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Research Article
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Subsequent Primary Malignancies in Patients with Nonmelanoma Skin Cancer in England: A National Record-Linkage Study

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Abstract

Background: Conflicting evidence exists about whether people with a history of nonmelanoma skin cancer (NMSC) are at higher risk of subsequent primary malignant cancers than those without.

Methods: An all England record-linked hospital and mortality dataset spanning from 1999 to 2011 was used. We constructed two cohorts: one that comprised people with a history of NMSC (502,490 people), and a control cohort that comprised people without. We "followed up" these two cohorts electronically to determine observed and expected numbers of people with subsequent primary cancers in each, based on person-years at risk, and calculated standardized risk ratios (RR).

Results: Comparing the NMSC cohort with the non-NMSC cohort, the RR for all subsequent malignant cancers combined was 1.36 [95% confidence interval (CI), 1.35–1.37]. Significantly increased RRs ($P < 0.05$) were found for 26 of the 29 cancer types studied, in particular for salivary gland, melanoma, bone, and upper gastrointestinal tract cancers. The RRs were also particularly high when comparing younger people with and without NMSC.

Conclusions: NMSC is strongly associated with a broad spectrum of other primary cancers, particularly in younger age groups. The pattern suggests a genetic or early-acquired etiologic association.

Impact: These results represent what can be done using very large, linked, routinely collected administrative datasets; but such datasets lack detail. Further work to establish the mechanisms behind these associations is warranted. *Cancer Epidemiol Biomarkers Prev; 23(3); 490–8. ©2014 AACR.*

Introduction

Nonmelanoma skin cancer (NMSC) is the commonest malignancy in white populations, and its incidence is increasing (1, 2). The two key known mechanisms of cutaneous carcinogenesis are UV-induced genetic damage and suppression of skin immune tumor surveillance responses (3). UV exposure is considered to account for an increased risk of subsequent NMSC and melanoma in individuals after a first NMSC (4, 5).

There is conflicting literature on whether individuals with NMSC are at increased risk of developing primary malignancies that are not known to be associated with UV radiation. Comparatively large individual studies investigating this question include two local UK registry-based studies (6, 7), a nationwide study in Finland (8), and a US prospective cohort study of health professionals (9), all of which showed significant increases in a range of cancers after NMSC. Another UK registry-based study, however, showed no such increased risks and indeed significant risk reductions in certain cancers, including of the breast and prostate (10). Of two worldwide meta-analyses that have investigated the literature on NMSC and other cancers, one found that the risk of cervical, colon, gastric, and rectal cancers is significantly reduced in people with NMSC, and concluded that solar UVB (shortwave) irradiance reduces the risk of many internal cancers, with the likely mechanism being the protective effects of increased production of vitamin D (11); the other meta-analysis concluded that NMSC is associated with a significantly increased risk of a broad spectrum of subsequent malignancies (5). Certain cancers, such as salivary, have consistently been found to be particularly associated with NMSC (5, 11). Some evidence exists that second primary cancer risks are higher in younger individuals with NMSC than older (12), suggesting a genetic or early-acquired etiology.

We aimed to contribute to the literature by using a linked dataset covering the whole of England during the period from 1999 to 2011, making this the largest single epidemiologic study so far to investigate whether a

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history of NMSC is a significant risk factor for other subsequent primary cancers.

Materials and Methods

Setting and dataset

The dataset contained Hospital Episode Statistics (administrative data routinely collected for each hospital admission or episode of day-case care in all NHS hospitals) and data on mortality, obtained from national death registrations, from January 1, 1999, to December 31, 2011. The hospital data were supplied by the English National Information Centre for Health and Social Care and mortality data by the Office for National Statistics. Both sources of data contain diagnosis codes using the International Classification of Diseases 10th Revision (ICD-10). Successive records for each individual were linked together to create a single dataset for analysis. The record linkage was carried out by the Oxford record-linkage group (13).

Subjects

A cohort was constructed comprising people with a record of hospital day-case care or inpatient admission for NMSC in which NMSC was the principal diagnosis on the record, by identifying the earliest episode of day-case care, or inpatient admission, for the condition in an NHS hospital during the study period (the "NMSC cohort"). NMSC was defined using code C44 in the 10th revision of the International Classification of Diseases (ICD).

A "reference cohort" was constructed (as a control group) by identifying individuals with a record of hospital day-case care or inpatient admission for various other, mainly minor, medical and surgical conditions and injuries (see footnote in Table 1). We selected a wide range of different conditions, rather than relying on a narrow range (in case the latter are themselves atypical in their risk of subsequent disease). Any individual in the reference cohort who was found to have a subsequent record of NMSC contributed person-days, first, to the reference cohort and were then placed into the NMSC cohort from the exact date of the first record of NMSC, in which they then contributed person-days to the NMSC cohort.

For each outcome cancer studied (below), we excluded anyone who had a record of that outcome cancer before, or at the same time as, their record of the NMSC or reference cohort condition, so as to establish the correct chronology of events for the investigation of NMSC as a potential risk factor for the subsequent outcome cancers.

Outcomes

The individuals in the NMSC cohort and reference cohort were then "followed up" by searching the database for any subsequent NHS care for, or death from, other primary malignant cancers besides NMSC ("outcome cancers"), during the study period. We searched, first, for any outcome cancer within the range ICD-10 C00–C41, C45–C75, and C81–C97, taking the earliest record of a cancer event within that range as the individual's outcome event. We then searched for specific outcome cancers individually within that range (listed in Tables 2, 3, 4, and 5).

Statistical analysis

Both cohorts were stratified for analysis, by age in 5-year groups, sex, calendar year of first recorded admission, region of residence, and quintile of patients' index of multiple deprivation (IMD) score (a measure of socioeconomic status widely used in England). We calculated the observed incidence rate of individuals with each outcome cancer in each stratum of each of the two cohorts, based on person-days of "follow-up." "Date of entry" into each cohort was the date of earliest record of NMSC or any one of the reference cohort conditions. "Date of exit" was the date of the earliest subsequent record for the outcome cancer, death, or the end of data collection period (December 31, 2011).

The indirect method of standardization was used, with the NMSC and reference cohorts taken together as the standard population. For analysis of each outcome cancer, we applied the stratum-specific incidence rates that were observed in the standard population to the number of people in each stratum of the NMSC cohort and then, separately, to those in the reference cohort, to obtain the expected number of people with the outcome cancer in each stratum of the NMSC and reference cohort. Observed (O) and expected (E) numbers for each stratum were then summed to give total observed and expected numbers of people with the outcome cancer in each of the cohorts. We then compared the observed and expected numbers of people with the outcome cancer in the NMSC cohort with those in the reference cohort, using the formula: $(O^{\mathrm{NMSC}}/E^{\mathrm{NMSC}}) : (O^{\mathrm{REF}}/E^{\mathrm{REF}})$, where the Os and Es are the observed and expected numbers in the NMSC and reference cohorts, respectively. The notation $(O^{\mathrm{NMSC}}/E^{\mathrm{NMSC}})$ gives the calculation of relative risk in the NMSC group, relative to the standard population; that of $(O^{\mathrm{REF}}/E^{\mathrm{REF}})$, gives a calculation of relative risk in the reference cohort, relative to the standard population; and we termed the result, $(O^{\mathrm{NMSC}}/E^{\mathrm{NMSC}}) : (O^{\mathrm{REF}}/E^{\mathrm{REF}})$, the "risk ratio (RR)." The RR, its confidence interval, and χ^2 statistics for its significance were calculated using standard statistical methods (14).

We used stratification, rather than matching, for the variables of age, sex, year, region, and deprivation to maximize the availability of the data, statistical power, and reduction of confounding. We did so because there is no merit in discarding data simply to have equal numbers (e.g., 1:1 or 2:1 matching) in each subgroup. To illustrate, in the age group 20 to 24 years there were 828 people in the NMSC cohort, 506,141 in the reference cohort, and 506,969 in the combined "standard" cohort. The stratum-specific rates within the 506,969 people in the standard cohort are then applied to the numbers in each substratum in the NMSC cohort and then the reference cohort. In this way, available data are maximized; statistical power is as high as it can be; there are adequate numbers to populate every

Table 1. Age distribution of people with NMSC in the study, the percentage who were women, and the number and age distribution of people in the reference cohort[a]

	England (1999–2011)		
Age at admission to the NMSC cohort	Number in the NMSC cohort (% of total)	% of Women	Number in the reference cohort
0–4	51 (<0.1)	63	589,344
5–9	119 (<0.1)	60	610,791
10–14	221 (<0.1)	53	492,236
15–19	417 (0.1)	56	466,250
20–24	813 (0.2)	60	506,114
25–29	1,773 (0.4)	58	517,977
30–34	3,618 (0.7)	55	498,316
35–39	6,602 (1.3)	55	507,940
40–44	11,041 (2.2)	54	487,475
45–49	15,988 (3.2)	52	458,286
50–54	23,497 (4.7)	49	469,656
55–59	33,157 (6.6)	46	499,147
60–64	47,141 (9.4)	43	514,123
65–69	58,452 (11.6)	41	499,152
70–74	70,951 (14.1)	41	501,378
75–79	80,465 (16)	43	484,323
80–84	72,375 (14.4)	47	369,574
85–120	75,809 (15.1)	57	315,431
All ages	502,490 (100)	46	8,787,513

[a]The reference cohort consisted of people admitted with the following conditions coded under the Office of Population, Censuses, and Surveys code (OPCS) edition 4 for operations and the ICD revision 10 for diagnoses: adenoidectomy (OPCS4 E20), tonsillectomy (F34 + F36), appendectomy (H01–H03), total hip replacement (W37–W39), total knee replacement (W40–W42), cataract (ICD 10 H25), squint (H49–H51), otitis externa/media (H60–H67), varicose veins (I83), hemorrhoids (I84), upper respiratory tract infections (J00–J06), deflected septum, nasal polyp (J33 + J34.2), impacted tooth and other disorders of teeth (K00–K03), inguinal hernia (K40), in growing toenail and other diseases of nail (L60), sebaceous cyst (L72.1), bunion (M20.1), internal derangement of knee (M23), superficial injury and contusion (S00, S10, S20, S30, S40, S50, S60, S70, S80, and S90), dislocations, sprains and strains (S03, S13, S23, S33, S43, S53, S63, S73, S83, and S93), head injury (S06), and selected limb fractures (S42, S52, S62, S82, and S92).

cell in the potential confounder data; and the resultant RRs are adjusted, as much as all available data allow, in respect of age, sex, year, region, and deprivation.

We carried out subanalyses by the age group and time interval, splitting results by age at first admission for the NMSC or reference cohort condition (grouped as <24, 25–44, 45–59, and 60+), and by time interval between the event of first admission for NMSC (or the reference cohort condition) and the event of the subsequent outcome cancer (<1, 1–4, and 5+ years).

Results

Table 1 shows the number, age, and sex distribution of people at entry to the NMSC cohort, and the number and age distribution of people in the reference cohort. In total, there were 502,490 people in the NMSC cohort and there were 8,787,513 people in the reference cohort. The mean period of follow-up in the NMSC cohort was 5.1 years; the mean period of follow-up in the reference cohort was 6.0 years. Of note, 462 people who started in the reference cohort later crossed over into the NMSC cohort. The RR, comparing the NMSC cohort with the reference cohort, for all outcome cancers combined in people across all ages and all time intervals, was 1.36 (95% CI, 1.35–1.37). When we excluded melanoma from the combined outcome cancers range, the RR decreased but remained high at 1.27 (95% CI, 1.26–1.28). We found increased risks in 26 of 29 individual outcome cancers ($P < 0.05$). The highest RRs were found for salivary gland (5.78 and 5.29–6.32), melanoma (5.54 and 5.37–5.71), bone (2.93 and 2.66–3.23), and upper gastrointestinal tract malignancies (2.36 and 2.25–2.48). Results for all individual outcome cancers are shown in Table 2. NMSC was not found to be protective against any cancer, but cervical, uterine, and testicular cancers were not significantly elevated ($P > 0.05$). Any differences between males and females were small (Supplementary Table S1).

Results by age

Table 3 and Table 4 show RRs for people ages <25, 25–44, 45–59, and 60+ years at the time of entry to their cohort. Generally, RRs for all outcome cancers decreased with

Table 2. Analysis by type of cancer: observed numbers of people with NMSC who had a subsequent record of primary malignant cancer, RRs and 95% CIs

	Cancer following admission for NMSC	
Site (ICD–10 code)	**O**	**RR (95% CI)**
Any malignant primary cancer excluding NMSC[a]	67,148	1.36 (1.35–1.37)
Any malignant primary cancer excluding all skin[b]	62,377	1.27 (1.26–1.28)
Bladder (C67)	5,372	1.13 (1.10–1.16)
Bone (C40–C41)	554	2.93 (2.66–3.23)
Brain (C71)	781	1.07 (1.00–1.16)
Breast (C50)	6,154	1.24 (1.21–1.28)
Cervix (C53)	193	0.97 (0.83–1.12)
Colon (C18–C19)	7,259	1.16 (1.13–1.19)
GI—upper (C00–C06.8, C09–C10, and C12–C14)	1,974	2.36 (2.25–2.48)
Kidney (C64–C65)	1,909	1.18 (1.13–1.24)
Larynx (C32)	649	1.32 (1.21–1.43)
Leukemia—lymphoid (C91)	2,096	2.01 (1.92–2.11)
Leukemia—myeloid (C92)	1,173	1.28 (1.21–1.37)
Liver (C22)	1,095	1.10 (1.03–1.17)
Lung (C33–C34)	10,942	1.31 (1.28–1.33)
Lymphoma—Hodgkins (C81)	298	1.68 (1.48–1.89)
Lymphoma—non-Hodgkins (C82–C85)	3,632	1.63 (1.58–1.69)
Melanoma—malignant (C43)	6,693	5.54 (5.37–5.71)
Multiple myeloma (C90)	1,225	1.13 (1.07–1.20)
Nasopharynx (C11)	98	1.48 (1.19–1.82)
Nervous system—other (C70)	62	1.91 (1.43–2.51)
Esophageal (C15)	2,274	1.10 (1.06–1.15)
Ovary (C56)	898	1.08 (1.01–1.16)
Pancreas (C25)	1,975	1.05 (1.00–1.10)
Prostate (C61)	11,730	1.12 (1.10–1.14)
Rectum (C20–C21)	3,529	1.43 (1.38–1.48)
Salivary gland (C07–C08)	881	5.78 (5.29–6.32)
Stomach (C16)	2,205	1.08 (1.04–1.13)
Testis (C62)	69	1.28 (0.99–1.62)
Thyroid (C73)	226	1.25 (1.08–1.43)
Uterus—body of (C54)	830	1.05 (0.98–1.13)

NOTE: All these ICD codes are specifically for primary malignancy.
[a]C00–C43, C45–C75, and C81–C97.
[b]C00–C41, C45–C75, and C81–C97.

increasing age but remained elevated throughout. Risk ratios for all outcome cancers combined at ages <25, 25–44, 45–59, and 60+, respectively, were 22.6 (95% CI, 18.0–28.2), 3.52 (95% CI, 3.30–3.75), 1.74 (95% CI, 1.70–1.79), and 1.32 (95% CI, 1.30–1.33).

Given that only 0.3% of the people in our NMSC cohort were under 25 years (Table 1)—a reflection of the fact that cancer incidence rates are very low in this age group generally—the observed and expected numbers of people in this age group with specific outcome cancers were small (usually less than 3), resulting in lower statistical power and wider confidence interval s. We report, in Table 3, RRs for specific outcome cancers in which the observed or expected values in this age group were 3 or more in the NMSC cohort. The RR for melanoma and salivary gland cancers were particularly high at 94.4 (95% CI, 65.3–133.0) and 93.4 (95% CI, 18.4–295.1), respectively.

Short- (<1 year), medium- (1–4 years), and long-term (5+ years) associations

Table 5 shows results by time intervals between entry to the NMSC or reference cohort and the first cancer outcome event for each individual cancer. For most outcome cancers, the RRs were highest within the first year and, for most outcome cancers, the RRs decreased but remained significantly high for first cancer events at 1 to 4 years, and for first events after 5+ years. The RRs for several specific outcome cancers—of the bladder, brain, breast, colon, liver, lung, pancreas, prostate, and stomach—remained consistently elevated across all time intervals; some

Table 3. People younger than 25 years with NMSC who had a subsequent record of another cancer: observed numbers, RRs and 95% CIs

	Ages 0–24	
Site (ICD–10 code)	**O**	**RR (95% CI)**
Any malignant primary cancer excluding NMSC[a]	82	22.64 (17.97–28.16)
Any malignant primary cancer excluding all skin[b]	48	14.45 (10.63–19.19)
Bone (C40–C41)	9	53.43 (24.15–103.05)
Brain (C71)	4	20.18 (5.46–52.27)
Leukemia—lymphoid (C91)	5	26.75 (8.65–62.79)
Melanoma—malignant (C43)	37	94.41 (65.25–133.01)
Salivary gland (C07–C08)	3	93.44 (18.43–295.10)

[a]C00–C43, C45–C75, and C81–C97.
[b]C00–C41, C45–C75, and C81–C97.

increased with increasing time (brain, colon, and prostate).

Discussion

Principal findings

A previous record of NMSC was associated with an increased subsequent risk of a broad spectrum of other primary malignant cancers in this national cohort study. Younger people with NMSC, in particular, are at much higher risk of subsequent primary malignant cancer incidence than people without NMSC, although cancer incidence is, overall, rarer in younger people.

Strengths, weaknesses, and potential biases

With 502,490 NMSC cases, this is the largest study on this topic so far, with high statistical power and precision in analyses split by cancer site, age, and time interval.

The main shortcoming is that we were unable to distinguish squamous cell carcinomas (SCC) from basal cell carcinomas (BCC) because these cancers are coded together in the ICD. It might be that one type of NMSC is more strongly associated with increased risks of subsequent primaries; however, only subtle differences have been noted in studies that do differentiate SCCs and BCCs (5, 9). T-cell lymphomas should be coded separately, but might occasionally be miscoded as NMSC; however, given their rarity compared with SCCs and BCCs, any effect on our results is likely to be very small.

We have not adjusted for multiple comparisons of cancer sites, but because almost all of the RRs go in the same direction of excess risk, it is highly improbable that these are chance findings. The height of some of the RRs, and the ubiquity of elevated risk across so many cancer sites, is such that the associations are very unlikely to be attributable to artefacts of data collection or study design.

In our stratified analysis, we accounted for age, sex, calendar year of first recorded admission, region of residence, and IMD score, but were unable to adjust for other potential confounders like body mass index, smoking, and UV exposure. However, smoking-related cancers, such as lung, had a RR of less than the average elevation of cancer site risk, and, after excluding melanoma from the analyses, the RRs for cancer overall were still significantly high, suggesting that factors other than smoking and UV exposure are at play. Studies that have been able to control for these potentially confounding variables have not found substantial difference between the age-adjusted and multivariable-adjusted risks, demonstrating that the observed association is unlikely to be explained by such factors (9). Furthermore, the effects of acquired risks, such as smoking and other behavioral factors, are cumulative, and one would expect an increasing relative risk with increasing age if they were major factors behind our associations. We found the opposite (higher relative risks at young ages), suggesting a genetic cause or early environmental exposure might explain our results rather than a later acquired cause of association.

It was not possible for us to directly ascertain the number of NMSC cases that were missed by our dataset. Most dermatologic excisions in ambulatory care should be captured under hospital day-case admissions (15), but some will be classified as outpatient sand some will be treated wholly in primary care. The people admitted as a day case or inpatient may be at the more severe end of the diseases spectrum. It seems unlikely, however, that the profile of RRs seen in our study is attributable to missing cases of NMSC that are treated in primary care. Furthermore, the decision to treat a person with NMSC as a day case or inpatient, rather than within primary care or as an outpatient, is perhaps more likely to relate to the preferences of the treating clinician than the characteristics of the NMSC.

We do not have data on the cohorts' migration into or out of the study area. However, migration bias is unlikely to be an issue because there is no apparent reason why the migration pattern of one cohort would be significantly different from the other.

We examined associations at different time intervals between the first known record of NMSC and the first subsequent record of the outcome cancer. This was partly

Table 4. People ages 25–44, 45–64, and 65+ with NMSC who had a subsequent record of another cancer: observed numbers, RRs, and 95% CIs

	Ages 25–44		Ages 45–59		Ages 60+	
Site (ICD–10 code)	**O**	**RR (95% CI)**	**O**	**RR (95% CI)**	**O**	**RR (95% CI)**
Any malignant primary cancer excluding NMSC[a]	1,001	3.52 (3.30–3.75)	5,787	1.74 (1.70–1.79)	60,278	1.32 (1.30–1.33)
Any malignant primary cancer excluding all skin[b]	674	2.47 (2.29–2.67)	4,951	1.52 (1.47–1.56)	56,704	1.25 (1.24–1.26)
Bladder (C67)	20	2.30 (1.39–3.58)	213	1.12 (0.97–1.29)	5,139	1.13 (1.10–1.16)
Bone (C40–C41)	32	12.19 (8.13–17.73)	84	4.38 (3.42–5.56)	429	2.66 (2.37–2.98)
Brain (C71)	24	2.03 (1.29–3.04)	92	1.36 (1.09–1.69)	661	1.02 (0.93–1.10)
Breast (C50)	174	1.79 (1.53–2.08)	853	1.25 (1.17–1.34)	5,127	1.23 (1.20–1.27)
Cervix (C53)	12	1.31 (0.67–2.30)	23	0.99 (0.62–1.50)	157	0.94 (0.79–1.10)
Colon (C18–C19)	21	1.20 (0.74–1.84)	395	1.30 (1.17–1.44)	6,841	1.15 (1.12–1.18)
GI—upper (C00–C06.8, C09–C10, and C12–C14)	52	4.42 (3.28–5.86)	354	2.62 (2.34–2.93)	1,567	2.34 (2.21–2.48)
Kidney (C64–C65)	14	1.59 (0.86–2.68)	148	1.32 (1.11–1.56)	1,747	1.17 (1.11–1.23)
Larynx (C32)	2	0.81 (0.10–2.99)	85	1.57 (1.24–1.96)	562	1.30 (1.18–1.42)
Leukemia–lymphoid (C91)	10	2.97 (1.41–5.55)	90	1.73 (1.38–2.15)	1,991	2.06 (1.96–2.17)
Leukemia—myeloid (C92)	10	2.05 (0.98–3.82)	59	1.31 (0.99–1.70)	1,103	1.28 (1.20–1.37)
Liver (C22)	5	1.53 (0.49–3.62)	81	1.32 (1.04–1.65)	1,009	1.08 (1.01–1.16)
Lung (C33—C34)	34	1.95 (1.35–2.75)	787	1.74 (1.61–1.87)	10,121	1.28 (1.26–1.31)
Lymphoma—Hodgkins (C81)	10	1.87 (0.89–3.47)	52	2.16 (1.59–2.87)	236	1.65 (1.42–1.90)
Lymphoma—non-Hodgkins (C82–C85)	28	1.80 (1.19–2.61)	318	1.90 (1.69–2.14)	3,285	1.63 (1.57–1.69)
Melanoma—malignant (C43)	377	20.63 (18.36–23.13)	1,040	9.40 (8.72–10.13)	5,239	5.08 (4.90–5.27)
Multiple myeloma (C90)	4	1.33 (0.36–3.46)	65	1.14 (0.87–1.46)	1,156	1.13 (1.06–1.21)
Nasopharynx (C11)	1	0.62 (0.02–3.52)	28	2.28 (1.49–3.38)	69	1.33 (1.01–1.72)
Nervous system—other (C70)	3	7.85 (1.53–25.33)	5	1.67 (0.52–4.13)	53	1.84 (1.33–2.51)
Esophageal (C15)	12	1.98 (1.01–3.49)	157	1.19 (1.01–1.40)	2,105	1.10 (1.05–1.15)
Ovary (C56)	16	1.54 (0.88–2.53)	92	1.06 (0.85–1.31)	788	1.08 (1.00–1.16)
Pancreas (C25)	9	2.24 (1.01–4.32)	103	1.07 (0.87–1.31)	1,862	1.05 (1.00–1.10)
Prostate (C61)	9	1.72 (0.78–3.29)	493	1.21 (1.10–1.32)	11,228	1.12 (1.09–1.14)
Rectum (C20–C21)	105	10.68 (8.60–13.15)	423	2.59 (2.33–2.87)	2,999	1.29 (1.24–1.35)
Salivary gland (C07–C08)	19	12.34 (7.20–20.05)	70	5.98 (4.51–7.84)	789	6.33 (5.71–7.02)
Stomach (C16)	13	2.70 (1.43–4.68)	89	1.08 (0.86–1.34)	2,102	1.08 (1.03–1.13)
Testis (C62)	7	1.00 (0.40–2.07)	18	1.58 (0.92–2.54)	43	1.26 (0.89–1.76)
Thyroid (C73)	10	1.30 (0.62–2.40)	36	1.44 (0.99–2.02)	179	1.22 (1.03–1.42)
Uterus—body of (C54)	10	1.58 (0.75–2.95)	105	1.06 (0.86–1.29)	715	1.05 (0.97–1.13)

[a]C00–C43, C45–C75, and C81–C97.
[b]C00–C41, C45–C75, and C81–C97.

to judge any effect of surveillance bias. This would arise if, for example, care for NMSC led to the prompt identification of another cancer. For all primary outcome cancers combined, the RR decreased after the first year, but remained significantly high. Increased surveillance might partially account for the increased rates of melanoma, but is unlikely to account for the increased rates of other nonvisible internal cancers, particularly in which the increased risk continues beyond 5 years after the diagnosis of NMSC, as was the case with most outcome cancers.

We cannot rule out the possibility of some misclassification of secondary cancer sites as primary in the source data, although we selected ICD codes for primary cancers only. We are unable to link our records to histologic samples. If misclassification of secondary cancers were an explanation for the pattern of our results, the effects of it would have to be not only considerable, but also long-term because the RRs for most cancers remain significantly increased after 5 years. The incidence of metastasis in people with BCC is extremely rare, with reported incidences ranging from 0.0028% to 0.5% (16).

Treatment and mortality bias is likely to be negligible, as almost all NMSCs are treated curatively by excision without the use of potentially carcinogenic radiotherapy or systemic chemotherapy (17). Despite the high incidence of NMSC, mortality rates from NMSC are low at 0.91 per 100,000 persons per year (18).

Comparison with other studies

A meta-analysis that combined the results of three cohort studies (5) and accounted for individual level risk factors, like smoking, showed an overall summary

Table 5. People who were admitted with NMSC and had a subsequent record of another cancer, by time interval between admissions (<1 year, 1–4 years, and 5 or more years): observed numbers, RRs, and 95% CIs

	<1 year time interval		1–4 years time interval		5+ years time interval	
Cancer site (ICD–10 code)	**O**	**RR (95% CI)**	**O**	**RR (95% CI)**	**O**	**RR (95% CI)**
Any malignant primary cancer excluding NMSC[a]	16,485	1.64 (1.61–1.67)	33,304	1.30 (1.29–1.32)	17,359	1.27 (1.25–1.29)
Any malignant primary cancer excluding all skin[b]	14,104	1.41 (1.38–1.43)	31,667	1.25 (1.23–1.26)	16,606	1.22 (1.20–1.24)
Bladder (C67)	1,087	1.08 (1.01–1.16)	2,792	1.14 (1.10–1.19)	1,493	1.14 (1.08–1.20)
Bone (C40–C41)	264	5.37 (4.59–6.27)	211	2.37 (2.03–2.76)	79	1.66 (1.30–2.10)
Brain (C71)	128	0.85 (0.70–1.02)	371	1.05 (0.94–1.17)	282	1.25 (1.11–1.42)
Breast (C50)	1,228	1.31 (1.23–1.39)	3,075	1.20 (1.15–1.24)	1,851	1.29 (1.23–1.35)
Cervix (C53)	38	1.08 (0.76–1.51)	110	1.05 (0.86–1.28)	45	0.75 (0.55–1.01)
Colon (C18–C19)	1,376	1.07 (1.01–1.13)	3,817	1.18 (1.14–1.22)	2,066	1.19 (1.14–1.25)
GI—upper (C00–C06.8, C09–C10, and C12–C14)	713	3.45 (3.15–3.76)	827	2.05 (1.90–2.21)	434	1.98 (1.78–2.19)
Kidney (C64–C65)	366	1.22 (1.08–1.36)	976	1.17 (1.09–1.25)	567	1.18 (1.08–1.29)
Larynx (C32)	161	1.40 (1.17–1.66)	321	1.29 (1.15–1.46)	167	1.31 (1.11–1.54)
Leukemia—lymphoid (C91)	556	2.58 (2.33–2.85)	1,083	2.09 (1.95–2.24)	457	1.53 (1.38–1.69)
Leukemia—myeloid (C92)	234	1.28 (1.11–1.47)	620	1.31 (1.20–1.43)	319	1.24 (1.10–1.39)
Liver (C22)	194	1.04 (0.88–1.21)	565	1.11 (1.02–1.22)	336	1.12 (1.00–1.25)
Lung (C33–C34)	2,166	1.30 (1.24–1.37)	5,723	1.32 (1.29–1.36)	3,053	1.29 (1.24–1.34)
Lymphoma—Hodgkins (C81)	74	1.84 (1.42–2.35)	159	1.71 (1.44–2.02)	65	1.49 (1.14–1.93)
Lymphoma—non-Hodgkins (C82–C85)	878	1.85 (1.71–1.99)	1,842	1.64 (1.56–1.73)	912	1.48 (1.38–1.58)
Melanoma—malignant (C43)	2,912	12.42 (11.69–13.20)	2,553	4.26 (4.06–4.47)	1,228	3.72 (3.49–3.97)
Multiple myeloma (C90)	234	1.03 (0.89–1.18)	659	1.19 (1.09–1.29)	332	1.11 (0.99–1.24)
Nasopharynx (C11)	38	1.51 (1.05–2.12)	39	1.34 (0.93–1.87)	21	1.73 (1.04–2.74)
Nervous system—other (C70)	12	1.85 (0.90–3.51)	35	2.08 (1.39–3.02)	15	1.66 (0.90–2.86)
Esophageal (C15)	464	1.20 (1.08–1.33)	1,186	1.08 (1.01–1.14)	624	1.10 (1.01–1.19)
Ovary (C56)	152	0.98 (0.82–1.16)	474	1.08 (0.98–1.19)	272	1.15 (1.01–1.30)
Pancreas (C25)	348	1.02 (0.91–1.14)	1,027	1.03 (0.96–1.10)	600	1.11 (1.02–1.21)
Prostate (C61)	2,212	1.03 (0.98–1.08)	6,080	1.14 (1.11–1.17)	3,438	1.15 (1.11–1.19)
Rectum (C20–C21)	1,194	2.35 (2.20–2.51)	1,537	1.19 (1.13–1.26)	798	1.20 (1.11–1.29)
Salivary gland (C07–C08)	290	8.74 (7.27–10.52)	443	5.99 (5.26–6.81)	148	3.71 (3.05–4.49)
Stomach (C16)	434	1.08 (0.97–1.20)	1,149	1.06 (1.00–1.13)	622	1.12 (1.03–1.22)
Testis (C62)	22	1.55 (0.96–2.39)	32	1.23 (0.83–1.75)	15	1.10 (0.61–1.82)
Thyroid (C73)	66	1.90 (1.44–2.48)	114	1.19 (0.97–1.45)	46	0.92 (0.67–1.24)
Uterus—body of (C54)	140	0.96 (0.80–1.15)	456	1.11 (1.00–1.22)	234	1.01 (0.88–1.15)

[a]C00–C43, C45–C75, and C81–C97.
[b]C00–C41, C45–C75, and C81–C9.

relative risk of cancer after NMSC of 1.49 (95% CI, 1.12–1.98), similar to our RR of 1.36 (95% CI, 1.35–1.37), notwithstanding differences in methodology. Our results also corroborate a particularly high risk of melanoma and salivary gland cancer, found by others (5, 11).

Risks of breast, colorectal, and prostate cancers have been reported as low in people with NMSC (11, 19, 20). It has been suggested that increased sunlight exposure and vitamin D levels play a protective role in their development. We did not find low risks for these cancers.

Other subgroups known to have high risk of cancer are transplant patients. However, although SCCs are up to 65-fold more prevalent in transplant patients than matched controls (21), the percentage of people with NMSC in our study who have had a transplant is likely to be very small. The risk and pattern of cancers in people who have undergone transplantation, in whom the excess cancer risk particularly affects the kidney, liver, and non-Hodgkin lymphoma (22), would not in itself account for our results. Findings of a recent study also showed that, even among transplant recipients, SCC was a marker of increased risk for other cancers (23).

Interpretation and implications

Mechanisms for these associations remain elusive. It is plausible that UV-induced oxidative damage resulting in gene mutation, immunosuppression, and inflammation may also act more systemically to increase the risk of cancer in predisposed individuals in other sites, such as in immunosuppressed transplant recipients (24, 25) and

those with cancer-predisposing syndromes (26, 27). Recent studies suggest that genetic predisposition to reduced DNA repair capacity may be an underlying susceptibility factor for NMSC and other cancers (28–31). We considered that the occurrence of NMSC in people in our study ages <25 might be associated with certain congenital skin disorders, in particular xeroderma pigmentosum. We, therefore, conducted a *post-hoc* analysis to ascertain the number of people in this age group of the NMSC cohort who also had a record of xeroderma pigmentosum either before or after their record of NMSC. We found a total of 6, 5 of whom had a record of xeroderma pigmentosum before the record of NMSC. In a cohort of 1,621 people with NMSC ages <25, the occurrence of 6 cases of xeroderma pigmentosum is unlikely to be of significant impact.

Our findings should be regarded as supporting the hypothesis of a raised risk of other cancers after diagnosis of NMSC, but not as definitive. The results represent what can be done using very large, linked, routinely collected administrative datasets; but such datasets lack detail. Alternative designs of similar scope, which could incorporate data on genetic profiling and biomarkers, would be substantial undertakings, but the benefits of more precise characterization of those with NMSC who are at risk of other specific malignancies would be considerable.

For those cancers in which screening, or other approaches to cancer prevention, has proven benefit, a next step would be to define guidelines that translate these results into clinical practice and lifestyle advice, especially for younger individuals with NMSC. Guidelines on NMSC do not refer to surveillance for any specific cancer types apart from other skin cancers (32, 33); our results suggest surveillance for other cancers might be warranted if supported by further clinical research and cost-benefit analyses.

Further work to elucidate why people with NMSC, particularly the young, are at increased risk of other malignancies could be an important step to a more fundamental understanding of carcinogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Ethical approval for analysis of the record-linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176).

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