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End Results (SEER)-Medicare data set, which links SEER cancer

We selected subjects from the Surveillance, Epidemiology, and End

MATERIALS AND METHODS

Established risk factors for skin cancer include exposure to solar
ultraviolet radiation, white race, and advancing age (Gruber and
Armstrong). Immunosuppression also increases the risk of certain
skin cancers. The risk in solid organ transplant recipients and
people with human immunodeficiency virus (HIV) infection is
extremely high for Kaposi’s sarcoma (KS), a cutaneous tumour
causalknown by human herpesvirus 8, somewhat elevated for cutaneous
non-Hodgkin’s lymphoma (NHL), Merkel cell carcinoma, and
appendageal skin carcinomas and somewhat increased for
melanoma (Lanoy et al, 2010).

Autoimmune conditions may also increase skin cancer risk.
Chronic cutaneous inflammation that can characterise some
autoimmune conditions (including psoriasis and scleroderma,
which directly involve the skin) may plausibly cause DNA damage
that could promote development of skin cancer. Immuno-
suppressive medications used to treat autoimmune conditions
could have an additional role. This study aimed to investigate
associations between autoimmune conditions and the subsequent
risk of skin cancers among elderly US adults (aged 67 years
and over).

REGISTRY and Medicare claims data (Warren et al, 2002). Skin
cancer cases (other than basal and squamous cell carcinomas)
and cancer-free controls were selected as described elsewhere
(Lanoy et al, 2010), updated to include SEER Medicare data
through 2005. The presence of autoimmune conditions before
cancer diagnosis/control selections was assessed using Medicare
claims data: rheumatoid arthritis (International Classification of
Disease version 9 codes 714.0-714.3, 714.81, V82.1), Sjögren’s
syndrome (710.2), systemic lupus erythematosus (710.0), poly-
myalgia rheumatica (725), giant cell arteritis (446.5), Addison’s
disease (255.4), Graves disease (242.0), psoriasis (696.0-696.1),
localised scleroderma (701.0), Crohn’s disease (555), ulcerative
colitis (556), and pernicious anaemia (281.0).

We used polytomous logistic regression to derive odds ratios
(ORs) comparing the prevalence of each medical condition in skin
cancer cases to controls (Lanoy et al, 2010). We focused on
associations that met statistical significance after Benjamini
and Hochberg correction to account for multiple comparisons
(P-value <0.05, after correction based on 6 skin cancers subtypes × 12
autoimmune conditions = 72 tests) (Keselman et al, 2002), but we
also present uncorrected 95% CIs for ORs that indicate associations
of borderline significance (uncorrected P-value <0.05).

RESULTS

Characteristics of 44,613 skin cancer cases and 178,452 controls
(corresponding to 134,779 unique control individuals) are
shown in Table 1. Among 1540 appendageal carcinoma cases, the
most frequent histological subtypes were sebaceous carcinoma

| Background: | Immunosuppression is a risk factor for certain skin cancers. Autoimmune conditions can involve the skin, and may involve immunosuppressive therapies. |
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| METHODS: | We conducted a population-based case-control study among elderly US adults using Surveillance, Epidemiology, and End Results-Medicare-linked data of 44,613 skin cancer cases and 178,452 frequency-matched controls. Medicare claims identified autoimmune conditions. Adjusted odds ratios (ORs) compared prevalence in cases and controls. |
| RESULTS: | The most frequent autoimmune condition was rheumatoid arthritis (2.29%), which was associated with slightly increased risk of Merkel cell carcinoma (N = 1977; OR (95%CI): 1.39 (1.10–1.74)). Risk of cutaneous non-Hodgkin’s lymphoma (N = 2652) was increased with psoriasis (OR (95%CI): 3.20 (2.62–3.92)). Risk of Kaposi’s sarcoma (N = 773) was elevated with Graves disease (2.62 (1.30–5.31)). |
| CONCLUSIONS: | These findings suggest that immune disturbances in the skin, arising from autoimmune conditions or their treatment, promote development of skin cancer. |

Keywords: skin neoplasm; autoimmune conditions; aged

Short Communication

Skin cancers associated with autoimmune conditions among elderly adults

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Established risk factors for skin cancer include exposure to solar ultraviolet radiation, white race, and advancing age (Gruber and Armstrong). Immunosuppression also increases the risk of certain skin cancers. The risk in solid organ transplant recipients and people with human immunodeficiency virus (HIV) infection is extremely high for Kaposi’s sarcoma (KS), a cutaneous tumour caused by human herpesvirus 8, somewhat elevated for cutaneous non-Hodgkin’s lymphoma (NHL), Merkel cell carcinoma, and appendageal skin carcinomas and somewhat increased for melanoma (Lanoy et al, 2010).

Autoimmune conditions may also increase skin cancer risk. Chronic cutaneous inflammation that can characterise some autoimmune conditions (including psoriasis and scleroderma, which directly involve the skin) may plausibly cause DNA damage that could promote development of skin cancer. Immunosuppressive medications used to treat autoimmune conditions could have an additional role. This study aimed to investigate associations between autoimmune conditions and the subsequent risk of skin cancers among elderly US adults (aged 67 years and over).

MATERIALS AND METHODS

We selected subjects from the Surveillance, Epidemiology, and End Results (SEER)-Medicare data set, which links SEER cancer registry and Medicare claims data (Warren et al, 2002). Skin cancer cases (other than basal and squamous cell carcinomas) and cancer-free controls were selected as described elsewhere (Lanoy et al, 2010), updated to include SEER Medicare data through 2005. The presence of autoimmune conditions before cancer diagnosis/control selections was assessed using Medicare claims data: rheumatoid arthritis (International Classification of Disease version 9 codes 714.0-714.3, 714.81, V82.1), Sjögren’s syndrome (710.2), systemic lupus erythematosus (710.0), polymyalgia rheumatica (725), giant cell arteritis (446.5), Addison’s disease (255.4), Graves disease (242.0), psoriasis (696.0-696.1), localised scleroderma (701.0), Crohn’s disease (555), ulcerative colitis (556), and pernicious anaemia (281.0).

We used polytomous logistic regression to derive odds ratios (ORs) comparing the prevalence of each medical condition in skin cancer cases to controls (Lanoy et al, 2010). We focused on associations that met statistical significance after Benjamini and Hochberg correction to account for multiple comparisons (P-value <0.05, after correction based on 6 skin cancers subtypes × 12 autoimmune conditions = 72 tests) (Keselman et al, 2002), but we also present uncorrected 95% CIs for ORs that indicate associations of borderline significance (uncorrected P-value <0.05).

RESULTS

Characteristics of 44,613 skin cancer cases and 178,452 controls (corresponding to 134,779 unique control individuals) are shown in Table 1. Among 1540 appendageal carcinoma cases, the most frequent histological subtypes were sebaceous carcinoma

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### Table 1: Characteristics of skin cancer cases and controls among elderly US adults

| Skin cancer cases | Controls N = 178452 | Melanoma N = 36092 | Merkel cell carcinoma N = 1977 | Appendageal carcinomas N = 1540 | Cutaneous NHL N = 2652 | KS N = 773 | Sarcomas N = 1324 |
|-------------------|---------------------|---------------------|-----------------------------|-------------------------------|---------------------|---------------|-----------------|
| **Gender, n (%)** |                     |                     |                             |                               |                     |               |                 |
| Male              | 109,316 (61.3)       | 22,293 (61.8)       | 1,186 (60.0)                | 7,855 (51.0)                  | 1,478 (55.7)       | 51,4 (66.5)   | 935 (70.6)     |
| Female            | 69,136 (38.7)        | 13,799 (38.2)       | 791 (40.0)                  | 7,555 (49.0)                  | 1,174 (44.3)       | 25,933 (35.5) | 387 (29.4)     |
| **Age in years, n (%)** |                   |                     |                             |                               |                     |               |                 |
| 67 – 69           | 28,894 (16.2%)       | 6,692 (18.0%)       | 182 (9.2%)                  | 443 (16.7%)                   | 82 (10.6%)         | 158 (11.9%)   |                 |
| 70 – 74           | 42,792 (24.0%)       | 8,957 (24.9%)       | 330 (16.7%)                 | 645 (24.3%)                   | 136 (17.6%)        | 267 (20.2%)   |                 |
| 75 – 79           | 43,392 (23.4%)       | 8,870 (24.6%)       | 439 (22.2%)                 | 661 (24.9%)                   | 147 (19.0%)        | 309 (23.3%)   |                 |
| 80 – 84           | 34,928 (19.6%)       | 6,838 (18.9%)       | 512 (25.9%)                 | 516 (19.3%)                   | 171 (21.1%)        | 320 (24.2%)   |                 |
| 85+               | 28,495 (15.9%)       | 5,285 (14.6%)       | 514 (26.0%)                 | 387 (14.6%)                   | 237 (30.7%)        | 270 (20.4%)   |                 |
| **Median age (years)** |                   |                     |                             |                               |                     |               |                 |
| 80 – 84           | 34 (884)             | 928 (6142)          | 182 (6142)                  | 317 (186)                     | 43 (4392)          | 80 (285)     |                 |
| 75 – 79           | 43 (3492)            | 887 (6142)          | 512 (6142)                  | 171 (3492)                    | 320 (887)          | 79 (76)     |                 |
| 67 – 69           | 28 (887)             | 6142 (3492)         | 317 (887)                   | 320 (887)                     | 79 (28)            | 79 (76)     |                 |
| **Number of hospital claims, median (IQR)** |                   |                     |                             |                               |                     |               |                 |
| 2001 (1996 – 2003) | 95 (50 – 150)        | 93 (49 – 146)       | 118 (71 – 171)              | 93 (50 – 143)                 | 90 (47 – 146)      | 103 (58 – 156) |                 |
| 2000 (1993 – 2003) | 37 (6 – 96)          | 38 (7 – 91)         | 106 (9 – 110.5)             | 33 (1 – 94)                   | 43 (8 – 102)       | 31 (7 – 39)  |                 |
| **Number of outpatient claims, median (IQR)** |                   |                     |                             |                               |                     |               |                 |
| 2001 (1996 – 2003) | 0 (0 – 2)            | 0 (0 – 2)           | 1 (0 – 3)                   | 1 (0 – 2)                     | 1 (0 – 2)           | 1 (0 – 2)    |                 |
| 2000 (1993 – 2003) | 0 (0 – 2)            | 0 (0 – 2)           | 1 (0 – 3)                   | 1 (0 – 2)                     | 1 (0 – 2)           | 1 (0 – 2)    |                 |
| **Median age (years)** |                   |                     |                             |                               |                     |               |                 |
| 80 – 84           | 76 (884)             | 76 (6142)           | 512 (6142)                  | 387 (887)                     | 237 (887)          | 270 (887)   |                 |
| 75 – 79           | 76 (3492)            | 887 (6142)          | 512 (6142)                  | 320 (887)                     | 79 (3492)          | 79 (3492)   |                 |
| 67 – 69           | 28 (887)             | 6142 (3492)         | 317 (887)                   | 320 (887)                     | 79 (28)            | 79 (28)     |                 |

Abbreviations: IQR = interquartile range; KS = Kaposi’s sarcoma; NHL = non-Hodgkin’s lymphoma. *The number of claims excludes the 12 months before skin cancer diagnosis (cases) or selection (controls).

(N = 610), skin appendage carcinoma (N = 316), and sweat gland adenocarcinoma (N = 144). Of the 2652 cutaneous NHLs, 1854 were T-cell NHLs (of which 945 were mycosis fungoides/Sezary syndrome (MF/SS)) and 798 were B-cell NHLs. Among 1324 sarcomas, the most frequent histological subtypes were malignant fibrous histiocytoma (N = 682), dermatofibrosarcoma (N = 235), haemangiosarcoma (N = 173), and leiomyosarcoma (N = 121).

As shown in Table 2, an increased risk of Merkel cell carcinoma was observed in persons with rheumatoid arthritis (OR 1.39). Psoriasis was associated with an increased risk of cutaneous NHL (OR 3.20), caused by associations specifically with MF/SS (OR 5.81), 95% CI 4.43 – 7.63) and other cutaneous T-cell NHLs (OR 2.90, 95% CI 2.07 – 4.06), whereas cutaneous B-cell NHL risk was not elevated (OR 1.04, 95% CI 0.57 – 1.89). Ulcerative colitis was associated with risk of KS (OR 2.76), and an increased risk of sarcoma was found with Graves disease (OR 2.62). Among sarcomas, when we considered only malignant fibrous histiocytoma, the association with Graves disease remained significant (OR 2.90, 95% CI 2.07 – 4.06), whereas cutaneous B-cell NHL risk was neither associated with cutaneous B-cell NHL nor, in a prior study (Anderson et al, 2009), with non-cutaneous T-cell NHL.

Our finding of elevated KS risk associated with ulcerative colitis is supported by several case reports in such patients receiving immunosuppressive drugs (Svrcek et al, 2009). The association of sarcoma with Graves disease mentioned above may relate to immunosuppressive therapies (Simon et al, 2009), as may that of rheumatoid arthritis with Merkel cell carcinoma, which is increased in HIV-infected people and transplant recipients (Lonay et al, 2010) and may be caused by a recently discovered polyomavirus. Finally, we observed an unexpected significant deficit of melanoma among people with giant cell arteritis. A Danish study found no association between autoimmune diseases and melanoma incidence (Kaae et al, 2007), although others have reported an increased melanoma risk with pernicious anaemia (Brinton et al, 1989) and psoriasis (Stern, 2001).

The strength of our study is its large size, allowing us to evaluate associations between uncommon autoimmune conditions and skin cancers. Nonetheless, limitations of our study include that it was restricted to elderly adults, that basal and squamous cell skin cancers were not covered, and that we could not ascertain the presence of medical conditions below 65 years of age; we also had no data on immunosuppressive treatments.

Several associations identified between autoimmune conditions and skin cancer risk suggest that such conditions affecting the skin, or treated with immunosuppression, promote the development of skin cancer; their further investigation will require additional large studies.

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Table 2  Associations of autoimmune conditions with skin cancer risk among elderly US adults

| Associations with autoimmune condition: OR (95%CI) and number of subjects with the specified condition | Controls with condition (%) | Melanoma N = 36 092 | Merkel cell carcinoma N = 1977 | Appendageal carcinomas N = 1540 | Cutaneous NHL N = 2 652 | KS N = 773 | Sarcomas N = 1 324 |
|---|---|---|---|---|---|---|---|
| Systemic/connective tissue | | | | | | | |
| Rheumatoid arthritis | 2.29 | 0.93 (0.86 – 1.01) | 1.39 (1.10 – 1.75) ¹ | 1.02 (0.74 – 1.39) | 1.15 (0.90 – 1.46) | 1.65 (1.09 – 2.49) | 1.13 (0.79 – 1.60) |
| Sjögren’s syndrome | 0.21 | 1.00 (0.77 – 1.30) | 1.46 (1.02 – 2.06) | 1.76 (0.83 – 3.74) | 1.02 (0.45 – 2.30) | 0.73 (0.10 – 5.22) | 1.97 (0.81 – 4.82) |
| Systemic lupus erythematosus | 0.20 | 0.80 (0.60 – 1.06) | 1.02 (0.42 – 2.47) | 1.62 (0.73 – 3.66) | 1.73 (0.91 – 3.27) | 1.65 (0.41 – 6.65) | 0.85 (0.21 – 3.45) |
| Polymyalgia rheumatica | 0.97 | 1.04 (0.92 – 1.17) | 1.03 (0.71 – 1.51) | 0.90 (0.55 – 1.46) | 0.71 (0.45 – 1.12) | 1.73 (0.99 – 3.01) | 0.74 (0.40 – 1.40) |
| Cardiovascular | | | | | | | |
| Giant cell arteritis | 0.30 | 0.70 (0.54 – 0.90) ¹ | 1.41 (0.79 – 2.50) | 0.83 (0.34 – 2.02) | 0.85 (0.40 – 1.80) | 0.87 (0.22 – 3.50) | 1.50 (0.67 – 3.38) |
| Endocrine | | | | | | | |
| Addison’s disease | 0.13 | 1.06 (0.77 – 1.45) | 0.56 (0.14 – 2.27) | 1.28 (0.41 – 4.02) | 1.13 (0.42 – 3.05) | 1.98 (0.48 – 8.15) | 0.53 (0.07 – 3.83) |
| Graves disease | 0.24 | 0.88 (0.68 – 1.13) | 1.43 (0.73 – 2.78) | 0.67 (0.21 – 2.09) | 1.20 (0.59 – 2.43) | 0.0 | 2.62 (1.30 – 5.31) ¹ |
| Skin | | | | | | | |
| Psoriasis | 1.33 | 0.87 (0.78 – 0.97) | 1.29 (0.94 – 1.76) | 1.36 (0.94 – 1.97) | 3.20 (2.62 – 3.92) ² | 1.20 (0.66 – 2.21) | 0.99 (0.61 – 1.58) |
| Localised scleroderma | 0.14 | 0.85 (0.60 – 1.19) | 1.39 (0.57 – 3.40) | 1.11 (0.35 – 3.47) | 2.06 (1.01 – 4.19) | 2.34 (0.58 – 9.45) | 1.27 (0.31 – 5.15) |
| Gastrointestinal | | | | | | | |
| Crohn’s disease | 0.27 | 1.12 (0.90 – 1.39) | 0.46 (0.15 – 1.45) | 2.25 (1.20 – 4.23) | 1.26 (0.65 – 2.46) | 1.07 (0.27 – 4.44) | 0.56 (0.14 – 2.26) |
| Ulcerative colitis | 0.48 | 0.80 (0.91 – 1.27) | 0.83 (0.44 – 1.56) | 0.98 (0.49 – 1.98) | 1.34 (0.82 – 2.17) | 2.76 (1.42 – 5.39) ² | 1.24 (0.61 – 2.49) |
| Pernicious anaemia | 1.57 | 0.90 (0.61 – 0.99) | 0.87 (0.63 – 1.20) | 0.84 (0.56 – 1.25) | 1.05 (0.78 – 1.43) | 0.77 (0.41 – 1.44) | 1.15 (0.78 – 1.71) |

Abbreviations: OR = odds ratio; CI = confidence interval; KS = Kaposi’s sarcoma; NHL = non-Hodgkin’s lymphoma. Odds ratios are adjusted for age (67 – 69, 70 – 74, 75 – 79, 80 – 84, and 85 – 99 years), gender, selection year (1987 – 1993, 1994 – 1997, 1998 – 2000, and 2000 – 2002), and number of physician claims (0 – 4, 5 – 39, 40 – 109, and 110+). For consistency, all odds ratios are displayed to two decimal places, although in some instances the number of subjects with the specified medical condition is small. When the number of subjects with the autoimmune condition was between 1 and 10, the result is listed as ‘n<1’ to preserve subjects’ anonymity in accordance with the SEER-Medicare data use agreement. ¹Association was significant after accounting for multiple testing using the Benjamini and Hochberg correction.