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Mortality in Danish patients with nonmelanoma skin cancer, 1978–2001

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Summary

Background—Nonmelanoma skin cancer (NMSC) is a growing public health problem among Caucasians, thus mortality data that may provide insight into the clinical course and foster our understanding of NMSC are important.

Objectives—We examined total and cause-specific mortality among patients with NMSC registered in the Danish Cancer Registry from 1978 to 2001.

Methods—A total of 82 837 patients with basal cell carcinoma (BCC) and 13 453 patients with squamous cell carcinoma (SCC) were followed through the National Death Registry for specific causes of death. Standardized mortality ratios (SMRs) were computed based on mortality rates in the general population.

Results—Among patients with BCC, we found a slightly reduced total mortality [SMR 0·97, 95% confidence interval (CI) 0·96–0·98] with decreased SMRs seen for chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD) and diabetes mellitus. The SMR for suicide was increased. Among patients with SCC, we found an increased total mortality (SMR 1·30, 95% CI 1·26–1·33) due primarily to excess deaths from cancers, COPD, CVD and infectious diseases.

Conclusions—We found markedly different mortality patterns among patients with BCC and those with SCC, suggesting important differences in the clinical course of these patients.

Keywords

basal cell carcinoma; cause-specific mortality; registry study; squamous cell carcinoma

Recently, we reported a 10% reduced mortality among patients with basal cell carcinoma (BCC), and a 60% increased mortality among patients with squamous cell carcinoma (SCC) during a 10-year follow-up in a cohort of Danish patients with nonmelanoma skin cancer (NMSC).[1] The results were based on a comparison of patients with NMSC diagnosed with a first primary NMSC at private or public outpatient dermatology clinics in 1995 with age-,

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Conflicts of interest
None declared.

gender- and residence-matched population controls. Another Danish study, examining patients registered in the Danish Cancer Registry (DCR) from 1981 to 1997, reported a similar increased survival rate among patients with NMSC compared with the general population.[2] They did not separate the type of NMSC and the result probably reflects the survival rate for patients with BCC because of the higher proportion of patients with BCC compared with those with SCC in the study population. However, one Finnish[3] and one U.S. study[4] showed no differences in mortality between patients with BCC and NMSC and the general population. The Finnish study identified all patients with BCC and SCC cases registered in the Finnish Cancer Registry from 1974 to 1981 and followed them for an average of 10 years. The U.S. study followed 35 062 patients with NMSC (identified through 1982) for an average period of 12 years. The study did not stratify by type of NMSC but adjusted for multiple risk factors of mortality such as age, gender, education, smoking and health-related factors (body mass index, alcohol use and exercise level). The differences in calendar periods, settings, adjustments for covariates and type of NMSC studied may explain the disagreement between the various studies.

Therefore, the effects of a NMSC diagnosis on mortality remain to be established. Such data are important because they provide further insight into the clinical course, and foster our understanding, of NMSC and diseases associated with NMSC. As NMSC is the most common of all cancers among Caucasians,[5] these findings will have a significant public health interest.

We examined the total and cause-specific mortality of all Danish patients with NMSC stratified by gender and type of NMSC over a 23-year period and compared them with the general Danish population. In supplementary analyses, we evaluated the potential impact of surveillance and selection bias on the results. We also addressed a potential ‘healthy patient effect’ (similar to the ‘healthy worker effect’[6,7]) among, in particular, patients with BCC.

Patients and methods

Study cohort

From the DCR, we identified all patients recorded with a diagnosis of BCC or SCC during the period 1978–2001. The DCR has collected information about primary cases of cancer on a nationwide basis since 1943 and has been shown to have accurate and almost complete records of nonskin cancer cases.[8] However, incomplete registration of NMSC has been estimated to range from 12% to 40%.[9,10] The files of the DCR include information on cancer type, site, morphology and history of cancer. Tumours in the DCR are coded according to the 7th revision of the *International Classification of Diseases* (ICD-7) and since 1978, the first version of the *International Classification of Diseases for Oncology* (ICD-O-1), which includes a four-digit code for tumour morphology.[11] Throughout the study period, the ICD-7 codes were generated by uniform conversion of the two (topography and morphology) ICD-O-1 codes for each case. If a person develops more than one primary tumour, each tumour is entered and counted as an individual record; however, multiple tumours of the skin with identical morphological characteristics (i.e. same first three digits of the ICD-O-1 morphology code) are recorded only once, even when they are located on different parts of the body. Such tumours are, however, allocated a specific code for multiple occurrences.

Initially, we identified patients with NMSC by ICD-7 codes 1910–1919 (covering all NMSC diagnoses). Secondly, we included BCC patients with the following ICD-O-1 morphology codes: 80903 (BCC), 80913 (multicentric BCC), 80923 (BCC, morphoea type), 80933 (BCC, fibroepithelial type) and 81233 (basaloid carcinoma), and SCC patients with the ICD-O-1 codes 80513 (verrucous carcinoma), 80703 (SCC), 80713 (keratinized SCC), 80743

(SCC, spindle cell type), 80763 (microinvasive SCC), 80943 (basosquamous carcinoma) and 80953 (metatypical carcinoma), thus identifying a study population of 82 837 patients with BCC and 13 453 with SCC.

Patients who developed BCC subsequent to a primary diagnosis of SCC (n = 972) and patients who developed SCC following a primary BCC diagnosis (n = 1486) were included in a separate group (defined as mixed NMSC), as well as separately in the BCC and SCC groups.

We were unable to evaluate specifically the mortality experience among patients with multiple carcinomas of specific (BCC or SCC) type because of the coding tradition in the DCR (assignment of date of diagnosis to the primary cancer of the specific type). A mortality analysis among these patients based on the DCR data would introduce a bias,[12] due to introduction of a period of observation time between primary and secondary BCC or SCC diagnosis during which death could not occur.[13,14] Therefore, using the specific code for multiple occurrences, NMSC patients with either multiple BCC or multiple SCC were excluded from the analyses.

Mortality data

Causes of death were obtained by linkage to the National Danish Death Register which contains computerized records on all deaths occurring among Danish residents since 1943.[15] The linkage was performed by using of the personal identification number, a unique number, assigned to all Danish residents since 1968 that encodes date of birth and gender.[16] For our analysis, we used the underlying cause of death reported on the death certificate grouped, as defined by the National Board of Health, into 49 standard categories based on ICD-8 and ICD-10 codes.[15]

Statistical analyses

Patients with NMSC were followed from the date of diagnosis to the date of their death, emigration, or the end of the study, 31 December 2001, whichever occurred first. The follow-up ended in 2001 because the Death Register was not updated for more recent years. We recorded age, gender and date of diagnosis, morphology, date and cause of death, cancer registered prior to NMSC and calendar time in 5-year groups. The number of deaths in the standard cause of death categories observed among the NMSC cohort members was compared with the number of deaths expected in the general Danish population. To obtain the expected number of deaths, gender-specific death rates, computed according to 5-year age groups and 5-year calendar periods, were multiplied with the corresponding person-years of the NMSC cohort members. The standardized mortality ratio (SMR), computed as the ratio of the observed to the expected number of deaths, served as an estimate of relative risk of death, and 95% confidence intervals (CI) were computed based on the assumption that the observed number of deaths followed a Poisson distribution.

We stratified our analyses according to gender. Using information in the DCR (from 1943 onwards), we categorized patients with NMSC according to a previous history of cancer (other than NMSC) prior to the NMSC diagnosis, and we restricted the cancer-specific mortality analyses to those patients without prior cancer.

To explore the impact of surveillance and selection bias on our results, we examined the total mortality of NMSC patients both with and without another cancer before NMSC diagnosis.

Finally, we addressed a potential ‘healthy patient effect’ by stratifying person-years of risk according to time since diagnosis into less than 1 year, 1–4 years, 5–9 years and more than

10 years. If a 'healthy patient effect' was present we would expect an increase of SMR with time.[7]

We analysed data with SAS® software version 8.2 (SAS Institute Inc., Cary, NC, U.S.A.) and the study was approved by the Danish Data Protection Agency (record number 2004-41-4298).

Results

Descriptive data

Among 82 837 patients with BCC (591 332 person-years of follow-up), 58·3% were aged over 65 years at the date of diagnosis, and 51·8% were female. Among 13 453 patients with SCC (71 197 person-years of follow-up), 78·3% were aged over 65 years, and 39·4% were female. Of the patients with BCC, 1486 (1·8%) developed a subsequent SCC and 972 (7·2%) of SCC patients developed a subsequent BCC (mixed NMSC). A previous history of cancer (other than NMSC) was found among 7871 patients (9·5%) with BCC, 1569 (11·6%) of patients with SCC and 283 (11·5%) of those with mixed NMSC (data not shown).

Mortality among patients with primary basal cell carcinoma

We found a slightly reduced total mortality among patients with BCC compared with that of the general population (SMR 0·97, 95% CI 0·96–0·98), lowest among females (SMR 0·95, 95% CI 0·94–0·97).

Patients with BCC had a reduced risk of death from ischaemic heart diseases (SMR 0·93, 95% CI 0·91–0·95), nonischaemic heart diseases (SMR 0·94, 95% CI 0·90–0·99), cerebrovascular diseases (SMR 0·93, 95% CI 0·90–0·97), peripheral vascular diseases (SMR 0·94, 95% CI 0·89–1·00), chronic obstructive pulmonary disease (COPD) (SMR 0·87, 95% CI 0·83–0·92), diseases of the digestive tract (SMR 0·91, 95% CI 0·83–1·00) and diabetes (SMR 0·78, 95% CI 0·70–0·86) with no substantial differences according to gender. Risk of death from suicide was increased, most notably among female patients with BCC (SMR 1·31, 95% CI 1·06–1·61). Mortality rates for suicide were 29·9 per 100 000 person-years (95% CI 24·2–36·6) among female patients with BCC and 54·5 per 100 000 person-years (95% CI 46·2–64·0) among male patients. In addition, we found an increased risk of death from cancer overall (SMR 1·15, 95% CI 1·13–1·18) with no substantial differences according to gender (Table 1).

After restriction of BCC patients to those without prior cancer, we found a reduced total mortality (SMR 0·92, 95% CI 0·91–0·94) and reduced mortality from cancer deaths overall (SMR 0·95, 95% CI 0·93–0·98) (Table 2). However, excess mortality of similar magnitude among men and women was still seen for cancers of the larynx, trachea and bronchus (SMR 1·10, 95% CI 1·04–1·16) and cancers of the skin, including malignant melanoma (SMR 2·05, 95% CI 1·75–2·38).

Mortality among patients with primary squamous cell carcinoma and mixed nonmelanoma skin cancer

We found an increased total mortality among patients with SCC (SMR 1·30, 95% CI 1·26–1·33), which was highest among females (SMR 1·39, 95% CI 1·34–1·45). A similar excess mortality was seen among patients with mixed NMSC (data not shown).

Patients with SCC had an increased risk of death from ischaemic heart diseases (SMR 1·15, 95% CI 1·10–1·21), non-ischaemic heart diseases (SMR 1·15, 95% CI 1·04–1·27), cerebrovascular diseases (SMR 1·10, 95% CI 1·02–1·19), peripheral vascular diseases (SMR

1·29, 95% CI 1·14–1·45), COPD (SMR 1·21, 95% CI 1·08–1·35) and cancer (SMR 2·17, 95% CI 2·08–2·26) with no apparent gender differences. Further, elevated SMRs were observed for deaths from acute infections (SMR 2·19, 95% CI 1·43–3·21), pneumonia (SMR 1·28, 95% CI 1·09–1·49) and genital diseases (SMR 1·36, 95% CI 1·02–1·76), which were most pronounced among male patients with SCC (Table 3).

Total mortality among patients with SCC remained increased after restriction to patients without a prior history of cancer (SMR 1·23, 95% CI 1·20–1·26) (Table 2). Elevated SMRs were seen for cancer of the rectum and anal region (SMR 6·44, 95% CI, 5·76–7·18), cancers of the larynx, trachea and bronchus (SMR 1·50, 95% CI 1·34–1·68), cancer of the buccal cavity (SMR 2·30, 95% CI 1·81–2·89), cancer of the skin including malignant melanoma (SMR 22·9, 95% CI 20·3–25·6) and leukaemia (SMR 1·52, 95% CI 1·25–1·83). SMRs were similar among females and males, except for cancer of the rectum and anal region (females: SMR of 13·6, 95% CI 11·7–15·6; males: SMR 3·70, 95% CI, 3·10–4·38). The corresponding mortality rates for cancer of the rectum and anal region were 745·39 per 100 000 person-years among females (95% CI 643·17–859·24) and 343·09 per 100 000 person-years (95% CI 287·66–406·09) among males. The cause-specific mortality pattern for mixed NMSC was similar to that for SCC-only patients (data not shown).

Variation with time since diagnosis

We found an increasing SMR for overall mortality among female patients with BCC with increasing time since diagnosis. SMRs were 0·81 (95% CI 0·77–0·86) within the first year of follow-up, 0·93 (95% CI 0·91–0·96) within 1–4 years, 0·99 (95% CI 0·96–1·02) within 5–9 years and 1·02 (95% CI 0·99–1·06) after more than 10 years since diagnosis. A similar trend was found among male patients with BCC, whereas opposite trends were seen among patients with SCC of both gender (Fig. 1).

Discussion

In this population-based study we found that patients with BCC had reduced mortality from cardiovascular diseases, COPD, diseases of the digestive tract and diabetes. We also found that patients with SCC had elevated mortality from acute infections, cardiovascular diseases, COPD and cancer. Our findings suggest substantially different clinical courses for BCC and SCC.

Several factors may explain the different mortality pattern observed among Danish patients with BCC and SCC. As NMSC may remain undiagnosed for longer periods, surveillance bias in the diagnosis of NMSC may influence the mortality pattern among these patients. However, if important, this bias has a different impact on the findings for BCC and SCC patients, as we found a reduced mortality among patients with BCC for most causes of death. Nonetheless, the prevalence of BCC patients with a prior diagnosis of cancer was similar to that of patients with SCC, arguing against any major differential surveillance. Another possibility is that mortality may differ between patients with BCC registered in the DCR and those patients with BCC not registered. Our results support the existence of such selection bias because mortality was only slightly different between BCC patients with a prior cancer and those without. If all BCC cases occurring among patients with other cancer diseases had been registered, we would have expected a larger difference in these estimates, as seen among patients with SCC. Moreover, the proportion of patients with BCC occurring after SCC was well below that estimated in a meta-analysis of the risk of developing a subsequent NMSC in patients with a history of NMSC.[17] A differential reporting to the DCR among patients with BCC according to differences in patients' socioeconomic status (SES) and lifestyle could also potentially bias our mortality estimates. It is widely known

that SES affects morbidity and mortality,[18–22] and generally a high SES is an important prognostic determinant of cancer patient survival.[23]

Such differential underdiagnosis and under-reporting of BCC patients with a general low SES would underestimate the mortality among this group of patients. Supporting this is our result, suggesting that patients with BCC have a better overall health status ('healthy patient effect') than the general population used for comparison.[7] Further, we observed a reduced mortality from cardiovascular, lung and obesity-related diseases among patients with BCC.

Our finding of increased mortality from suicide among patients with BCC may be explained by a common relation between psychopathology and sun exposure. People with depression tendencies may be more inclined to seek sun exposure because sunlight relieves affective disorders such as depression.[24] Alternatively, the disfigurement and scars arising after treatment for BCC may be unacceptable for some patients with associated psychological problems, thereby leading to an increased risk of suicide. The latter explanation is supported by a Danish study, which showed that location of NMSC on the face was more frequent in the suicide group.[25]

We found an increased mortality from smoking-related causes among patients with SCC which supports smoking as an underlying risk factor for SCC.[26] This relationship is further supported by a recent finding of an increased risk of SCC among patients hospitalized for chronic pulmonary diseases.[27] We also found that a diagnosis of SCC increased risk of death from acute infections, notably among men. This may partly be alcohol related, since an increased prevalence of NMSC and death from acute infections[28] has been found among patients with alcoholic cirrhosis;[29] and partly by a higher prevalence of SCC among patients with human immunodeficiency virus.[30] The higher mortality from pneumonia in men, but not women, is in accordance with previous findings.[31–34] The underlying mechanisms for this association have not been established but may be alcohol related or involve differences in socioeconomic factors. Finally, we observed an increased mortality for cancers in the rectum and anal region, buccal cavity and laryngeal and pharyngeal cancers among patients with SCC. This finding is in accordance with another Danish study, reporting an elevated risk for these cancers subsequent to a diagnosis of SCC.[35] Human papillomavirus, which is a common risk factor for anal, pharyngeal, laryngeal and buccal cavity cancers and SCC,[36–38] may underlie this relationship.

Advantages of our study are the use of a large nationwide cohort, with complete continuous data on death and migration, and the long follow-up period. Nevertheless, certain inherent limitations must be considered. Firstly, it is well known that the reported diagnosis on a death certificate is not always correct.[39,40] This may have influenced the results of the cause-specific mortality. The resulting misclassification would (except for cancer of the skin) probably be nondifferential between patients with NMSC and the general population, and thus be expected to underestimate the true effects. Secondly, in our record linkage study we only had information of those variables that are collected as part of the notification routines in the cancer registry and potential confounding factors, such as other medical conditions, smoking and drinking habits, physical activity, sun exposure, psychological constitution, SES and general health status were not available. Thus, the inability to adjust for these unmeasured and other potential confounding factors should be recognized.

In summary, in this nationwide cohort of patients with NMSC we found a reduced mortality among patients with BCC, which is probably explained by either underdiagnosis or under-reporting of BCC patients with a general lower social class and an unhealthy lifestyle. We observed an increased mortality among patients with SCC which may be explained by an increased mortality related to diseases associated with alcohol and smoking. Although, BCC

and SCC share mutual aetiological factors, such as sun exposure, our study points to important differences in the clinical course of patients with BCC and SCC.

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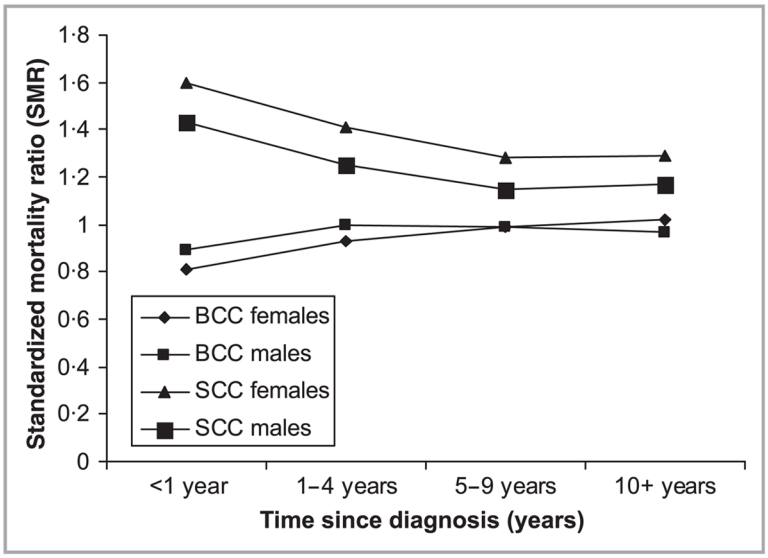

Fig 1.
Variation in mortality of patients with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with time since diagnosis.

Table 1

Total and cause-specific mortality among patients with primary basal cell carcinoma (BCC) from 1978 to 2001, stratified by gender

	Women		Men		Total	
Cause of death	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**
All causes	13 486	0·95 (0·94–0·97)	15 272	0·98 (0·96–0·99)	28 758	0·97 (0·96–0·98)
Cancer, overall[a]	3198	1·12 (1·08–1·16)	4421	1·17 (1·14–1·21)	7619	1·15 (1·13–1·18)
Chronic obstructive pulmonary disease	530	0·91 (0·84–1·00)	800	0·85 (0·79–0·91)	1330	0·87 (0·83–0·92)
Ischaemic heart disease	2912	0·91 (0·88–0·95)	3746	0·94 (0·91–0·97)	6658	0·93 (0·91–0·95)
Nonischaemic heart disease	899	0·95 (0·89–1·01)	860	0·94 (0·88–1·00)	1759	0·94 (0·90–0·99)
Cerebrovascular disease	1571	0·96 (0·91–1·01)	1256	0·91 (0·86–0·96)	2827	0·93 (0·90–0·97)
Peripheral vascular disease	519	0·92 (0·84–1·00)	523	0·97 (0·89–1·05)	1042	0·94 (0·89–1·00)
Diabetes mellitus	165	0·73 (0·62–0·85)	200	0·82 (0·71–0·95)	365	0·78 (0·70–0·86)
Diseases of the digestive tract	232	0·87 (0·76–0·99)	204	0·96 (0·83–1·10)	436	0·91 (0·83–1·00)
Suicide	94	1·31 (1·06–1·61)	151	1·08 (0·92–1·27)	245	1·16 (1·02–1·31)
Pneumonia	469	0·93 (0·84–1·01)	498	1·02 (0·93–1·11)	967	0·97 (0·91–1·04)

SMR, standardized mortality ratio; CI, confidence interval.

[a]Cancer-specific mortality of all patients regardless of cancer status prior to nonmelanoma skin cancer.

Table 2

Total and cancer-specific mortality among patients with primary basal cell carcinoma and squamous cell carcinoma from 1978 to 2001, restricted to those patients without cancer prior to nonmelanoma skin cancer (NMSC)

	Women		Men		Total	
Cause of death	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**
Basal cell carcinoma						
All causes (no prior cancer)	11 552	0·91 (0·90–0·93)	13 446	0·93 (0·92–0·95)	24 998	0·92 (0·91–0·94)
Cancer, overall[a]	2317	0·90 (0·87–0·94)	3446	0·99 (0·96–1·02)	5763	0·95 (0·93–0·98)
Cancer of the larynx, trachea, bronchus	432	1·13 (1·03–1·25)	997	1·08 (1·02–1·15)	1429	1·10 (1·04–1·16)
Cancer of the skin	85	2·45 (1·95–3·02)	85	1·77 (1·41–2·18)	170	2·05 (1·75–2·38)
Squamous cell carcinoma						
All causes (no prior cancer)	2257	1·32 (1·27–1·38)	3721	1·18 (1·14–1·22)	5978	1·23 (1·20–1·26)
Cancer, overall[a]	657	2·28 (2·11–2·46)	989	1·43 (1·34–1·52)	1646	1·68 (1·60–1·76)
Cancer of the rectum and anal region	190	13·6 (11·7–15·6)	135	3·70 (3·10–4·38)	325	6·44 (5·76–7·18)
Cancer of the larynx, trachea, bronchus	7	1·33 (0·98–1·77)	257	1·53 (1·35–1·73)	304	1·50 (1·34–1·68)
Cancer of the buccal cavity	16	2·18 (1·25–3·54)	59	2·34 (1·78–3·01)	75	2·30 (1·81–2·89)
Cancer of the skin	119	30·4 (25·2–36·4)	181	19·7 (16·9–22·8)	300	22·9 (20·3–25·6)
Leukaemia	33	1·56 (1·08–2·19)	77	1·50 (1·18–1·87)	110	1·52 (1·25–1·83)

SMR, standardized mortality ratio; CI, confidence interval.

[a]Cancer-specific mortality of patients without prior cancer before NMSC.

Table 3

Total and cause-specific mortality among patients with primary squamous cell carcinoma from 1978 to 2001, stratified by gender

	Women		Men		Total	
Cause of death	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**
All causes	2658	1·39 (1·34–1·45)	4340	1·24 (1·21–1·28)	6998	1·30 (1·26–1·33)
Cancer, overall[a]	842	2·61 (2·44–2·79)	1511	1·98 (1·88–2·08)	2353	2·17 (2·08–2·26)
Chronic obstructive pulmonary disease	86	1·37 (1·09–1·69)	234	1·16 (1·02–1·32)	320	1·21 (1·08–1·35)
Ischaemic heart disease	579	1·24 (1·14–1·34)	1038	1·11 (1·04–1·18)	1617	1·15 (1·10–1·21)
Nonischaemic heart disease	160	1·19 (1·01–1·39)	239	1·12 (0·99–1·28)	399	1·15 (1·04–1·27)
Cerebrovascular disease	273	1·16 (1·03–1·31)	350	1·06 (0·95–1·18)	623	1·10 (1·02–1·19)
Peripheral vascular disease	114	1·32 (1·08–1·58)	167	1·27 (1·09–1·48)	281	1·29 (1·14–1·45)
Genital diseases	14	1·13 (0·62–1·89)	55	1·36 (1·02–1·76)	69	1·30 (1·01–1·65)
Acute infections	14	1·61 (0·88–2·69)	26	2·19 (1·43–3·21)	40	1·94 (1·39–2·65)
Pneumonia	87	1·11 (0·89–1·37)	167	1·28 (1·09–1·49)	254	1·22 (1·07–1·38)

SMR, standardized mortality ratio; CI, confidence interval.

[a]Cancer-specific mortality of all patients regardless of cancer status prior to non-melanoma skin cancer.