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Nonmelanoma skin cancer and risk of all-cause and cancer-related mortality: A systematic review

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Abstract

Some reports suggest a history of nonmelanoma skin cancer (NMSC) may be associated with increased mortality. NMSCs have very low fatality rates, but the high prevalence of NMSC elevates the importance of the possibility of associated subsequent mortality from other causes. The variable methods and findings of existing studies leave the significance of these results uncertain. To provide clarity, we conducted a systematic review to characterize the evidence on the associations of NMSC with: 1) all-cause mortality, 2) cancer-specific mortality, and 3) cancer survival. Bibliographic databases were searched through February 2016. Cohort studies published in English were included if adequate data were provided to estimate mortality ratios in patients with-versus-without NMSC. Data were abstracted from the total of 8 studies from independent data sources that met inclusion criteria (n=3 for all-cause mortality, n=2 for cancer-specific mortality, and n=5 for cancer survival). For all-cause mortality, a significant increased risk was observed for patients with a history of squamous cell carcinoma (SCC) (mortality ratio estimates (MR) 1.25 and 1.30), whereas no increased risk was observed for patients with a history of basal cell carcinoma (BCC) (MRs 0.96 and 0.97). Based on one study, the association with cancer-specific mortality was stronger for SCC (MR 2.17) than BCC (MR 1.15). Across multiple types of cancer both SCC and BCC tended to be associated with poorer survival from second primary malignancies. Multiple studies support an association between NMSC and fatal outcomes; the associations tend to be more potent for SCC than BCC. Additional investigation is needed to more precisely characterize these associations and elucidate potential underlying mechanisms.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest: The authors report no potential conflicts of interest.

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Keywords

nonmelanoma skin cancer; keratinocyte carcinoma; mortality; survival; fatality; epidemiology; systematic review; neoplasms

INTRODUCTION

Nonmelanoma skin cancer (NMSC) is diagnosed more commonly than all other malignancies combined, and it is a growing public health problem due to its increasing incidence [27] and attendant medical care costs [8]. NMSC consists of two major histologic subtypes, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). NMSC is generally easily curable with surgical excision and is rarely fatal. Despite such a favorable prognosis, there is evidence that NMSC may be a marker of other adverse health outcomes. An association between NMSC and increased risk of other malignancies has been well documented [1, 30, 37]. A smaller but growing body of evidence raises the possibility that NMSC may also be associated with increased mortality [4,12, 14–19, 24, 26, 34]. The variable methods and findings of existing studies make it difficult to discern the consistency and strength of the association between NMSC and mortality, necessary first steps for assessing whether the association is genuine or rather is artifactual. For example, this link could be related to confounding factors, such as socioeconomic status or smoking. Further, because NMSC is associated with increased risk of other types of cancer, an increase in all-cause mortality could be the result of an increase in cancer-specific mortality.

To clarify the relationship between NMSC and mortality, we summarized the existing evidence by performing a systematic review to address the following three questions: 1) is NMSC associated with all-cause mortality? 2) is NMSC associated with cancer-specific mortality? and 3) is NMSC associated with poorer survival among patients diagnosed with another type of cancer? Characterizing the published evidence for each of these interrelated questions will help to unify a currently disparate body of evidence and help to bring clarity to questions that currently elude clear interpretation.

METHODS

In February 2016, a literature review within the PubMed and SCOPUS databases was conducted. The search strategy was a title search that used the following specific search terms and Boolean logic: ((cutaneous basal cell OR cutaneous squamous cell OR keratinocyte OR nonmelanoma OR skin) AND (cancer OR carcinoma)) AND (death OR mortality OR prognosis OR survival). Other databases searched, including the Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus and Health Source, did not retrieve any additional relevant studies. The electronic searches were supplemented with hand-searches of references in related articles identified in PubMed citations.

Studies eligible for inclusion in this systematic review met the following criteria: a) were cohort studies involving patients with a NMSC diagnosis, b) provided an estimate of a mortality ratio or relative risk of death for the association of NMSC and mortality; and c) were reported in English. Exclusion criteria included: a) only reported associations with

cause-specific fatal outcomes other than cancer such as suicide [22]; b) evaluation of NMSC-specific mortality; and c) assessment of rare skin cancers other than BCC or SCC, such as Merkel cell carcinoma and adnexal cell carcinoma, or precursor skin conditions, such as actinic keratosis [11].

The initial electronic bibliographic database search yielded 191 studies, of which 6 studies met the inclusion criteria. An additional 6 studies that met the inclusion criteria were ascertained via hand-searches of related articles, for a total of 12 articles eligible for inclusion in the systematic review. However, the evidence was complicated by the fact that of the seven published reports that included evidence for the association between NMSC and all-cause mortality, five were from Denmark and had a considerable degree of overlapping data [5, 14–17]. In these Danish studies by Jensen and colleagues and by Brøndum-Jacobsen et al., the NMSC patient populations were derived from either the Gerda Frentz Cohort (GFC), a Danish cohort of prospectively recorded patients with NMSC seen by dermatologists in 1995, or the Danish Cancer Registry (DCR) between the years of 1978 to 2006, as shown in Table 1. The 2007 report used almost the same patient data as the previous 2006 report, with the addition of two more years of data from the GFC and DCR, as its purpose was to compare data between the two registries. The DCR and GFC cohorts overlap as patients with NMSC in the GFC cohort are a subset of the DCR population [17]. The 2008 report sought to examine total and cause-specific mortality among patients with NMSC by comparing mortality rates to those computed from the general population and used a larger set of patient data from years 1978 to 2001. This time period includes much of the DCR data used in the other three reports of Jensen et al. Not surprisingly, given the large degree of overlap (i.e., lack of statistical independence) in the study populations from all four of these publications from Denmark by Jensen and colleagues, each of the four reports yielded similar results. Therefore, to avoid redundancy the 2008 report data are used as the sole data source presented in the evidence tables, but for completeness the results from the other Danish reports are noted in the text. After this step, the number of studies summarized in the evidence tables was 3 for all-cause mortality, 2 for cancer-specific mortality, and five studies of survival after diagnosis with a type of cancer other than NMSC.

Data extracted from the reports were measurements of relative mortality risks, including mortality rate ratios (MRR), standardized mortality ratios (SMR), hazard ratios (HR), and relative risks of death (RR). Henceforth, for our purposes the term “mortality ratio” (MR) is used to generically refer to this spectrum of measures of association that are calculated in different ways. When multiple mortality ratio estimates were provided with different adjustments, the estimates with the greatest number of adjustments were used. When sub-analyses with multiple stratifications were provided, the least-stratified results were used. If data for both NMSC and individual histologic subtypes were provided, all of the estimates were included in the results for comparative purposes.

SCC and BCC commonly occur in the same patients. In studies that explicitly stated how these patients were handled, they were either assigned to both BCC and to SCC separately [17, 24], assigned to the SCC group [15], or assigned to both groups as well as analyzed separately as a group of patients with “mixed NMSC” [14].

In studies for which only sex-specific but no overall mortality ratios were reported, the sex-specific mortality ratios were combined to calculate an overall mortality ratio for the total study population. Calculations were performed algebraically on the log scale, resulting in combined averages and errors weighted by sample size [33]. Standard errors of the sex-specific mortality ratios were calculated by dividing the width of the reported 95% confidence interval by 2×1.96. The final combined estimates were exponentiated back to the original scale.

RESULTS

NMSC and all-cause mortality

Three published reports that included evidence for the association between NMSC and all-cause mortality are summarized in Table 2, two prospective cohort studies [19, 26] and a retrospective cohort study [14]. Kahn et al. used data from the American Cancer Society's (ACS) Cancer Prevention Study II(CPS-II) that enrolled 1,184,659 ACS volunteers ≥30 years of age in 1982 throughout the United States and Puerto Rico, assessed history of NMSC through self-report, and ascertained outcomes through 1994 via active follow-up and linkage to the National Death Index [19]. NMSC was observed to be associated with a slight increase in relation to all-cause mortality (mortality ratio (MR) 1.04; 95% CI 1.01–1.06). The results of the additional report from Denmark by Brondum-Jacobsen et al. [5] was slightly in the inverse direction (mortality ratio 0.97; 95% CI 0.96–0.99).

Two studies presented results stratified by histologic type. The cohort study of Rees et al. followed 2,713 participants from a population-based case-control study, the New Hampshire Skin Cancer Study. Outcomes were ascertained by linking deaths to the New Hampshire State Cancer Registry and National Death Index from 1993 to 2002 [26]. Patients with a history of BCC had a hazard ratio of 0.96 (95% CI 0.77–1.19) in the study of Rees et al. [26] and standardized mortality ratio of 0.97 (95% CI 0.96–0.98) in the study of Jensen et al. [14]. The results of the additional reports from Denmark by Jensen and colleagues [15–17] were slightly stronger inverse associations ranging from 0.89 (95% CI 0.83–0.95) [16] to 0.96 (95% CI 0.91–1.00) [17].

Whereas the evidence for BCC pointed toward an inverse association with all-cause mortality, the evidence for SCC was in the opposite direction. Specifically, the associations for SCC were a hazards ratio of 1.25 (95% CI 1.01–1.54) [24] and SMR of 1.30 (95% CI 1.26–1.33) [14]. The results of the additional reports from Denmark by Jensen and colleagues [15–17] were consistently in the direction of increased risk and of comparable [17] or greater [16] magnitude. In the age-stratified data presented in the 2010 report [15] there was evidence of a strong interaction with a stronger association in those <70 years of age (MRR 1.54; 95% CI 1.41–1.68) compared to older age groups. The sole study to explicitly evaluate "mixed NMSC" patients described a "similar excess mortality" as was observed among patients with SCC alone [14].

NMSC and cancer-specific mortality

Two studies provided data to assess the association between NMSC and cancer-specific mortality (Table 3). In the ACS CPS II Cohort, NMSC was associated with a significantly elevated cancer death rate (MR 1.28; 95% CI 1.22–1.34) [19]. In the study of Jensen et al. carried out in Denmark [14], significantly increased mortality from malignancy was observed for a personal history of BCC (MR 1.15; 95% CI 1.13–1.18) and an even stronger association for SCC (MR 2.17; 95% CI 2.08–2.26) (Table 3) [14]. The results of an additional report from Denmark by Jensen et al. [16] revealed a similar pattern of associations but attenuated, with MRs of 1.01 for BCC and 1.63 for SCC.

NMSC and survival in cancer patients

Five studies provide evidence for the association between a history of NMSC and survival in cancer patients. They include patient populations from Denmark, Sweden, Canada, and the United States (Table 1)[4, 12, 18, 24, 34] and assess a variety of cancer sites, including multiple cancer sites grouped, Non-Hodgkin lymphoma (NHL) and the phenotypic variant chronic lymphocytic leukemia (CLL), colon cancer, lung cancer, breast cancer, and prostate cancer.

In a cohort comprised of patients with heterogeneous types of cancer, both BCC (MR 1.14; 95% CI 1.10–1.18) and SCC (MR 1.33; 95% CI 1.15–1.55) were associated with significantly increased mortality [24] (Table 4). The significantly worse survival in patients with-versus-without a prior history of SCC was also corroborated by Johannesdottir et al. [18].

Some studies reported on survival after diagnosis with specific types of cancer. In a study of CLL, mortality was significantly increased among those with NMSC compared with those with no personal history of NMSC (MR 1.29; 95% CI 1.10–1.52) [34]; the association for SCC was even stronger (MR 1.86; 95% CI 1.46–2.36) [34]. However, this study was unable to distinguish to what extent deaths from SCC contributed to this association as patients with CLL have an elevated risk of death from SCC [21]. In all other reports that studied the association of mortality in NHL patients with and without NMSC, the mortality ratios were in the direction of increased risk even if not statistically significant. In the two studies that presented results stratified by histologic type, the mortality ratios were slightly stronger for SCC than for BCC in both: 1.75 vs. 1.51 [12] and 1.21 vs. 1.06 [24].

Among patients with colon cancer, BCC was associated with a statistically significant increase in mortality (MR 1.24; 95% CI 1.10–1.40) in one report [24] but no association was observed in another report [12]. For SCC, however, the four MR estimates were consistently in the risk direction with three of these statistically significant. In patients with lung cancer, the evidence pointed in the direction of increased risk in all three studies. In the study of Nugent et al. [24], increased mortality was observed for lung cancer patients with a history of BCC (MR 1.11; 95% CI 1.01–1.22) and with a history of SCC (MR 1.25; 95% CI 1.05–1.48); the mortality ratio estimates for SCC from two other studies mimicked the results of Nugent et al. [4, 18]. Of the three reports assessing mortality in breast cancer patients with a history of NMSC, the MRs for SCC were 1.09 (95% CI 0.82–1.43), 1.12 (95% CI 0.31–

2.88), and 1.37 (95% CI 0.97–2.36) and for BCC was 1.02 (0.88–1.88). Three reports also assessed mortality in NMSC patients with prostate cancer. One of these observed a significant decrease in mortality for prostate cancer patients with a history of BCC (MR 0.85) whereas one observed a significant increase in mortality in patients with a history of SCC (MR 1.17); the two remaining reports were specific to SCC and the mortality ratio estimates were close to the null and not statistically significant.

DISCUSSION

In this systematic review the existing evidence was summarized related to the associations between a personal history of NMSC and 1) all-cause mortality, 2) cancer-specific mortality, and 3) survival in cancer patients. The systematic review identified 12 published reports from 8 independent data sources that met the eligibility criteria. These reports included data from four different countries published from 1998 to 2015. Two overarching themes emerged from the results. First, there was at least some signal that NMSC was associated with increased risk for each of the fatal outcomes studied. Second, the results for each outcome revealed heterogeneity by histologic type, with associations consistently stronger for SCC than BCC. For all-cause mortality the risk association was actually completely confined to those with SCC. Studies of relative survival in NMSC patients only were not eligible for inclusion, but a study of relative survival in SCC and BCC patients in Germany observed that relative survival in SCC patients was 93.6% compared with 102.9% in BCC patients [6]. Although relative survival estimates do not map back directly to mortality ratios, these estimates corroborate our findings for all-cause mortality in indicating that compared with the general population without NMSC, SCC is associated with excess mortality whereas BCC is associated with reduced mortality. Hollestein et al. [13] observed a similar relative survival rate for SCC and commented "…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 over-estimated SCC-specific mortality, resulting in lower relative survival estimates." In the one study of cancer-specific mortality the association was much stronger for SCC compared with BCC (MR 2.17 vs. 1.15) [14]. Given the importance of this heterogeneity by histologic type, the ensuing discussion focuses on the stratified results.

A key question is if the association between SCC and all-cause mortality is driven by an increase in cancer-specific mortality, and therefore perhaps due to fact that SCC is a marker of increased risk for other malignancies. The reasons outlined below make it safe to infer that this is not the case. First, both SCC and BCC are markers of increased risk for other malignancies but only SCC was associated with increased all-cause mortality, suggesting that the all-cause mortality increase in SCC is not due solely to increasing risk of other cancers. Second, Rees et al. specifically addressed this question and the findings indicated that the overall mortality increase in SCC patients could not be attributed solely to the increased occurrence of cancer in SCC patients [26]. Third, if the excess all-cause mortality in SCC patients was driven exclusively by cancer mortality, then no increased mortality from causes of death other than cancer would be expected. In at least one report that examined cause-specific mortality from several causes, BCC showed an elevation in risk of other cancers but was significantly inversely associated with chronic and infectious causes of

mortality whereas SCC was associated with significant increases in mortality not only from cancer, but also from chronic obstructive pulmonary disease, cardiovascular diseases, acute infections, and pneumonia [14]. These results not only reinforce the substantive difference in the associations of all-cause mortality with SCC but not BCC, but the heterogeneous causes of death observed to be associated with SCC is thought-provoking and consistent with an association with underlying immune dysfunctions.

The risk of cardiovascular disease is known to be increased in individuals with underlying inflammatory diseases including psoriasis and rheumatoid arthritis [25]. The increase in mortality among SCC patients from acute infection and pneumonia [14] raises the possibility of an underlying immunosuppression among individuals with SCC which predisposes to infection. Patients with underlying immunosuppression, including due to solid organ transplantation and underlying chronic lymphocytic leukemia, are at increased risk of developing cutaneous SCC [20]. Further evidence that immune dysregulation may be a contributing factor to the stronger associations with mortality observed for SCC than BCC stems from the observation that even though BCC is more common than SCC by approximately a 4:1 ratio in the general population, the incidence of BCC and SCC is reversed in transplant patients who are immunosuppressed; in immunosuppressed patients, SCC occurs ten times more frequently than BCC [38]. The notion that SCC is more strongly linked than BCC to immune dysregulation provides a viable explanation for why SCC but not BCC would be associated with all-cause mortality and how SCC could be associated with an increase in all-cause mortality via pathways other than increased cancer incidence.

This line of reasoning is further buttressed by differences in the role of exposure to solar ultraviolet radiation (UVR) in the etiology of SCC and BCC. UVR is the strongest environmental risk factor for both BCC and SCC, but BCC is most strongly associated with intermittent UVR exposure whereas SCC is most strongly linked with cumulative lifetime UVR exposure [20]. UVR exposure is known to result in immune suppression [35]. Further, humans have no response, such as photoadaptation or photoprotection, which diminishes UVR-induce immune suppression over time; thus, long-term chronic UVR exposure results in long-term chronic immune suppression [23]. SCC is therefore more likely than BCC to be a marker of greater cumulative immune suppression over a lifetime. In turn, immune dysregulation is hypothesized to play a central role in the pathogenesis of chronic diseases that are leading causes of death in middle and upper income nations, such as cardiovascular disease and cancer [7, 9].

The socioeconomic status (SES) differential between SCC and BCC may also come into play as either a confounder or a mediator. The risk of both SCC and BCC increase with higher levels of SES, but the association is much stronger for BCC than for SCC [32]. SES is inversely associated with overall mortality [29]. If on average patients diagnosed with BCC are of higher SES than those with SCC, then the stronger associations with mortality for SCC compared with BCC could be due partly to the SES differential between the two, with SES acting as a confounder. Conversely, SES could play a mediating role. Across a broad spectrum of specific microorganisms the prevalence of infection increases with lower SES [10]. The complex interplay between SES, infectious diseases, and SCC/BCC aligns with the hypothesis described above that immune status may be a factor contributing to why

SCCs but not BCCs are associated with excess mortality rates. Compared with persons of higher SES, persons from lower SES levels have increased risk of both SCCs and infections.

The heterogeneity in the findings by histologic type also impact the research approaches to this topic. When considering fatal outcomes, stratifying by histologic type is essential because any grouped category of NMSC will mix the divergent influence of SCC and BCC. This is illustrated by the MRs for “NMSC” being intermediate between those of BCC and SCC, more closely approximating the lesser MRs of BCC because the incidence rates of BCC greatly exceed those of SCC [20]. The SCC/BCC heterogeneity also elevates the importance of paying direct attention to patients who have been diagnosed with both SCC and BCC. This group comprises only a small proportion of all NMSC patients, but evaluating the associations for this group separately—rather than embedding them within both SCC and BCC patients—holds promise for generating new insights into the differential associations in SCC vs. BCC.

Limitations of this study include the relatively small number of studies that have been conducted for each specific type of fatal outcome considered in this review, with further uncertainty introduced by the fact that the relevant data were generated using heterogeneous approaches to study design and control of potential confounding variables. Most of the studies were limited to pathology-confirmed NMSC cases but one study relied on self-reported NMSC [19].

The lack of rigorous control for potential confounding factors is a limitation for the existing body of evidence on the topic of NMSC in relation to the fatal outcomes reviewed, leaving open the possibility that the observed associations could be due to confounding factors and therefore indirect. That is, if factors associated with multiple causes of death were also more prevalent in NMSC patients then this would contribute to NMSC appearing to be associated with greater mortality rates.

A potential example of such a factor is cigarette smoking. Cigarette smoking is causally associated with many major causes of death [2, 3] and has been observed in at least some studies to be more common in NMSC patients, especially those with SCC [28, 31]. Further, smoking is more prevalent among individuals of lower SES [36]. The results for cigarette smoking also tie into the hypothesis that immune dysregulation is an important underlying contributor to the stronger role of SCC-versus-BCC in relation to fatal outcomes, as cigarette smoking is a cause of inflammation and immune dysregulation [36].

Only two of the published studies acquired individual-level data in which more confounding factors could be adjusted for, including cigarette smoking [19, 26] plus a variety of health, behavior, and environmental exposures [19] versus the other registry-based studies in which often only age, gender, and calendar period could be adjusted for. The fact that the associations still persisted in these studies that adjusted for potential confounding variables [19, 26] provides preliminary evidence to suggest that the association between SCC and fatal outcomes may not be due to confounding, but this issue awaits more thorough assessment in future studies.

The current body of evidence indicating that SCC may be associated with increased mortality rates is intriguing, and the public health importance of these associations is underscored by the high prevalence of SCC. Further research is needed to establish the validity of these associations, particularly studies with the capability of adjusting for individual-level factors and stratifying by histologic subtype of NMSC. Further study is also needed to elucidate the mechanisms underlying these associations to determine if these associations may have significance for translation into the clinical setting. For example, knowing why SCC is a marker of decreased survival in cancer patients could potentially impact cancer treatment planning. Further, simple interventions such as recommending age-appropriate cancer screening and thorough review of systems for patients diagnosed with SCC may help to increase earlier detection of second malignancies at an earlier and more treatable stage.

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References

1. Alberg AJ, Fischer AH. Is a personal history of nonmelanoma skin cancer associated with increased or decreased risk of other cancers? Cancer Epidemiol Biomarkers Prev. 2014; 23(3):433–6. [PubMed: 24609852]
2. Alberg AJ, Shopland DR, Cummings KM. The 2014 Surgeon General's report: commemorating the 50th Anniversary of the 1964 Report of the Advisory Committee to the US Surgeon General and updating the evidence on the health consequences of cigarette smoking. Am J Epidemiol. 2014; 179(4):403–12. [PubMed: 24436362]
3. Alberg AJ. Cigarette smoking: health effects and control strategies. Drugs Today (Barc). 2008; 44(12):895–904. [PubMed: 19198699]
4. Askling J, Sørensen P, Ekbom A, Frisch M, Melbye M, Glimelius B, Hjalgrim H. Is history of squamous-cell skin cancer a marker of poor prognosis in patients with cancer? Ann Intern Med. 1999; 131(9):655–9. [PubMed: 10577327]
5. Brøndum-Jacobsen P, Nordestgaard BG, Nielsen SF, Benn M. Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause. Int J Epidemiol. 2013; 42(5):1486–96. [PubMed: 24038635]
6. Eisemann N, Jansen L, Castro FA, Chen T, Eberle A, Nennecke A, Zeissig SR, Brenner H, Katalinic A. GEKID Cancer Survival Working Group. Survival with nonmelanoma skin cancer in Germany. Br J Dermatol. 2016; 174(4):778–85. [PubMed: 26676514]
7. Givennikov SI, Greten Fr, Karin M. Immunity, inflammation, and cancer. Cell. 2010; 140:883–899. [PubMed: 20303878]
8. Guy GP Jr, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002–2006 and 2007–2011. Am J Prev Med. 2015; 48(2):183–7. [PubMed: 25442229]
9. Haas MJ, Mooradian AD. Regulation of high-density lipoprotein by inflammatory cytokines: establishing links between immune dysfunction and cardiovascular disease. Diabetes Metab Res Rev. 2010; 26(2):90–9. [PubMed: 20047197]
10. Hadler JL, Vugia DJ, Bennett NM, Moore MR. Emerging Infections Program efforts to address health equity. Emerg Infect Dis. 2015; 21(9):1589–94. [PubMed: 26291875]

11. He W, Zhu F, Ma X, Zhao X, Zheng M, Chen Z, Heymsfield SB, Zhu S. Actinic skin damage and mortality--the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. PLoS One. 2011; 6(5):e19907. [PubMed: 21603643]
12. Hjalgrim H, Frisch M, Storm HH, Glimelius B, Pedersen JB, Melbye M. Non-melanoma skin cancer may be a marker of poor prognosis in patients with non-Hodgkin's lymphoma. Int J Cancer. 2000; 85(5):639–42. [PubMed: 10699942]
13. 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. Eur J Cancer. 2012; 48(13):2046–53. [PubMed: 22342554]
14. Jensen AØ, Bautz A, Olesen AB, Karagas MR, Sørensen HT, Friis S. Mortality in Danish patients with nonmelanoma skin cancer, 1978–2001. Br J Dermatol. 2008; 159(2):419–25. [PubMed: 18616784]
15. Jensen AØ, Lamberg AL, Jacobsen JB, Braae Olesen A, Sørensen HT. Non-melanoma skin cancer and ten-year all-cause mortality: a population-based cohort study. Acta Derm Venereol. 2010; 90(4):362–7. [PubMed: 20574600]
16. Jensen AØ, Olesen AB, Dethlefsen C, Sørensen HT. Ten year mortality in a cohort of nonmelanoma skin cancer patients in Denmark. J Invest Dermatol. 2006; 126(11):2539–41. [PubMed: 16778794]
17. Jensen AØ, Olesen AB, Dethlefsen C, Sørensen HT. Do incident and new subsequent cases of non-melanoma skin cancer registered in a Danish prospective cohort study have different 10-year mortality? Cancer Detect Prev. 2007; 31(5):352–8. [PubMed: 18031945]
18. Johannesdottir SA, Lash TL, Jensen AØ, Farkas DK, Olesen AB. Mortality in cancer patients with a history of cutaneous squamous cell carcinoma--a nationwide population-based cohort study. BMC Cancer. 2012; 12:126. [PubMed: 22458954]
19. Kahn HS, Tatham LM, Patel AV, Thun MJ, Heath CW Jr. Increased cancer mortality following a history of nonmelanoma skin cancer. JAMA. 1998; 280(10):910–2. [PubMed: 9739976]
20. Karagas, M., Weinstock, M., Nelson, H. Cancer epidemiology and prevention. 3. New York: Oxford University Press; 2006. Keratinocyte carcinomas (basal and squamous cell carcinomas of the skin); p. 1230-1250.
21. Mehrany K, Weenig RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. J Am Acad Dermatol. 2005; 53(6):1067–71. [PubMed: 16310071]
22. Muff Christensen ML, Yousaf U, Engholm G, Storm HH. Increased suicide risk among Danish women with non-melanoma skin cancer, 1971–1999. Eur J Cancer Prev. 2006; 15(3):266–8. [PubMed: 16679871]
23. Norval M, McLoone P, Lesiak A, Narbutt J. The effect of chronic ultraviolet radiation on the human immune system. Photochem Photobiol. 2008; 84(1):19–28. [PubMed: 18173697]
24. Nugent Z, Demers AA, Wiseman MC, Mihalcioiu C, Kliewer EV. Risk of second primary cancer and death following a diagnosis of nonmelanoma skin cancer. Cancer Epidemiol Biomarkers Prev. 2005; 14(11 Pt 1):2584–90. [PubMed: 16284382]
25. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, Troxel AB, Hennessy S, Kimmel SE, Margolis DJ, Choi H, Mehta NN, Gelfand JM. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis. 2015; 74(2):326–32. [PubMed: 25351522]
26. Rees JR, Zens MS, Celaya MO, Riddle BL, Karagas MR, Peacock JL. Survival after squamous cell and basal cell carcinoma of the skin: A retrospective cohort analysis. Int J Cancer. 2015; 137(4): 878–84. [PubMed: 25598534]
27. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. Population, 2012. JAMA Dermatol. 2015; 151(10): 1081–6. [PubMed: 25928283]
28. Rollison DE, Iannacone MR, Messina JL, Glass LF, Giuliano AR, Roetzheim RG, Cherpelis BS, Fenske NA, Jonathan KA, Sondak VK. Case-control study of smoking and non-melanoma skin cancer. Cancer Causes Control. 2012; 23(2):245–254. [PubMed: 22101452]

29. Signorello LB, Cohen SS, Williams DR, Munro HM, Hargreaves MK, Blot WJ. Socioeconomic status, race, and mortality: a prospective cohort study. Am J Public Health. 2014; 104(12):e98–e107.

30. Small J, Barton V, Peterson B, Alberg AJ. Keratinocyte carcinoma as a marker of a high cancer-risk phenotype. Adv Cancer Res. 2016; 130:257–91. [PubMed: 27037755]

31. Song F, Qureshi AA, Gao X, Li T, Han J. Smoking and risk of skin cancer: a prospective analysis and a meta-analysis. Int J Epidemiol. 2012; 41(6):1694–1705. [PubMed: 23064412]

32. Steding-Jessen M, Birch-Johansen F, Jensen A, Schüz J, Kjær SK, Dalton SO. Socioeconomic status and non-melanoma skin cancer: a nationwide cohort study of incidence and survival in Denmark. Cancer Epidemiol. 2010; 34(6):689–95. [PubMed: 20638927]

33. Tatebe, K. Combining multiple averaged data points and their errors. White Paper. 2005. Retrieved from http://isi.ssl.berkeley.edu/~tatebe/whitepapers/Combining%20Errors.pdf

34. Toro JR, Blake PW, Björkholm M, Kristinsson SY, Wang Z, Landgren O. Prior history of non-melanoma skin cancer is associated with increased mortality in patients with chronic lymphocytic leukemia. Haematologica. 2009; 94(10):1460–4. [PubMed: 19794092]

35. Ullrich SE. Sunlight and skin cancer: lessons from the immune system. Mol Carcinog. 2007; 46(8): 629–33. [PubMed: 17443748]

36. U.S. Department of Health and Human Services. The health consequences of smoking: A report of the Surgeon General. Atlanta, GA: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, Office on Smoking and Health; 2014.

37. Wheless L, Black J, Alberg AJ. Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2010; 19(7):1686–95. [PubMed: 20570907]

38. Xie, J. Molecular biology of basal and squamous cell carcinomas. In: Reichrath, J., editor. Sunlight, vitamin D and skin cancer. Springer; New York: 2008. p. 241-251.

Table 1

A summary of studies with relevant data on the association between nonmelanoma skin cancer and 1) all-cause mortality; 2) cancer-specific mortality, and 3) survival after the diagnosis with another form of cancer.

First Author (Year)	Location	Study type	Study period	Case Ascertainment	NMSC type	# NMSC cases	Outcome(s)	Adjustments
Askling (1999) [4]	Sweden	Retrospective cohort (Swedish Cancer Registry)	1958–1996	ICD codes from registry data	SCC	1,660	Cancer survival	A, G, C
Brøndum-Jacobsen (2013) [5]	Denmark[a]	Case-control (Danish Cancer Registry)	1980–2006	ICD codes from registry	NMSC	129,206	All-cause mortality	Matched w/ 5 controls on A,G,C, plus adj.for SES, exercise
Hjalgrim (2000) [12]	Denmark	Registry based (Danish Cancer Registry)	1978–1994	ICD codes from registry	NMSC (BCC, SCC)	605	Cancer survival	A, G, C
Jensen (2006) [16]	Denmark[a]	Registry based (Gerda Frentz Cohort)	1995–2004	ICD codes from registry	BCC, SCC	3,209	All-cause mortality; Cancer-specific mortality	CO, civil status
Jensen (2007) [17]	Denmark[a]	Registry based (Gerda Frentz Cohort & Danish C.R.)	1995–2006	ICD codes from registry	BCC, SCC	9,709	All-cause mortality	A, G, RL
Jensen (2008) [14]	Denmark	Registry based (Danish Cancer Registry)	1978–2001	ICD codes from registry	BCC, SCC	96,290	All-cause mortality; Cancer-specific mortality	A, G, C
Jensen (2010) [15]	Denmark[a]	Registry based (Danish Cancer Registry)	1999–2005	ICD codes from registry	BCC, SCC	83,896	All-cause mortality	A, G, SES, CO
Johannesdottir (2012) [18]	Denmark	Registry based (Danish Cancer Registry)	1982–2003	ICD codes from registry	SCC	745	Cancer survival	A, G, C, CO, auto-immune dx, cancer stage, cancer tx
Kahn (1999) [19]	United States	Prospective study (Cancer Prevention Study II)	1982–1994	Self-report	NMSC	47,706	All-cause mortality; Cancer-specific mortality[b]	A, R, MS, CO, S, SES, MULT
Nugent (2005) [24]	Canada	Registry based (Manitoba	1956–2000	ICD codes from registry	BCC, SCC	36,789	Cancer survival	A, G, cancer site

First Author (Year)	Location	Study type	Study period	Case Ascertainment	NMSC type	# NMSC cases	Outcome(s)	Adjustments
		Cancer Registry)						
Rees (2015) [26]	New Hampshire	Retrospective cohort (New Hampshire Skin Cancer Study)	1993–2009	Pathologic confirmation	BCC, SCC	2,713	All-cause mortality	A, G, S
Toro (2009) [34]	Sweden	Registry based (Swedish Cancer Registry)	1958–2003	ICD codes from registry	NMSC, SCC	236	Cancer survival	A, G, C

A, age; G, gender; C, calendar period; CO, comorbidity; MS, marital status; R, race; RL, residence location; S, smoking; SES, socioeconomic status; MULT= family cancer hx, BMI, alcohol use, exercise, diet, aspirin use, women hormone use, reproductive hx.

[a] Not included in evidence tables due to overlap with Jensen et al. 2008.

[b] Only study that explicitly stated deaths attributed to NMSC were excluded from the calculation of the mortality ratios.

Table 2

A summary of the evidence from prospective studies reporting on the association between nonmelanoma skin cancer (NMSC), basal cell carcinoma of the skin (BCC), and squamous cell carcinoma of the skin (SCC) in relation to all-cause mortality.

First Author (Year)	Measure of Association	NMSC MR (95% CI)	BCC MR (95% CI)	SCC MR (95% CI)
Kahn (1998) [19]	RR	1.04 (1.01–1.06)	NP	NP
Jensen (2008) [14]	SMR	NP	0.97 (0.96–0.98)	1.30 (1.26–1.33)
Rees (2015) [26]	HR	NP	0.96 (0.77–1.19)	1.25 (1.01–1.54)

MR, mortality ratio; RR, relative risk; SMR, standardized mortality ratio; HR, hazard ratio NP, Not Presented

Table 3

A summary of the evidence from prospective studies reporting on the association between nonmelanoma skin cancer (NMSC), basal cell carcinoma of the skin (BCC), and squamous cell carcinoma of the skin (SCC) in relation to cancer-specific mortality.

First Author (Year)	Measure of Association	NMSC MR (95% CI)	BCC MR (95% CI)	SCC MR (95% CI)
Kahn[a] (1998) [19]	RR	1.28 (1.22–1.34)	NP	NP
Jensen[a] (2008) [14]	SMR	NP	1.15 (1.13–1.18)	2.17 (2.08–2.26)

MR, mortality ratio; RR, relative risk; SMR, standardized mortality ratio

NP, Not presented

[a]The study of Kahn et al. explicitly excluded NMSC deaths from the calculation of the mortality ratio, the study of Jensen et al. did not.

Table 4

A summary of the evidence from prospective studies reporting on the association between nonmelanoma skin cancer (NMSC), basal cell carcinoma of the skin (BCC), and squamous cell carcinoma of the skin (SCC) in relation to cancer survival.

	First Author (Year)	All MR(95% CI)	NHL/CLL MR(95% CI)	Colon MR(95% CI)	Lung MR(95% CI)	Breast MR(95% CI)	Prostate MR(95% CI)
NMSC	Toro (2009) [34]	NA	1.29 (1.10–1.52)*	NA	NA	NA	NA
	Hjalgrim (2000) [12]	NA	1.32 (1.07–1.63)	0.99 (0.86–1.14)	NA	NA	NA
BCC	Nugent (2005) [24]	1.14 (1.10–1.18)	1.06 (0.88–1.27)	1.24 (1.10–1.40)	1.11 (1.01–1.22)	1.02 (0.88–1.18)	0.85 (0.77–0.94)
	Hjalgrim (2000)[12]	NA	1.51 (1.15–1.99)*	0.95 (0.79–1.14)	NA	NA	NA
SCC	Johannesdottir (2012) [18]	1.13 (1.04–1.23)	1.09 (0.81–1.47)	1.13 (0.92–1.40)	1.23 (1.05–1.43)	1.09 (0.82–1.43)	0.97 (0.81–1.15)
	Toro (2009) [34]	NA	1.86 (1.46–2.36)	NA	NA	NA	NA
	Nugent (2005) [24]	1.33 (1.15–1.55)	1.21 (0.88–1.67)	1.29 (1.01–1.65)	1.25 (1.05–1.48)	1.12 (0.31–2.88)	1.07 (0.91–1.27)
	Hjalgrim (2000) [12]	NA	1.75 (0.98–3.13)*	1.60 (1.06–2.40)	NA	NA	NA
	Askling (1998) [4]	NA	1.39 (1.17–1.64)	1.26 (1.09–1.47)	1.23 (0.95–1.60)	1.37 (0.97–2.36)○	1.17 (1.04–1.33)

MR, mortality ratio

NA, Not Applicable;

*studied only the chronic lymphocytic leukemia (CLL) subtype of NHL;

○in patients >70 years of age