Do incident and new subsequent cases of non-melanoma skin cancer registered in a Danish prospective cohort study have different 10-year mortality?

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Abstract

Background: The Danish Gerda Frentz Cohort (GFC) was created for registering all incident and new subsequent cases of non-melanoma skin cancer (NMSC) among patients seen by Danish dermatologists in 1995. We have recently found, in this cohort, a lower 10-year mortality than in the general population in patients with basal cell carcinoma (BCC). Differences in mortality between incident and new subsequent cases, incomplete registration or selection bias may be responsible for this finding. Methods: We aimed to quantify differences in mortality between incident and new subsequent cases of NMSC in the GFC and to compare mortality among incident cases recorded in the GFC and those recorded in the Danish Cancer Registry (DCR). We followed 10,830 skin cancer patients and 106,696 age-, gender- and residence-matched population controls through 2006 and computed their cumulative mortality and mortality rate ratio (MRR). Results: One-, 5-, and 10-year cumulative mortality of incident and new subsequent cases of BCC and SCC in the GFC were similar. Likewise, MRR for incident BCC (MRR = 0.91; 95% CI 0.84–0.98) and incident SCC (MRR = 1.29; 95% CI 1.05–1.56) among patients registered in the GFC were similar to their counterparts in the DCR (MRR = 0.96; 95% CI 0.91–1.00 and MRR = 1.36; 95% CI 1.22–1.52). Conclusion: Mortality of incident and new subsequent cases of NMSC was similar and thus did not explain the reduced mortality of BCC patients.

1. Introduction

Non-melanoma skin cancer (NMSC), classified as basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), is the most common cancer among Caucasians [1]. The incidence of NMSC increases worldwide, partly owing to the population ageing [2].

Though considered a benign lesion, NMSC has been linked to chronic diseases (such as other cancers [3–6], psoriasis [7], atopic dermatitis [8], rheumatologic diseases [9] and lymphoma [10]), and treatments (including radiation therapy, phototherapy, psoralen and long-wave ultraviolet radiation (PUVA) [11] and immunosuppressant’s [12]). However, data on mortality subsequent to NMSC are few [13–16]. In a recent study we found a reduced mortality, relative to population controls, among patients with BCC registered in the Gerda Frentz Cohort (GFC) (which is a Danish cohort of prospectively recorded patients with NMSC seen by dermatologists in 1995) after controlling for...
co-morbidity recorded in hospital discharge summaries (MRR = 0.88; 95% CI: 0.81–0.94 for nodular and ulcerative BCC and MRR = 0.69; 95% CI: 0.60–0.81 for superficial BCC). Mortality was further reduced if nodular and ulcerative BCC was located on the trunk (MRR = 0.79; 95% CI: 0.63–0.99) or if superficial BCC was located on the extremities (MRR = 0.60; 95% CI: 0.39–0.91) [17]. The reason for this apparent protective effect of BCC is not clear. Besides the causal explanation, several types of bias may play a role. In contrast to our findings, a few other mortality studies of NMSC found an increased mortality [16,18,19] for both BCC and SCC patients. Neither our [17] nor other studies [13–16] distinguished between incident and new subsequent cases. Mixing of incident and new subsequent cases may cause bias because patients with new subsequent disease are better survivors [20]. Alternatively, prospective cohort studies based on primary collection of NMSC data may suffer from incomplete registration and reporting [3,4,7,21–23].

To examine if differences in mortality between incident and new subsequent cases or different mortality among patients registered in different data repositories could explain an earlier finding of a reduced mortality among BCC patients, we compared 10-year mortality of incident and new subsequent cases of NMSC registered in the GFC. In addition, we examined whether mortality among patients with incident NMSC in the GFC was similar to that of patients with incident cases registered in the nationwide Danish Cancer Registry (DCR).

2. Materials and methods

This study was based on data from patients with NMSC collected by Danish dermatologists in 1995 (the GFC) and on the Danish Cancer Registry (DCR). Mortality and migration updates for the patients and the population controls were obtained from the files of the Danish Civil Registration System [24]. In 1995, Denmark had 52,15,718 inhabitants, and the entire population received tax-supported health care from the National Health Service, allowing free access to private practitioners and hospitals [25].

2.1. The Gerda Frentz Cohort (GFC)

Professor Gerda Frentz created a nationwide cohort in order to prospectively register all patients with non-melanoma skin cancer (NMSC) seen by Danish dermatologists in 1995 (the cohort included both incident and new subsequent cases). There were two groups of patients with NMSC. The first group included patients presenting at dermatology private or outpatient clinics with a NMSC, with tumor’s clinical data available for each person. The clinical data included site, size and suspected type of skin cancer, histological analysis availability, treatment type and a previous history of NMSC (reported as “yes” for new subsequent cases, as “no” for incident cases and as “don’t know” for cases with an unknown history of NMSC). Patients from this group with available clinical data were included in our recent study, but we did not account for their previous history of NMSC [17].

The second group included NMSC patients with the histological data on any sample from suspected NMSC, sent from any healthcare provider to a pathologist. These data also included biopsies diagnosed as NMSC, even if the referring physician had not originally suspected it. The histological data included the actual diagnosis, type of clinic from which the sample was received, and if appropriate, details regarding tumors growth pattern and excision. As data on a history of NMSC were not available in this group, they were considered in the analysis as being cases with an unknown history of NMSC.

We included the whole cohort of 10,749 patients in this study. Of these, we excluded 1040 patients with Bowens disease, keratoacanthoma and actinic keratosis and a few were misclassified as non-melanoma skin cancers. The remaining (9709 patients) were comprised of a mixture of incident (n = 1898), new subsequent cases (n = 2405) and cases with an unknown history of NMSC (n = 5406).

2.2. The Danish Cancer Registry (DCR)

The DCR is a population-based registry containing nationwide data on cancer cases since 1943. In 1987 malignant and related diseases became reportable to the DCR on the obligatory basis. Cancer cases can also be identified through linkage to the National Patient Registry, established 1 January 1977 (which records all hospitalisations in Denmark and the Danish Registry of Causes of Death [26], so that missing cases could be included. All DCR data were reclassified according to the modified international classification of diseases, seventh revision (ICD-7) [27]. Using ICD-7 codes 1910–1919 for NMSC we identified 5054 incident cases of NMSC in Denmark in 1995 and included these in this study. A number of 129 patients were misclassified as NMSC and excluded.

For the cases with an unknown history of NMSC (n = 5406) in the GFC, we made linkage to the DCR and found the recorded cases of incident (n = 2289) and new subsequent (n = 1346) NMSC and cases with an unknown history of NMSC (n = 1771).

2.3. Record linkage

Through the use of a 10-digit civil registration number, assigned to all Danish residents by the Danish Civil Registration System [24], unambiguous data linkage between registries was possible and accurate. The Civil Registration System, which is updated daily, also contains information on vital status, date of death, and the residence.
Table 1
Mortality among NMSC patients in the Gerda Frentz Cohort (GFC) and their age-, gender- and residence-matched population controls (multiple carcinomas included)

<table>
<thead>
<tr>
<th>Age (years at index date)(^a)</th>
<th>Male/ female</th>
<th>1 year cumulative mortality, % (95% CI)(^b)</th>
<th>5 year cumulative mortality, % (95% CI)(^b)</th>
<th>10 year cumulative mortality, % (95% CI)(^b)</th>
<th>Mortality rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with incident BCC ((n = 1730)), population controls ((n = 17152))</td>
<td>68 (22–98)</td>
<td>1:1</td>
<td>3.4 (2.6–4.3)</td>
<td>19 (17–21)</td>
<td>35 (33–38)</td>
</tr>
<tr>
<td>Patients with new subsequent BCC ((n = 2294)), population controls ((n = 22589))</td>
<td>70 (24–102)</td>
<td>1:1</td>
<td>3.7 (3.0–4.6)</td>
<td>20 (18–22)</td>
<td>39 (37–41)</td>
</tr>
<tr>
<td>Patients with an unknown history of NMSC BCC ((n = 4870)), population controls ((n = 48099))</td>
<td>69 (18–100)</td>
<td>1:1</td>
<td>4.0 (3.5–4.6)</td>
<td>20 (19–21)</td>
<td>38 (37–39)</td>
</tr>
<tr>
<td>Patients with incident SCC ((n = 162)), population controls ((n = 1548))</td>
<td>80 (44–99)</td>
<td>2:1</td>
<td>6.2 (3.4–11.1)</td>
<td>49 (42–57)</td>
<td>71 (64–78)</td>
</tr>
<tr>
<td>Patients with new subsequent SCC ((n = 111)), population controls ((n = 1067))</td>
<td>78 (48–99)</td>
<td>2:1</td>
<td>10.0 (5.6–17)</td>
<td>48 (39–57)</td>
<td>74 (65–82)</td>
</tr>
<tr>
<td>Patients with an unknown history of NMSC SCC ((n = 536)), population controls ((n = 5142))</td>
<td>79 (26–97)</td>
<td>1:1</td>
<td>13 (10–16)</td>
<td>41 (37–46)</td>
<td>67 (63–71)</td>
</tr>
</tbody>
</table>

BCC, basal cell carcinoma; CI, confidence interval; SCC, squamous cell carcinoma.
\(^a\) Median (range).
\(^b\) The cumulative mortality and associated 95% CI for patients with BCC and SCC was computed by the Kaplan Meier life table method.

Table 2
Mortality among those NMSC patients in the Gerda Frentz Cohort (GFC) with an unknown history of NMSC after linkage to the Danish Cancer Registry (DCR) and their age-, gender- and residence-matched population controls (multiple carcinomas included)

<table>
<thead>
<tr>
<th>Age (years at index date)(^a)</th>
<th>Male/ female</th>
<th>1 year cumulative mortality, % (95% CI)(^b)</th>
<th>5 year cumulative mortality, % (95% CI)(^b)</th>
<th>10 year cumulative mortality, % (95% CI)(^b)</th>
<th>Mortality rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with incident BCC ((n = 2065)), population controls ((n = 20491))</td>
<td>67 (18–100)</td>
<td>1:1</td>
<td>3.7 (3.0–4.6)</td>
<td>19 (17–21)</td>
<td>36 (34–38)</td>
</tr>
<tr>
<td>Patients with new subsequent BCC ((n = 1234)), population controls ((n = 12169))</td>
<td>72 (20–98)</td>
<td>1:1</td>
<td>4.6 (3.6–6.0)</td>
<td>25 (23–28)</td>
<td>45 (42–48)</td>
</tr>
<tr>
<td>Patients with an unknown history of NMSC BCC ((n = 1571)), population controls ((n = 15439))</td>
<td>68 (21–97)</td>
<td>1:1</td>
<td>3.9 (3.1–5.0)</td>
<td>19 (17–21)</td>
<td>35 (33–38)</td>
</tr>
<tr>
<td>Patients with incident SCC ((n = 224)), population controls ((n = 2123))</td>
<td>79 (44–97)</td>
<td>1:1</td>
<td>14 (10–20)</td>
<td>44 (38–51)</td>
<td>68 (62–74)</td>
</tr>
<tr>
<td>Patients with new subsequent SCC ((n = 112)), population controls ((n = 1067))</td>
<td>80 (42–97)</td>
<td>2:1</td>
<td>18 (12–26)</td>
<td>50 (41–60)</td>
<td>79 (71–86)</td>
</tr>
<tr>
<td>Patients with an unknown history of NMSC SCC ((n = 290)), population controls ((n = 1951))</td>
<td>75 (26–96)</td>
<td>1:1</td>
<td>8.0 (5.0–13)</td>
<td>34 (28–41)</td>
<td>60 (53–67)</td>
</tr>
</tbody>
</table>

\(^a\) Median (range).
\(^b\) The cumulative mortality and associated 95% CI for patients with BCC and SCC was computed by the Kaplan Meier life table method.
2.4. Reference population cohort

To compute the age-, gender- and residence-adjusted mortality rate ratio of the NMSC patients compared with the general population, 10 population controls ($n = 106,696$) were selected, matched on age, gender and area of residence from the pool of eligible persons who were alive on the date their index patient had the NMSC diagnosis (index date).

2.5. Mortality data

Mortality and migration updates for the patients and the population controls were obtained from the Danish Civil Registration System [24]. The follow-up period began at the index date and ended at the date of emigration, death, or on 1 July 2006, whichever occurred first.

2.6. Statistical analysis

We constructed Kaplan–Meier mortality curves and computed the cumulative 1-, 5- and 10-year mortality for the incident cases in the DCR and for all groups of NMSC patients in the GFC (incident, new subsequent and patients with an unknown history of NMSC) by life table techniques.

The mortality rate ratios (MRR) and associated 95% confidence intervals (CI) were estimated by comparing all groups of patients with NMSC in the GFC and incident cases in the DCR, with the population controls.

We compared the MRR of incident cases of NMSC in the GFC with the MRR of incident cases in the DCR using a Mantel–Haenszel (M–H) estimate of their ratio, controlling for age and gender [28]. We used the variance estimator proposed by Greenland and Robins [29] to compute the M–H $p$-value, testing the hypothesis that the M–H estimate of the ratio equaled 1 (implying no difference in MRR of incident cases in the GFC and those in the DCR). We considered $p$-values less than 0.05 to be significant. The assumption of homogeneity across categories of age and gender was assessed using a chi-squared test.

In this study, BCC and SCC were regarded as two separate entities, and patients were assigned to two subcohorts defined by these diagnoses.

Statistical analyses were performed with STATA® software (version 9.0, STATA, College Station, Texas). The study was approved by the Danish Data Protection Agency and by the Ethics Committee of the County of Copenhagen (no. 01-083/94).

3. Results

3.1. Descriptive data

In 1995, 10,830 patients with either BCC ($n = 9789$, 90%) or SCC ($n = 1041$, 10%) were registered in the GFC or the DCR. Among the 10,830 patients, 362 (3%) – mainly BCC patients – had multiple carcinomas (>5). We did the analyses with and without these cases. Since the mortality estimates did not change substantially, we only reported the results of the analyses of patients with multiple carcinomas included.

By making linkage between the GFC and the DCR, we found that 1121 (10%) patients were only registered in the DCR; 3804 (35%) patients were registered in both the GFC and the DCR.

Table 3

Mortality among patients with incident NMSC in the Gerda Frentz Cohort (GFC) and patients with incident NMSC in the Danish Cancer Registry (DCR) and their age-, gender- and residence-matched population controls (multiple carcinomas included)

<table>
<thead>
<tr>
<th>Age (years at index date)</th>
<th>Male/ female</th>
<th>1 year cumulative mortality, % (95% CI)</th>
<th>5 year cumulative mortality, % (95% CI)</th>
<th>10 year cumulative mortality, % (95% CI)</th>
<th>Mortality rate ratio (95% CI)</th>
<th>M-H $p$-value (controlling for age and gender)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with incident BCC in GFC ($n = 1736$), population controls ($n = 17152$)</td>
<td>68 (22–98)</td>
<td>1:1</td>
<td>3.4 (2.6–4.3)</td>
<td>19 (17–21)</td>
<td>35 (33–38)</td>
<td>0.91 (0.84–0.98)</td>
</tr>
<tr>
<td>Patients with incident BCC in DCR ($n = 4407$), population controls ($n = 43700$)</td>
<td>68 (18–100)</td>
<td>1:1</td>
<td>3.5 (3.0–4.1)</td>
<td>19 (18–20)</td>
<td>36 (35–37)</td>
<td>0.96 (0.91–1.00)</td>
</tr>
<tr>
<td>Patients with incident SCC in GFC ($n = 162$), population controls ($n = 1548$)</td>
<td>80 (44–99)</td>
<td>2:1</td>
<td>6.2 (3.4–11)</td>
<td>49 (42–57)</td>
<td>71 (64–78)</td>
<td>1.29 (1.05–1.56)</td>
</tr>
<tr>
<td>Patients with incident SCC in DCR ($n = 518$), population controls ($n = 5036$)</td>
<td>77 (30–97)</td>
<td>1:5</td>
<td>9.5 (7.2–12)</td>
<td>43 (39–48)</td>
<td>67 (63–71)</td>
<td>1.36 (1.22–1.52)</td>
</tr>
</tbody>
</table>

BCC, basal cell carcinoma; CI, confidence interval; SCC, squamous cell carcinoma; GFC, Gerda Frentz Cohort; DCR, Danish Cancer Registry.

$^a$ Median (range).

$^b$ The cumulative mortality and associated 95% CI for patients with BCC and SCC was computed by the Kaplan Meier life table method.

$^c$ We used the variance estimator proposed by Greenland and Robins to compute the M–H $p$-value, testing the hypothesis that the M–H estimate of the ratio, comparing the MRR in the GFC with the MRR in the DCR, equalled 1 (saying that there was no difference between the MRR of incident cases in the GFC and the DCR).
and the DCR; and 5905 (55%) patients were registered only in the GFC.

The age and gender distribution among patients with incident, new subsequent and with an unknown history of BCC and SCC were similar (Tables 1 and 2). Likewise, the age and gender distribution of patients with incident BCC and SCC in the GFC were similar to that in the DCR (Table 3).

All descriptive data appear in Figs. 1 and 2 and in Tables 1–3.

3.2. Mortality among patients with incident, new subsequent and cases with undetermined cases of BCC and SCC in the GFC

We found no substantial difference in 1-, 5- and 10-year cumulative mortality from 1996 through 2006 among patients with incident BCC and SCC, new subsequent BCC and SCC and BCC and SCC patients with an unknown history of NMSC. The mortality rate ratio was 0.91 (95% CI: 0.84–0.98) for patients with incident BCC, 0.89 (95% CI: 0.83–0.95) for patients with new subsequent BCC and 0.95 (95% CI: 0.91–1.00) for BCC patients with an unknown history of NMSC. The respective MRR estimates for SCC patients were 1.29 (95% CI: 1.05–1.56), 1.34 (95% CI: 1.06–1.68) and 1.22 (95% CI: 1.09–1.35) (Table 1).

After linking GFC data of patients with an unknown history of NMSC with DCR records, the MRR among BCC patients with incident, new subsequent and with an unknown history of NMSC compared with their population controls were 0.96 (95% CI: 0.89–1.03), 0.97 (95% CI: 0.89–1.05) and 0.93 (95% CI: 0.86–1.02). The MRR among SCC patients with incident, new subsequent and an unknown history of NMSC compared with their population controls were 1.19 (95% CI: 1.00–1.40), 1.42 (95% CI: 1.13–1.76) and 1.15 (95% CI: 0.95–1.39) (Table 2).

3.3. Mortality among patients with incident BCC and SCC patients in the GFC and the DCR

We found no major difference in 1-, 5-, or 10-year cumulative mortality during 1996 through 2006 among patients with incident BCC and SCC in the GFC and in the DCR. The MRR among patients with incident BCC compared with their population controls was 0.91 (95% CI: 0.84–0.98) in the GFC and 0.96 (95% CI: 0.91–1.00) in the DCR (M–H p-value = 0.85). The MRR among patients with incident SCC was 1.29 (95% CI: 1.05–1.56) in the GFC and 1.36 (95% CI: 1.22–1.52) in the DCR (M–H p-value = 0.10) (Table 3).

4. Discussion

4.1. Mortality among incident, new subsequent and cases with an unknown history of NMSC of BCC and SCC in the GFC

We found no substantial differences in mortality among patients with incident, new subsequent and with an unknown history of NMSC of BCC and SCC in this cohort study. The only exception to this was among the group of patients with an unknown history of NMSC of SCC in the GFC where patients with new subsequent disease (as recorded in the DCR) had a higher mortality than patients with incident disease (as recorded in the DCR). These results indicate that mixing of incident and new subsequent cases of BCC and SCC are not likely to explain an earlier finding of a reduced mortality among BCC patients.
Epidemiological studies of NMSC based on primary data collection by physicians entails difficulties in distinguishing incident and new subsequent cases; in addition registration and reporting are incomplete [3,4,7,21–23]. The main reasons for incomplete registration are high cure rate leading clinicians to regard these skin cancers as trivial; large number of these cancers threatening to overwhelm cancer surveillance systems; and difficulties in ascertaining cases, since multiple lesions are often diagnosed simultaneously and many people have multiple lesions in their lifetime [30]. It is therefore impossible to completely exclude persons with a history of NMSC from the cancer registries, and therefore a mixture of incident and new subsequent cases of NMSC are studied (misclassification bias).

4.2. Mortality among incident BCC and SCC patients in the GFC and the DCR

We found similar mortality between patients registered in the GFC and patients registered in the DCR.

We had hypothesized that since patients registered in the GFC were mainly treated in office settings, they were healthier and therefore more likely to survive than the overall population of NMSC patients registered in the DCR. Contrary to our expectation, mortality among patients registered in the GFC was similar to that of patients registered in the DCR.

A major limitation of our (and other) studies is the incomplete registration of NMSC in the DCR [3,4,7,21–23], making it a questionable gold standard. Two Danish studies have estimated underreporting to be as high as 40% [7,32], which is comparable to what has been found in other countries [21,22,33]. Such bias may therefore still influence our mortality estimates, in particular for BCC. Very low fatality of BCC in Denmark could result in its being regarded as trivial in patients with severe comorbidities, leading to underreporting. Systematic under-ascertainment of BCC cases with poor prognosis could produce underestimation of BCC-related mortality [34] in cohort studies. Recently, in a subset of this cohort, we found a reduced cause-specific mortality of cardiovascular diseases and gastrointestinal diseases [17]. This finding supports our suspicion of under-ascertainment of BCC cases with poor prognosis.

A more common bias known from case control studies is the Berkson’s bias [35], whereby the most severe cases are usually under closer scrutiny and, therefore are the ones that are diagnosed with diseases that otherwise would go undetected. This could theoretically be the reason for the elevated mortality among patients with SCC, but such bias must be differential between BCC and SCC to explain the differences in mortality.

5. Conclusion

Incident and new subsequent cases of NMSC registered in the GFC have similar 10-year mortality. Patients with incident NMSC registered in the GFC have similar mortality as patients with incident NMSC registered in the DCR. Thus, differences in mortality between incident and new subsequent cases or different mortality among patients registered in different data repositories are not likely to explain an earlier finding of a reduced mortality among BCC patients. However, incomplete registration in the DCR may still have influenced our findings.

Acknowledgements

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Conflict of interest

None.

References


