by the clinician and pathologist, as well as linked data from hospital (COSD, HES) datasets. Moreover, reliance upon histological data means that cSCCs and mcSCC managed without histological confirmation are excluded which may exclude older, frailer patients.

Immunosuppression is likely to have been underestimated due to reliance upon hospital diagnosis and operation coding. Also, causes of immunosuppression such as long-term treatment with immunosuppressive drugs and anti-cancer immunotherapies, were not captured.

Conclusions

Although only a small proportion of cSCC develop mcSCC, the high mortality of mcSCC results in a majority of cSCC patients undergoing close clinical surveillance for many years. Due to the high frequency of cSCC, this has a large impact on health care services. The availability of a nation-wide population-based cancer registration allows the capture of all patients diagnosed with a cSCC or mcSCC in England, an epidemiological tool likely to greatly enhance interpretation of the quality and cost-efficiency of preventive, screening, staging, and treatment activities.

Acknowledgements

Data for this study is based on patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE). SML is supported by a Wellcome Senior Clinical fellowship in Science (205039/Z/16/Z). ZCV is supported by the British Association of Dermatologists and Genetic Medicine informatics fellowship.

Author Contributions: Dr(s) Venables, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Venables, Harwood, Proby, Leigh, Rashbass, Autier, Langan.

Acquisition, analysis, and interpretation of data: Venables, Wong, Broggio, Rous

Drafting of the manuscript: Venables, Autier, Nijsten

Critical revision of the manuscript for important intellectual content: Autier, Rashbass, Leigh, Harwood, Proby, Henson, Langan

Statistical analysis: Wong, Autier

Obtained funding: Venables – BADGEM informatics fellowship, Langan – Wellcome trust

Administrative, technical, or material support: N/A

Study supervision: Leigh, Autier, Nijsten, Rashbass

Financial disclosure should be divided as follows:

- Relationships relevant to this manuscript
- All other relationships

Funding/Support: This study was supported in part by BADGEM, Wellcome trust.

Funding/Sponsor was involved?

Design and conduct of the study No

Collection, management, analysis and interpretation of data No

Preparation, review, or approval of the manuscript No

Decision to submit the manuscript for publication No

References:

1. Burton KA, Ashack KA, Khachemoune A. Cutaneous Squamous Cell Carcinoma: A Review of High-Risk and Metastatic Disease. American journal of clinical dermatology. 2016;17(5):491-508.
2. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: Increased incidence rates, but stable relative survival and mortality 1989-2008. European Journal of Cancer. 2012;48(13):2046-53.
3. Trakatelli M, Ulrich C, del Marmol V, Euvrard S, Stockfleth E, Abeni D. Epidemiology of nonmelanoma skin cancer (NMSC) in Europe: accurate and comparable data are needed for effective public health monitoring and interventions. Br J Dermatol. 2007;156 Suppl 3:1-7.
4. Diepgen TL, Mahler V. The epidemiology of skin cancer. Br J Dermatol. 2002;146 Suppl 61:1-6.
5. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012;166(5):1069-80.
6. Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(4):327-34.
7. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the us population, 2012. JAMA Dermatol. 2015;151(10):1081-6.
8. Pandeya N, Olsen CM, Whiteman DC. The incidence and multiplicity rates of keratinocyte cancers in Australia. The Medical journal of Australia. 2017;207(8):339-43.
9. Perera E, Gnaneswaran N, Staines C, Win AK, Sinclair R. Incidence and prevalence of non-melanoma skin cancer in Australia: A systematic review. The Australasian journal of dermatology. 2015;56(4):258-67.
10. Nelson TG, Ashton RE. Low incidence of metastasis and recurrence from cutaneous squamous cell carcinoma found in a UK population: Do we need to adjust our thinking on this rare but potentially fatal event? Journal of surgical oncology. 2017;116(6):783-8.
11. Farasat S, Yu SS, Neel VA, Nehal KS, Lardaro T, Mihm MC, et al. A new American Joint Committee on Cancer staging system for cutaneous squamous cell carcinoma: creation and rationale for inclusion of tumor (T) characteristics. Journal of the American Academy of Dermatology. 2011;64(6):1051-9.
12. Eisemann N, Jansen L, Castro FA, Chen T, Eberle A, Nennecke A, et al. Survival with nonmelanoma skin cancer in Germany. Br J Dermatol. 2016;174(4):778-85.
13. Dal H, Boldemann C, Lindelof B. Trends during a half century in relative squamous cell carcinoma distribution by body site in the Swedish population: Support for accumulated sun exposure as the main risk factor. The Journal of Dermatology. 2008;35(2):55-62.
14. National Health Service Act 2006 [Available from: http://www.legislation.gov.uk/ukpga/2006/41/contents.
15. Ministry of Housing UK. Index of Multiple Deprivation 2015 [Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015.
16. Office of National Statistics. National Life Tables 2016 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables.
17. Healy E, Brown SJ, Langan SM, Nicholls SG, Shams K, Reynolds NJ, et al. Identification of translational dermatology research priorities in the U.K.: results of an electronic Delphi exercise. Br J Dermatol. 2015;173(5):1191-8.
18. Doherty VR, Brewster DH, Jensen S, Gorman D. Trends in skin cancer incidence by socioeconomic position in Scotland, 1978–2004. British journal of cancer. 2010;102(11):1661-4.

503 19. Brantsch KD, Meisner C, Schönfisch B, Trilling B, Wehner-Caroli J, Röcken M, et al. Analysis of
504 risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. The
505 Lancet Oncology. 2008;9(8):713-20.
506 20. Rowe DE, Carroll RJ, Day CL, Jr. Prognostic factors for local recurrence, metastasis, and
507 survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment
508 modality selection. Journal of the American Academy of Dermatology. 1992;26(6):976-90.
509 21. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk Factors for Cutaneous
510 Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death: A Systematic Review
511 and Meta-analysis. JAMA Dermatol. 2016;152(4):419-28.
512 22. de Visscher JG, van der Waal I. Etiology of cancer of the lip. A review. International journal of
513 oral and maxillofacial surgery. 1998;27(3):199-203.
514 23. Motley RJ, Preston PW, Lawrence CMBritish Association of Dermatologist's Multi-
515 professional Guidelines for the Management of the Patient with Primary Cutaneous Squamous Cell
516 Carcinoma 2009 [updated Revision Date 12/11/09. Available from: http://www.bad.org.uk/library-
517 media%5Cdocuments%5CSCC_2009.pdf.

518 24. Flohil SC, van der Leest RJ, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous
519 malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis.
520 European journal of cancer (Oxford, England : 1990). 2013;49(10):2365-75.
521 25. de Vries E, Micallef R, Brewster DH, Gibbs JH, Flohil SC, Saksela O, et al. Population-based
522 estimates of the occurrence of multiple vs first primary basal cell carcinomas in 4 European regions.
523 Archives of dermatology. 2012;148(3):347-54.

524 26. Lucke TW, Hole DJ, Mackie RM. An audit of the completeness of non-melanoma skin cancer
525 registration in Greater Glasgow. Br J Dermatol. 1997;137(5):761-3.
526 27. Dawson H, Serra S. Tumours and inflammatory lesions of the anal canal and perianal skin
527 revisited: an update and practical approach. J Clin Pathol. 2015;68(12):971-81
528

529

530

531