European Journal of Cancer (2012) **48**, 2046–2053

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Trends of cutaneous squamous cell carcinoma in the Netherlands: Increased incidence rates, but stable relative survival and mortality 1989–2008

L.M. Hollestein [a,*], E. de Vries [a,b,c], T. Nijsten [a]

[a] *Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands*
[b] *Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands*
[c] *Eindhoven Cancer Registry, Eindhoven, The Netherlands*

Available online 16 February 2012

KEYWORDS
Cutaneous squamous cell carcinoma
Epidemiology
Incidence
Mortality
Population-based
Survival

Abstract *Background:* Incidence rates of cutaneous squamous cell carcinoma (SCC) are increasing in many countries, though detailed information is scarce.
Objectives: To describe detailed trends in incidence rates, relative survival and estimate mortality rates of SCC in the Netherlands.
Methods: Information on newly diagnosed SCC patients between 1989 and 2008 was obtained from the Netherlands Cancer Registry (NCR). Information of non-melanoma skin cancer (NMSC) mortality was obtained from Statistics Netherlands. European Standardised Rates (ESR) and Estimated Annual Percentage Change (EAPC) were calculated. Incidence rates were fitted to two different models and predicted by the best fitted model. Cohort-based and multivariate survival analyses were performed to assess changes over time.
Results: The ESR increased from 22.2 to 35.4 per 100,000 inhabitants for males and from 7.8 to 20.5 for females. The EAPC was 6.9% (95% confidence interval: 5.8–8.7) for males and 9.2% (95% CI: 7.5–11.0) for females. Incidence rates increased for all body sites, except for the lips, where a decreasing trend for males was observed. The predicted ESR in 2020 is 46.9 per 100,000 inhabitants for males and 28.7 for females. The 5-year relative survival rate was 92.0% (95% CI: 91.3–92.8) for males and 94.9% (95% CI: 94.0–95.7) for females and remained stable over time. Overall relative survival was better for females, but females with advanced disease had a 30.4 relative excess risk of dying compared to those in stage I. This difference was 9.9 for men. The estimated mortality rate decreased with –1.9% (95% CI: –3.1% to –0.7%) annually.
Conclusions: Incidence rates of SCC increased rapidly. Relative survival was high, as most SCCs were diagnosed in stage I. Nevertheless, the number of newly diagnosed patients may exceed 11,000 by 2020, emphasising the need to improve methods to prevent skin cancer.

* *Corresponding author:* Address: Department of Dermatology, Erasmus MC, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands. Tel.: +31 10 70 35 886; fax: +31 10 70 33 822.
E-mail address: l.hollestein@erasmusmc.nl (L.M. Hollestein).

0959-8049
doi:10.1016/j.ejca.2012.01.003

1. Introduction

Incidence rates of cutaneous squamous cell carcinoma (SCC) are rising in many countries.[1–5] Despite the high incidence rates, population based data on SCC incidence, survival and mortality in many countries are rather sparse. Recently, population based studies on incidence were performed in Ireland, Sweden and Denmark and demonstrated that age-standardised incidence rates are rapidly increasing with absolute increases of approximately 2000 new SCC cases annually in population of 4.5–9 million inhabitants.[1–3]

SCC and other non-melanoma skin cancers (NMSC) are not reported to cancer registries in many countries including Australia and the United States (US) and therefore incidence rates can only be estimated using other data sources. Results from a national survey in Australia in 2002 showed that 118,000 new SCC cases were diagnosed among the 21 million inhabitants.[4] According to estimates from medical claims data in the US, 2.2 million persons of the 298 million inhabitants in 2006 were treated for NMSC of which roughly 20–30% was SCC.[5]

Observational cancer registry studies are important because they provide input for a (European) keratinocytic cancer health care policy. Since the Dutch population is ageing and SCC is strongly age-dependent, this skin cancer will become more frequent. The cosmetic and functional morbidity associated with SCC is high because it often occurs on the face and is treated with surgical excision. About 5% of SCCs progresses to systemic disease for which there is no adequate therapy. Despite the straightforward treatment for early disease, but due to the very high incidence, SCC is a major public health problem and is one of the most costly cancers.[6]

The objective of this study was to describe the recent trends of SCC incidence rates and relative survival and to estimate SCC mortality rates in the general Dutch population.

2. Patients and methods

Information on newly diagnosed patients with an invasive cutaneous SCC was obtained from the nationwide Netherlands Cancer Registry (NCR), which covered the whole country by combining data from all Comprehensive Cancer Centres in the Netherlands since 1989.[7] The NCR is based on all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnosis, haematology departments and radiotherapy institutions.[7] The following morphology codes combined with topography 'skin' were considered to be invasive cutaneous SCC: 8010, 8050-8084 (excluding 8077: intraepithelial neoplasia, 8080: Erythroplasia of Queyrat, 8081: Bowen disease, 8082: lympho-epithelial carcinoma).

Patient's demographic characteristics such as gender and date of birth, and tumour characteristics such as date of diagnosis, subsite (as specified in the International Classification of Diseases for Oncology (ICD-O-3),[8] histology and stage (Tumour Lymph Node Metastasis [TNM] classification)[9] are obtained routinely from the medical records. The quality of the data is high, due to thorough training of the administrators and computerised consistency checks at regional and national levels. Completeness on cutaneous malignancies (excluding basal cell carcinomas) is estimated to be at least 92.9%.[10] Follow-up of vital status of all patients was calculated as the time from diagnosis to death or until the end of follow up on the 1st of February 2010. The information on vital status was initially obtained from municipal registries and from 1995 onwards from the nationwide population registries network. These registries provide virtually complete coverage of all Dutch citizens, including their dates of death. Information on the Dutch population size in the past and population size predictions were obtained from Statistics Netherlands (Centraal Bureau voor Statistiek [CBS]).

All patients with a first primary invasive cutaneous SCC who were diagnosed between 1st January 1989 and 31st December 2008 in the Netherlands were included ($n = 69{,}408$) (i.e. patients with multiple primary SCC were only counted once). Age was divided in three groups of equal size (<70, 70–79 and $\geqslant 80$ years). The study period was divided in four categories: 1989–1993, 1994–1998, 1999–2003, and 2004–2008 to study trends. TNM was determined postoperatively, in cases where postoperative stage was unknown clinical TNM stage was used. Stage I SCC was less than 2 cm in diameter. Stage II SCC was larger than 2 cm, stage III SCC invaded deep extradermal structures or with regional lymph node metastasis and stage IV SCC had distant metastasis.[9] Tumour localisation was categorised in the following anatomical subsites: lips (C44.0), eyelid (C44.1), ear (C44.2), face (C44.3), scalp/neck (C44.4), trunk (C44.5), arms (C44.6), legs (C44.7) and unknown (C44.8, C44.9). For the period from 1989–1994 only survival data of five regional cancer registries were available, which have been shown for other cancer types to be representative for the whole of the Netherlands.[11] In total, 2262 SCC patients (3.4% of all patients) with missing vital status were excluded from our survival analyses.

Mortality due to cutaneous SCC is not registered separately on death certificates in the Netherlands, but deaths due to NMSC (C44 of the ICD-10) are registered on death certificates. A recent study using the same data demonstrated that 91% of all NMSC associated mortality in the Netherlands is due to SCC.[12] SCC mortality rates were estimated by imputing information on NMSC deaths from Statistics Netherlands.

2.1. Statistical analyses

Annual age-standardised incidence and mortality rates (European Standardised Rates [ESR]) were calculated by using mid-year population obtained from Statistics Netherlands. The European standard population does not reflect the elderly very well and therefore crude incidence rates were calculated as well. Trends were analysed by calculating the Estimated Annual Percentage Change (EAPC) and by performing joinpoint regression analyses to identify the year in which a significant change in incidence rates occurred. Incidence rates were also calculated per sex, age group, body site and stage. One patient with unknown sex was excluded from all analyses which were stratified by sex.

To predict SCC incidence rates up to 2020 two models were fitted for predictions with a positive slope.[13,14] The fitted models were:

$$\mathrm{Ec}_{it} = n_{it}(\alpha_i + \beta_i t) \quad (1)$$

$$\mathrm{Ec}_{it} = n_{it}\alpha_i(1 + \beta t) \quad (2)$$

where Ec_{it} is the expected number of cases in age group i in the year t, n_{it} is the number of personyears in the same stratum and α_i and β are the model parameters. The first model assumes linear changes over time. The second model assumes proportional effects for different age groups and therefore within the period of prediction this model retains the age-dependent pattern of incidence rates existing in the data. Age-specific predictions can therefore be made with a greater accuracy. The second model was the best fitting model and was used for our predictions.

Five-year relative survival was calculated by traditional cohort-based analysis. Due to the very small numbers of patients diagnosed with stage IV SCC (maximal seven patients per year), stage III and IV patients were combined into one subgroup for survival analyses.

To study the possible changes in survival over time, multivariate relative survival analyses, using Poisson regression modelling, were carried out to estimate relative excess risk (RER) of dying adjusted for follow-up interval.[15] The model was fitted on the first 5 years of follow up after diagnosis. The proportional hazards assumption was tested with log minus log plots. Hazards for body site were not proportional, and numbers were too small for stratification, therefore body site was not included in the model. Exclusion of body site from the multivariate model had only a small effect on the RER estimates and did not change the results substantially. We ran separate models for males and females, because sex was an independent prognostic factor ($p < 0.01$) in a multivariate analysis and we felt it important to present sex-specific estimates.

The number of avoidable deaths represented the difference between the observed number of excess deaths and the expected number of excess deaths and was calculated by using the following formula: $(1\text{-relative survival}_{\text{stageIII/IV}}) * N_{\text{stageIII/IV}} - (1\text{-relative survival}_{\text{stageI}}) * N_{\text{stageIII/IV}}$ where N represents the number of diagnosed patients.

Statistical analyses were performed with SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA), SAS 9.2 statistical software (SAS Institute Inc., Cary, NC, USA) and Joinpoint version 3.4.3 (National Cancer Institute, http://surveillance.cancer.gov/joinpoint). All statistical tests were two-sided and considered significant at the $p < 0.05$ level.

3. Results

3.1. Incidence

In total, 69,408 patients were diagnosed with primary invasive SCC during the 20-year study period. The Dutch population size increased from 14.8 million in 1989 to 16.4 million inhabitants in 2008. The absolute annual number of SCC patients increased from 2247 in 1989 to 6158 in 2008. In males, the crude incidence rate doubled between 1989 and 2008 from 20.0 to 42.5 per 100,000 inhabitants. The age-standardised incidence rate (ESR) increased from 22.2 per 100,000 inhabitants in 1989 to 35.4 per 100,000 inhabitants in 2008. Crude incidence rates for females increased from 10.4 in 1989 to 32.5 per 100,000 inhabitants in 2008. The age-standardised incidence rates increased from 7.8 to 20.5 per 100,000 inhabitants. In Table 1, age-standardised incidence rates of SCC are provided by sex, period of diagnosis, age group, body site and TNM stage. Incidence rates were increasing for almost all subgroups. The face was the most affected body site for both sexes and SCCs on the ear, neck or scalp were much more frequent in males than females (Fig. 1). Of all SCCs, 73% was diagnosed in stage I. The incidence rates of SCC of the skin increased exponentially with age starting at the age of 50 (Table 1, Fig. 2). The age-specific incidence rates increased with each study period with the largest increment during the most recent period (Fig. 2). Incidence rates that were previously observed among the 85+ population were already observed in an almost 10 year younger population between 2004 and 2008. Joinpoint analyses showed an accelerated increase in incidence rates since 2002 with an EAPC of 9.2% (95% confidence interval: 7.5–11.0) for females and an EAPC of 6.9% (95% CI: 5.8–8.7) for males since 2003 (Fig. 3). Predictions showed expected increases of up to 11,827 newly diagnosed SCC patients per year in 2020 compared to 6158 in 2008 (Table 2), corresponding with predicted age-standardised incidence rates (ESR) of 49.7 per 100,000 inhabitants for males and 29.8 per 100,000 inhabitants for females.

3.2. Survival

The 5-year relative survival over the entire study period was 92.0% (95% CI: 91.3–92.8) for males and

Table 1
Numbers, age-standardised incidence rates (ESR) and 5-year relative survival of cutaneous squamous cell carcinoma (SCC) in the Netherlands.

	Males							Females						
	ESR[a]					5-Year relative survival[b]		ESR[a]					5-Year relative survival[b]	
	N	1989–1993	1994–1998	1999–2003	2004–2008	Relative survival	95% CI	*N*	1989–1993	1994–1998	1999–2003	2004–2008	Relative survival	95% CI
Overall	41,556	22.2	24.4	25.3	32.4	92	(91–93)	27,851	8.1	10.0	11.8	17.2	95	(94–96)
Age (years)														
<70	14,160	9.1	9.6	9.4	11.5	92	(92–93)	8206	3.6	4.6	5.5	8.1	95	(95–96)
70–79	15,220	149	171	175	226	90	(88–91)	7987	47	58	67	100	94	(93–95)
⩾80	12,176	314	347	390	520	95	(93–98)	11658	119	141	167	231	95	(93–98)
Body site														
Lips	1641	1.4	1.1	0.9	0.9	95	(92–98)	817	0.3	0.4	0.4	0.5	99	(94–103)
Eyelid	552	0.4	0.3	0.4	0.3	94	(88–100)	461	0.2	0.2	0.2	0.3	102	(96–107)
Ear	8257	5.1	5.3	5.0	5.6	93	(91–95)	553	0.2	0.2	0.2	0.3	93	(86–99)
Face	15,125	7.8	8.8	9.4	11.9	93	(92–94)	13463	4.0	4.8	5.3	7.3	95	(94–97)
Scalp/neck	6271	2.7	3.4	3.8	5.6	89	(87–91)	1317	0.4	0.5	0.5	0.8	90	(85–94)
Trunk	2107	0.7	1.0	1.3	2.0	90	(87–92)	2184	0.5	0.8	1.1	1.9	90	(88–93)
Arms	5692	3.2	3.6	3.2	4.3	91	(89–93)	5107	1.5	1.8	2.2	3.4	95	(94–97)
Legs	1423	0.6	0.7	0.9	1.3	95	(92–99)	3628	0.8	1.3	1.8	2.6	95	(93–97)
Unknown	488	0.2	0.2	0.3	0.5	92	(86–99)	321	0.1	0.1	0.1	0.2	95	(88–103)
Stage														
I	30,161	14.8	16.4	17.9	25.7	95	(94–95)	20,682	5.3	6.8	8.7	14.2	98	(97–99)
II	3447	1.9	2.0	2.2	2.7	76	(73–79)	2014	0.6	0.6	0.8	1.0	76	(72–80)
III	595	0.4	0.4	0.4	0.4	62	(56–68)[c]	296	0.1	0.1	0.1	0.1	46	(38–53)[c]
IV	47	0.0	0.0	0.0	0.0	62	(56–68)[c]	35	0.0	0.0	0.0	0.0	46	(38–53)[c]
Unknown	7306	5.0	5.5	4.7	3.7	91	(89–93)	4824	2.0	2.3	2.1	1.9	93	(91–95)

Abbreviations: CI, confidence interval; ESR, European Standardised Rate; *N*, number of cases.
[a] ESR per 100,000 person years.
[b] Relative survival in %.
[c] Stage III and IV were combined in the survival analyses due to small subgroups.

94.9% (95% CI: 94.0–95.7) for females (Table 1). The 5-year relative survival by sex, age group, body site and stage is shown in Table 1. No changes over time were observed (data not shown). Females diagnosed with a stage III or IV SCC had a significantly worse prognosis compared to males (relative survival of 46% versus 62%, $p < 0.001$). This combined stage III/IV group consisted of 7.2% and 11.1% stage IV SCC in males and females, respectively.

The relative survival of males with a SCC on the scalp or neck (88.9%, 95% CI: 86.7–91.0) was significantly lower than that of SCC on lip and ear (95.2%, 95% CI: 92.1–98.2 and 92.9%, 95% CI: 91.1–94.7, respectively).

To study possible changes in relative survival over time, multivariate regression analyses on relative survival were carried out (Table 3). Strikingly, the adjusted RER of dying among female SCC patients diagnosed with a stage III or IV SCC was 30.4 times increased compared to those in stage I. For males with stage III/IV SCC, this risk was 9.9-fold higher.

To translate this result to absolute differences, the number of 'avoidable deaths' over a period of 5 years after diagnosis was calculated. If these patients would have been diagnosed earlier with a stage I SCC, 143 deaths could have been avoided (84 avoidable deaths per 100 SCC deaths) of the 315 female patients who were diagnosed with a stage III/IV SCC during the study period. In the same situation, 203 deaths of the 621 males that were diagnosed with a stage III/IV SCC could have been avoided resulting in 86 avoidable deaths per 100 SCC deaths.

3.3. Mortality

During the 20-year study period, 1513 patients died due to NMSC. The crude mortality rate of NMSC remained 0.5 per 100,000 person-years between 1989 and 2008, whereas age-standardised mortality rates decreased slightly from 0.5 per 100,000 person-years in 1989 to 0.4 per 100,000 person-years in 2008, with an EAPC of –1.9% (95% CI:–3.1 to –0.7).

4. Discussion

To our knowledge, this is the first study which describes detailed trends of incidence rates, relative survival and mortality rates for cutaneous SCC in the Netherlands. As more population based information on keratinocytic malignancies in Europe is needed,[16,17] this

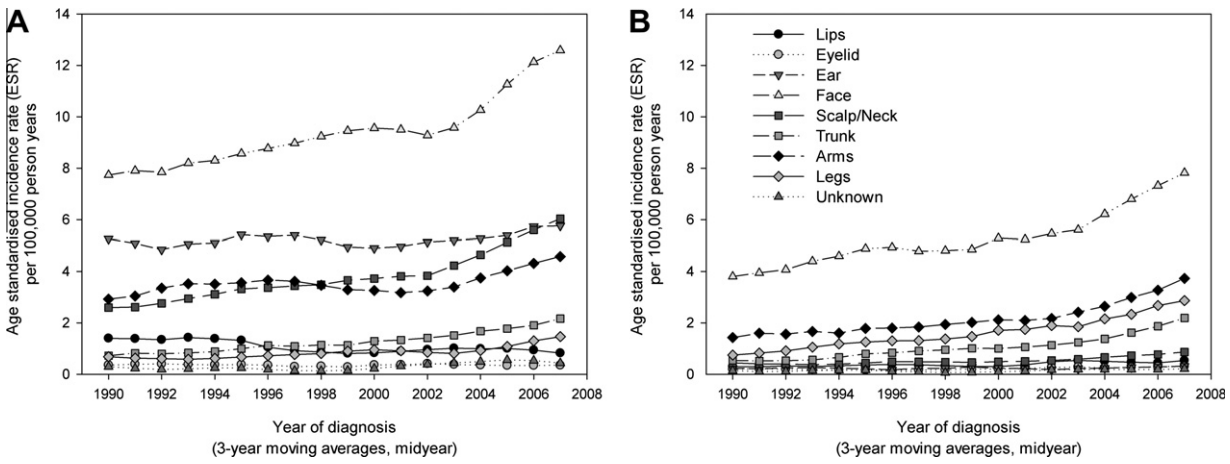

Fig. 1. Three-year moving averages of age standardised incidence rates of cutaneous squamous cell carcinoma (SCC) in the Netherlands by body site for males (A) and females (B).

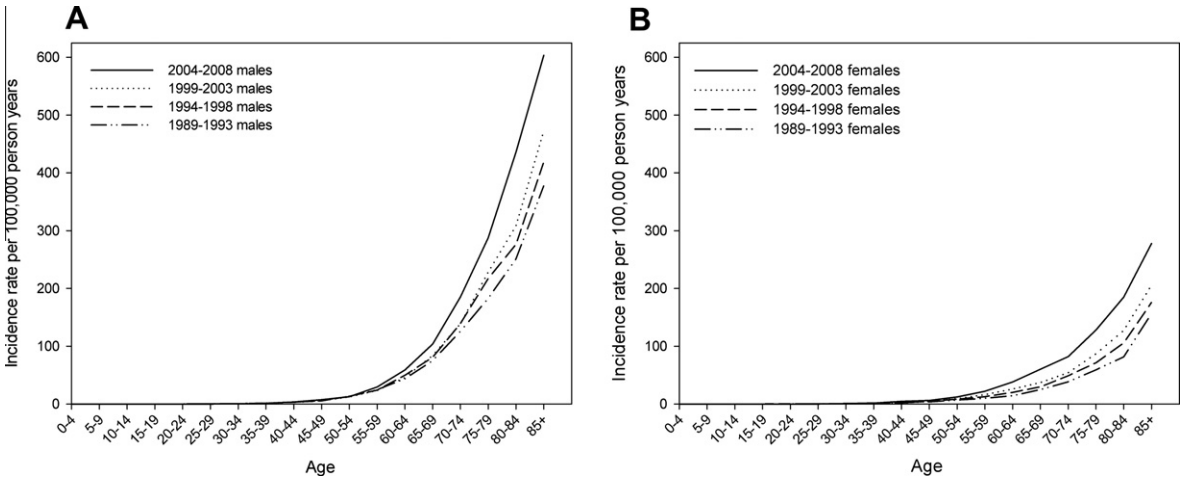

Fig. 2. Age-specific incidence rates of cutaneous squamous cell carcinoma (SCC) in the Netherlands by period of diagnosis for males (A) and females (B).

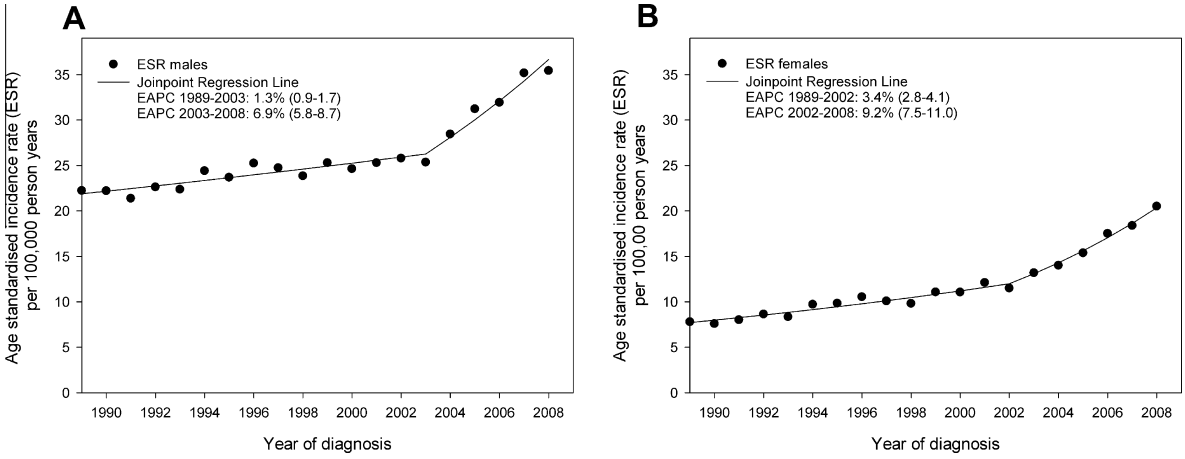

Fig. 3. Joinpoint analyses of age standardised incidence rates (European Standardised Rates) of cutaneous squamous cell carcinoma (SCC) in the Netherlands, 1989–2008 of males (A) and females (B) with Estimated Annual Percentage Change (EAPC).

Table 2
Predictions of age-standardised incidence rates and number of newly diagnosed squamous cell carcinoma (SCC) patients up to 2020.

	2008	2010		2015		2020	
	Observed	Predicted	95% PI	Predicted	95% PI	Predicted	95% PI
Males							
N	3453	3776	(3610–3942)	5177	(4916–5438)	6925	(6530–7320)
ESR	35.4	36.8	(35.2–38.4)	43.3	(41.1–45.5)	49.7	(46.9–52.2)
Females							
N	2705	2797	(2680–2913)	3761	(3620–3901)	4902	(4735–5069)
ESR	20.5	20.5	(19.6–21.4)	25.1	(24.1–26.1)	29.8	(28.7–30.9)

Abbreviations: ESR, European Standardised Rate; *N*, number of cases; PI, Prediction Interval.

study adds important information for the development of public health policies.

4.1. Incidence

Similar to observations from other countries,[2–5] age-standardised incidence rates increased rapidly: 1.5-fold for men and threefold for women between 1989 and 2008. Trends in crude rates were even stronger, but should be interpreted with caution as they are heavily influenced by ageing of the population. Relative increases in incidence were higher among females, because incidence rates at the beginning of the study were lower compared to males. The increase in absolute number of newly diagnosed patients was approximately equal for both sexes. This may be associated with an equal increase in the distribution of risk factors for both sexes.

As age-specific incidence rates also increased, ageing of the population only partly explains the observed increases. Most likely, increased number of people are reaching high levels of cumulative UV exposure, resulting in higher SCC risks. This is in line with the observation that incidence rates of other UV-related skin tumours increased more steeply than those of other skin malignancies in the Netherlands.[12,18] Holidays to sunny countries have become more affordable and popular and an increasing proportion of the retired Dutch population emigrates (temporarily during the winter) to sunny climates such as Spain, Portugal and South of France, increasing their cumulative UV exposure considerably. Also, people may spend more time outdoors during leisure activities (e.g. sports, gardening, walking and biking) compared to prior generations.

Public health campaigns (against melanoma) have primarily advocated avoidance of sunburns (especially in children) and to a lesser extent reducing cumulative UV exposure to the general population. Informing middle-aged and elderly people about the risk of (cumulative) UV exposure may be beneficial in reducing the burden of SCC. However, only informing people about the risk is not enough to change behaviour and more effective methods should be explored by health promotion researchers.

Steep increments in incidence rates were observed since 2002 for females and 2003 for males, for which there is no simple explanation. The public campaigns warning

Table 3
Multivariate analyses on relative survival of cutaneous squamous cell carcinoma (SCC).

	Males					Females				
	N	Univariate[a]		Multivariate[a]		*N*	Univariate[a]		Multivariate[a]	
		RER	95% CI	RER	95% CI		RER	95% CI	RER	95% CI
Period										
1989–1993	6353	1.00		1.00		3521	1.00		1.00	
1994–1998	8689	1.35	(0.96–1.91)	1.30	(1.04–1.63) [b]	5439	1.11	(0.69–1.78)	0.99	(0.73–1.32)
1999–2003	10,199	1.45	(1.05–2.02) [b]	1.34	(1.07–1.67) [b]	7049	0.91	(0.56–1.48)	0.95	(0.72–1.26)
2004–2008	14,897	1.08	(0.76–1.53)	1.14	(0.91–1.43)	10,998	0.71	(0.41–1.18)	0.83	(0.62–1.11)
Age (years)										
<70	13,642	1.00		1.00		7980	1.00		1.00	
70–79	14,685	1.30	(1.12–1.50)[b]	1.22	(1.06–1.41)[b]	7735	1.26	(0.99–1.61)	1.44	(1.16–1.78)[b]
⩾80	11,811	0.41	(0.20–0.82)[b]	0.91	(0.71–1.17)	11,292	1.06	(0.70–1.59)	1.32	(1.02–1.69)[b]
Stage										
I	29,303	1.0		1.0		20,204	1.0		1.0	
II	3341	6.5	(5.1–8.3)[b]	4.3	(3.6–5.1)[b]	1946	15.3	(8.9–26.2)[b]	7.7	(5.9–10.0)[b]
III + IV	621	14.1	(10.7–18.5)[b]	9.9	(8.1–12.1)[b]	315	55.1	(32.1–94.7)[b]	30.4	(23.2–39.7)[b]
Unknown	6873	2.3	(1.7–3.0)[b]	1.5	(1.2–1.9)[b]	4542	3.9	(2.2–7.1)[b]	1.9	(1.4–2.6)[b]

Abbreviations: CI, confidence interval; *N*, number of cases; RER, relative excess risk.

[a] All models are fitted on the first 5 years after diagnosis and adjusted for follow-up time of the patients.

[b] Significant.

for excessive sun exposure may in part be responsible for this increase, but a recent study showed that increased skin cancer surveillance resulted in a higher likelihood of being diagnosed with truncal BCC and not SCC suggesting that this bias has relatively little impact on our findings.[19] Another possibility is an improvement in completeness of the national cancer registration since 2002. However, in 1990 the completeness of skin malignancies (excluding basal cell carcinomas) was already 92.9%[10] and a small increase in completeness could not explain the observed increases in SCC. The increased number of solid organ transplantations and the associated immunosuppressive drug use may have contributed to the increased incidence rates as well.[20] The number of solid organ transplantations increased from 511 in 1989 to 1048 in 2008 and the total number of immunosuppressive drug users increased fourfold from 25,400 in 1994 to 101,600 users in 2008 (personal communication).[21,22] Unfortunately, in our database we are not able to identify SCC patients who had a solid organ transplantation or who were long term immunosuppressive drug users for other reasons. The increased use of biologics in immune mediated inflammatory diseases may also contribute to the increased SCC incidence in the last decade.[23,24] However, these iatrogenic risk factors would result in a more gradual increase in incidence rates and not the abrupt accelerations in incidence rates since 2002.

Incidence rates increased among almost all body sites, except for males with SCC on the lips. This pattern followed the decreasing trend of smoking among males and the increasing trend of smoking among females in the Netherlands, which is an important risk factor for developing lip cancer.[25,26] An Israeli study found a comparable pattern and observed a 40-fold higher incidence of cancer of the external lip compared to cancer of the internal lip, suggesting that the role of sun exposure is more important than smoking in causing SCC.[27]

We may have underestimated the SCC incidence rates, because we may have missed some cases due to the following reasons[16]: the number of non-hospital practices that treat SCC has increased in the last decade and not all of these private practices are affiliated to the national cancer registry. Furthermore, not all SCCs are diagnosed, especially in elderly people with multiple comorbidities where skin cancers are often not treated. Also a small proportion of SCC may be treated without histological confirmation and will therefore not be registered in the cancer statistics.[28]

4.2. Survival and mortality

Only a small proportion of all SCC patients were at high risk of dying at time of diagnosis (1.4% diagnosed in stage III/IV), but some lesions may progress after diagnosis also leading to death. It is estimated that in Europe, annually 2016 deaths are due to SCC.[29] In the Netherlands we observed a small decreasing trend in NMSC mortality, mainly caused by SCC, which is in line with studies from Finland and the United States.[30,31]

The observed 5-year relative survival rates were comparable with those observed in Denmark[32] and no significant changes over time were observed. Relative survival was better for females than for males, in contrast to relative survival of advanced disease: a third of all male patients and almost half of all female patients with advanced disease died. SCCs in the head and neck region were associated with a significantly lower relative survival. Truncal SCCs in men and women also had a negative impact on survival which may be explained by a diagnostic delay (i.e. truncal SCCs may have been missed more easily by patients and physicians).

Due to a higher prevalence of mortality risk factors (e.g. solid organ transplantation, use of immunosuppressive drugs) among SCC patients compared to the general population, we might have overestimated SCC-specific mortality, resulting in lower relative survival estimates.

Increased tumour thickness, increased horizontal size, immunosuppression and localisation on the ear and possibly the lips are known to be prognostic factors for the development of metastasis, but were not all available in the cancer registry.[33] The Dutch SCC guideline, approved in 2010, recommends recording the tumour thickness in the pathology report, which is of interest for future evaluations.[34]

4.3. Conclusion

Incidence rates of SCC increased rapidly. Overall relative survival was stable and the mortality rate due to NMSC decreased slightly during the study period. We recommend that primary prevention programmes aim to reduce the cumulative amount of UV exposure among the young and the older population. Secondary prevention programmes should encourage the elderly to recognise skin changes and to seek early diagnosis to prevent progression of the lesion.

Conflict of interest statement

None declared.

Acknowledgements

We gratefully acknowledge Rob Verhoeven and his colleagues of the Netherlands Cancer Registry for providing data and the registration clerks for the dedicated data collection. We would like to thank Dr. Senada Koljenovic for reviewing the selection of morphology codes. We also would like to thank Sten Willemsen and Gerard Borsboom for their support with the programming of

SAS. We thank Emmilia Dowlatshahi for critically reviewing the manuscript.

References

1. Carsin AE, Sharp L, Comber H. Geographical, urban/rural and socio-economic variations in nonmelanoma skin cancer incidence: a population-based study in Ireland. *Br J Dermatol* 2011;**164**(4):822–9.
2. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978–2007: rapid incidence increase among young Danish women. *Int J Cancer* 2010;**127**(9):2190–8.
3. Hussain SK, Sundquist J, Hemminki K. Incidence trends of squamous cell and rare skin cancers in the Swedish national cancer registry point to calendar year and age-dependent increases. *J Invest Dermatol* 2010;**130**(5):1323–8.
4. Staples MP, Elwood M, Burton RC, et al. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. *Med J Aust* 2006;**184**(1):6–10.
5. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol* 2010;**146**(3):283–7.
6. Housman TS, Feldman SR, Williford PM, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. *J Am Acad Dermatol* 2003;**48**(3):425–9.
7. http://www.ikcnet.nl/page.php?id=2898&nav_id=160.
8. Fritz A, Percy C, Jack A, et al. *International Classification of Diseases for Oncology (ICD-O)*. 3rd Ed. Geneva: World Health Organization; 2002.
9. Sobin LH, Wittekind Ch. *International Union Against Cancer (UICC) TNM classification of malignant tumours*. 6th ed. New York: Wiley; 2002.
10. Schouten LJ, Straatman H, Kiemeney LA, Gimbrere CH, Verbeek AL. The capture–recapture method for estimation of cancer registry completeness: a useful tool? *Int J Epidemiol* 1994;**23**(6):1111–6.
11. Elferink MA, van Steenbergen LN, Krijnen P, et al. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989–2006. *Eur J Cancer* 2010;**46**(8):1421–9.
12. Holterhues C, Vries E, Louwman MW, Koljenovic S, Nijsten T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989–2005. *J Invest Dermatol* 2010;**130**(7):1807–12.
13. Dyba T, Hakulinen T, Paivarinta L. A simple non-linear model in incidence prediction. *Stat Med* 1997;**16**(20):2297–309.
14. Dyba T, Hakulinen T. Comparison of different approaches to incidence prediction based on simple interpolation techniques. *Stat Med* 2000;**19**(13):1741–52.
15. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* 2004;**23**(1):51–64.
16. Trakatelli M, Ulrich C, del Marmol V, et al. 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.
17. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Action against Cancer: European Partnership. In. Brussels; 24 June 2009. pp. 7–8.
18. Flohil SC, de Vries E, Neumann HA, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. *Acta Derm Venereol* 2011;**91**(1):24–30.
19. Valery PC, Neale R, Williams G, et al. The effect of skin examination surveys on the incidence of basal cell carcinoma in a Queensland community sample: a 10-year longitudinal study. *J Invest Dermatol Symp Proc* 2004;**9**(2):148–51.
20. Depry JL, Reed KB, Cook-Norris RH, Brewer JD. Iatrogenic immunosuppression and cutaneous malignancy. *Clin Dermatol* 2011;**29**(6):602–13.
21. http://www.eurotransplant.org/cms/index.php?page=yearlystats.
22. http://www.gipdatabank.nl/index.asp?scherm=homepage&infoType=a.
23. Patel RV, Clark LN, Lebwohl M, Weinberg JM. Treatments for psoriasis and the risk of malignancy. *J Am Acad Dermatol* 2009;**60**(6):1001–17.
24. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomised controlled trials. *JAMA* 2006;**295**(19):2275–85.
25. Karim-Kos HE, Janssen-Heijnen ML, van Iersel CA, et al. The beginning of the end of the lung cancer epidemic in Dutch women? *Int J Cancer* 2008;**123**(6):1472–5.
26. Perea-Milla Lopez E, Minarro-Del Moral RM, Martinez-Garcia C, et al. Lifestyles, environmental and phenotypic factors associated with lip cancer: a case-control study in southern Spain. *Br J Cancer* 2003;**88**(11):1702–7.
27. Czerninski R, Zini A, Sgan-Cohen HD. Lip cancer: incidence, trends, histology and survival: 1970–2006. *Br J Dermatol* 2010;**162**(5):1103–9.
28. Morris AD, Gee BC, Emerson RM, Millard LG, Perkins W. Squamous cell carcinoma – are females missing the boat? *Br J Dermatol* 2002;**147**(Suppl. 62):3.
29. Lucas R, McMichael T, Smith W, Armstrong B. *Environmental burden of disease series, No. 13. Solar Ultraviolet Radiation. Global burden of disease from solar ultraviolet radiation*. Geneva: World Health Organization; 2006.
30. Lewis KG, Weinstock MA. Trends in nonmelanoma skin cancer mortality rates in the United States, 1969 through 2000. *J Invest Dermatol* 2007;**127**(10):2323–7.
31. Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. *Arch Dermatol* 1999;**135**(7):781–6.
32. Steding-Jessen M, Birch-Johansen F, Jensen A, et al. Socioeconomic status and non-melanoma skin cancer: a nationwide cohort study of incidence and survival in Denmark. *Cancer Epidemiol* 2010;**34**(6):689–95.
33. Brantsch KD, Meisner C, Schonfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol* 2008;**9**(8):713–20.
34. http://www.huidarts.info/documents/?v=2&id=192.