Herpes Zoster and Risk of Cancer in the Elderly U.S. Population
Parag Mahale1,2, Elizabeth L. Yanik1, and Eric A. Engels1

Abstract

Background: Herpes zoster (HZ) arises in older people due to age-related decline in immunity. We assessed whether HZ, as a marker of immune suppression, is associated with increased cancer risk.

Methods: We conducted a case-control study in U.S. adults with ages ≥65 years using the Surveillance, Epidemiology, and End Results (SEER)–Medicare linked database. Cases (n = 1,108,986) were people with first cancers identified in cancer registries (1992–2005). Controls (n = 100,000) were cancer-free individuals frequency matched to cases on age, sex, and year of selection. We identified HZ diagnosis using Medicare claims. Logistic regression models were constructed to determine adjusted associations between cancer and HZ.

Results: HZ prevalence was modestly higher in cases than controls (1.4% vs. 1.2%). We identified significant associations between HZ and oral cavity/pharyngeal [adjusted OR (aOR) = 1.21], colon (aOR = 1.10), lung (aOR = 1.11), and non-melanoma skin (aOR = 1.46) cancers; myeloma (aOR = 1.38); diffuse large B-cell lymphoma (aOR = 1.30); lymphoplasmacytic lymphoma (aOR = 1.99); and chronic lymphocytic leukemia/small lymphocytic lymphoma (aOR = 1.55). Among solid cancers, HZ was mostly associated with regional and/or distant stage tumors. Associations were strongest when HZ was diagnosed 13 to 35 months before cancer diagnosis/selection; they were significant for some cancers in the 36 to 59 months period, and 60+ months for lymphoplasmacytic lymphoma (OR = 1.99).

Conclusion: HZ is associated with modestly increased risk of a few cancers, particularly hematologic malignancies. Associations were strongest at short latency intervals for many cancers, and for regional/distant stages among solid cancers, perhaps reflecting reverse causality.

Impact: Age-related immune decline does not play a major role in cancer development in older people, but it may be important for some lymphomas. Cancer Epidemiol Biomarkers Prev; 25(1); 1–8. ©2015 AACR.

Introduction

Herpes zoster (HZ, or shingles) is a condition characterized by painful vesicular rash, which results from reactivation of latent varicella zoster virus (VZV) infection. The risk of HZ increases with age, with an estimated annual incidence of 0.12% in individuals over 65 years of age (1). The latency of VZV is maintained by potent VZV-specific cell-mediated immunity, which is known to decline with age (2). Increased incidence of HZ is also observed in immunosuppressive states such as human immunodeficiency virus (HIV) infection and associated with use of immunosuppressive medications (3, 4).

Aging is associated with declines in immune function, which increases the risk for infections (5). Because other immunosuppressive states (e.g., HIV infection, organ transplantation) are associated with an elevated risk for some cancers (6), it is possible that age-related immune function decline also contributes to the development of cancer.

Along these lines, HZ may indicate the presence of immunosuppression in otherwise healthy individuals and may thus point to a predisposition to development of some cancers. Several studies have suggested that HZ can be an indicator of future cancers, particularly hematologic malignancies (7–19). In addition, some cancers are themselves associated with a state of dysregulated immunity, and together with immunosuppressive chemotherapy used in their treatment, they may increase the risk of HZ (3, 8–13).

Immunosuppression may also affect the clinical behavior of certain cancers. For instance, melanoma and bladder cancer are more likely to be diagnosed at advanced stages in HIV-infected individuals and solid organ transplant recipients (20). HIV infection is associated with an elevated risk of mortality following a cancer diagnosis (21), suggesting that immunosuppression can influence progression of cancer.

In this study, we evaluated a large U.S. population of elderly adults to determine whether HZ is an indicator of future cancer risk. We also evaluated the association of HZ with the stage of cancer at diagnosis.

Materials and Methods

Data source: SEER–Medicare linked database

Surveillance, Epidemiology, and End Results (SEER) is a cancer surveillance program supported by the NCI since 1973, which collects information on cancer incidence and survival from 17 U.S. cancer registries covering approximately 26% of the U.S. population (22). Medicare is a federally funded program that...
provides health insurance to approximately 97% of the U.S. elderly (ages 65 or older). All Medicare-eligible individuals are entitled to Part A coverage for hospital inpatient care. Approximately 96% also subscribe to Part B coverage for physician and outpatient care. Beneficiaries can elect to enroll in a health maintenance organization (HMO); Medicare does not receive claims for individual medical conditions for people enrolled in HMOs.

The SEER–Medicare database is a linkage of SEER and Medicare data (23). The database thus includes all Medicare claims (1991 onward) for linked cancer cases in SEER. In addition, claims data for a 5% random sample of Medicare beneficiaries residing in SEER geographic areas are provided.

Study design and study population

We conducted a population-based case–control study using the SEER–Medicare database to determine if a diagnosis of HZ is associated with cancer risk (24). Eligible cases comprised people with a first cancer diagnosis identified in SEER, excluding basal cell and squamous cell skin carcinomas which are not captured by cancer registries. Cases diagnosed only at autopsy or by death certificates were also excluded. As the adult varicella zoster vaccine (Zostavax, Merck) received Food and Drug Administration approval in May 2006, we restricted our analyses to cases diagnosed before 2006. In ascertaining HZ before cancer diagnosis, we excluded the 1-year period prior to cancer diagnosis to minimize the possibility of reverse causation (i.e., incipient cancers leading to HZ). We, therefore, required that cases had at least 13 months of Medicare Part A, Part B, non-HMO coverage before cancer diagnosis (exclusion of 1 year of data would allow at least 1 month of Medicare claims for assessment of HZ). Thus, included cases were diagnosed at ages 66 to 99 years in calendar years 1992 to 2005. Cancer cases were categorized using the SEER site recode variable.

Controls (N = 100,000) were randomly selected from the 5% random sample of Medicare beneficiaries who were alive and cancer free as of July 1 of the calendar year of their selection. Like cases, they were required to have at least 13 months of prior Medicare Part A, Part B, non-HMO insurance coverage. Controls were frequency matched to cases on age (categories of 66–69, 70–74, 75–79, 80–84, 85–99 years), calendar year of selection, and sex. It was possible for people to be sampled as controls multiple times in different calendar years, as well as for controls to later become cases.

Ascertainment of HZ and HIV

Medicare claims data were examined for a diagnosis of HZ (ICD9 code 053.X) before cancer diagnosis/control selection, excluding the 12-month period before cancer diagnosis/control selection. A diagnosis of HZ required one inpatient or, to improve the specificity of HZ diagnosis, at least two physician or outpatient claims at least 30 days apart (23).

As HIV infection is a strong risk factor for zoster (4) and also increases the risk of certain cancers (6), we identified all individuals who had at least one Medicare claim for HIV (ICD9 codes 042.0, 042.1, 042.2, 042.9, or V08) any time before death or the last follow-up. In a sensitivity analysis, we determined the association between HZ and cancer after excluding people with an HIV diagnosis.

Statistical analyses

Characteristics of cases and controls were compared using \( \chi^2 \) tests. To compare HZ prevalence in cancer cases and controls, we fit separate unconditional logistic regression models for each cancer type. ORs were adjusted (aOR) for age (categorized, 66–69, 70–74, 75–79, 80–84, 85–99 years), sex, year of cancer diagnosis/control selection (1992–1995, 1996–1999, 2000–2001, 2002–2003, 2004–2005), race (white, non-white/unknown), and average annual number of physician claims more than 1 year before cancer diagnosis/control selection (0, 1–3, 4–6, ≥7). The variance of aORs obtained from these models was adjusted to accommodate repeated selection of some controls as well as inclusion of some controls that later became cases (24). We initially assessed a total of 48 cancer types, including major subtypes of leukemia and non-Hodgkin lymphoma (NHL) which were analyzed individually. We utilized a two-sided \( \alpha \) of 0.05, but to account for multiple testing, we selected cancers for further evaluation by using a false discovery rate of 10% according to the Benjamini and Hochberg method (25).

For cancers selected using this procedure, we conducted further analyses to identify specific subsite or histological categories associated with HZ. We conducted an analysis to assess the association of HZ with cancers classified according to stage at diagnosis (localized, regional, distant, or unknown, according to SEER summary stage classification). This analysis was restricted to solid tumors, for which this staging system is appropriate. We also assessed associations with HZ according to latency, i.e., time from first HZ diagnosis to cancer diagnosis/control selection (13–35, 36–59, and 60+ months) and conducted a test for trend to determine whether the association was stronger closer to the time of cancer diagnosis.

Results

Study population

The study population consisted of 1,108,986 cancer cases and 100,000 cancer-free controls aged 66–99 years (Table 1). By design, cases and controls were perfectly matched on sex, age, and year of selection. Cases were more likely than controls to be white, had a shorter duration of Medicare (Part A, Part B, non-HMO) coverage, and had more prior physician claims per year. However, the absolute differences between the two groups were small. The proportion of individuals with claims for HIV infection was very low in both groups (Table 1).

Associations between HZ and cancer

A total of 14,941 cases and 1,185 controls had a diagnosis of HZ [1.4% vs. 1.2%; aOR, 1.10; 95% confidence intervals (CI), 1.04–1.18]. Results of logistic regression models to test the association between HZ and individual cancers are presented in Fig. 1. Using the Benjamini–Hochberg procedure to correct for multiple comparisons, we identified significant associations between HZ and oral cavity/pharyngeal cancer (aOR, 1.21; 95% CI, 1.04–1.42), colon cancer (aOR, 1.10; 95% CI, 1.02–1.19), lung cancer (aOR, 1.11; 95% CI, 1.03–1.20), nonmelanoma skin cancer (aOR, 1.46; 95% CI, 1.17–1.82), myeloma (aOR, 1.38; 95% CI, 1.21–1.59), and among NHLs, diffuse large B-cell lymphoma (DLBCL; aOR, 1.30; 95% CI, 1.14–1.49), lymphoplasmacytic lymphoma (aOR, 1.99; 95% CI, 1.47–2.70), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; aOR, 1.55; 95% CI, 1.36–1.77). Among these cancers, HZ was significantly associated with specific subsites or histologic subtypes: gum/other mouth cancer (aOR, 1.49; 95% CI, 1.17–1.91), cecal/appendiceal cancer (aOR, 1.17; 95% CI, 1.04–1.31), small cell lung carcinoma (aOR...
Table 1. Characteristics of cancer cases and cancer-free controls (1992–2005)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 1,108,986)</th>
<th>Controls (n = 100,000)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>588,046 (53.0%)</td>
<td>53,025 (53.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Female</td>
<td>520,940 (47.0%)</td>
<td>46,975 (47.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Age category, years^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66–69</td>
<td>190,541 (17.2%)</td>
<td>17,181 (17.2%)</td>
<td>–</td>
</tr>
<tr>
<td>70–74</td>
<td>289,996 (26.2%)</td>
<td>26,348 (26.2%)</td>
<td>–</td>
</tr>
<tr>
<td>75–79</td>
<td>277,762 (25.1%)</td>
<td>25,047 (25.1%)</td>
<td>–</td>
</tr>
<tr>
<td>80–84</td>
<td>198,004 (17.9%)</td>
<td>17,857 (17.9%)</td>
<td>–</td>
</tr>
<tr>
<td>85–99</td>
<td>152,693 (13.8%)</td>
<td>13,767 (13.8%)</td>
<td>–</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>949,024 (85.6%)</td>
<td>85,603 (83.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black</td>
<td>87,690 (7.9%)</td>
<td>6,662 (7.0%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>28,196 (2.5%)</td>
<td>4,034 (4.0%)</td>
<td></td>
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<tr>
<td>Hispanic</td>
<td>11,482 (1.0%)</td>
<td>313 (0.0%)</td>
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<tr>
<td>Native American</td>
<td>2,540 (0.2%)</td>
<td>333 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20,840 (1.9%)</td>
<td>2,298 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3,204 (0.3%)</td>
<td>253 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Calendar year of selection^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1992–1995</td>
<td>299,648 (19.8%)</td>
<td>19,007 (19.8%)</td>
<td>–</td>
</tr>
<tr>
<td>1996–1999</td>
<td>220,346 (19.9%)</td>
<td>19,871 (19.9%)</td>
<td>–</td>
</tr>
<tr>
<td>2000–2001</td>
<td>235,943 (21.3%)</td>
<td>21,274 (21.3%)</td>
<td>–</td>
</tr>
<tr>
<td>2002–2003</td>
<td>211,239 (20.0%)</td>
<td>19,950 (20.0%)</td>
<td>–</td>
</tr>
<tr>
<td>2004–2005</td>
<td>211,810 (19.1%)</td>
<td>19,098 (19.1%)</td>
<td>–</td>
</tr>
<tr>
<td>Medicare coverage (Part A, Part B, non-HMO^b, months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–27</td>
<td>272,023 (24.5%)</td>
<td>24,239 (24.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>25–53</td>
<td>276,104 (24.9%)</td>
<td>21,701 (21.4%)</td>
<td></td>
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<tr>
<td>54–77</td>
<td>281,282 (25.4%)</td>
<td>28,029 (26.1%)</td>
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</tr>
<tr>
<td>&gt;78</td>
<td>279,577 (25.2%)</td>
<td>28,299 (28.3%)</td>
<td></td>
</tr>
<tr>
<td>Number of physician claims per year^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>280,023 (25.2%)</td>
<td>26,229 (26.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1–3</td>
<td>248,984 (22.5%)</td>
<td>23,501 (23.5%)</td>
<td></td>
</tr>
<tr>
<td>4–6</td>
<td>268,893 (24.2%)</td>
<td>23,741 (23.7%)</td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1,100,077 (99.2%)</td>
<td>99,561 (99.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ever</td>
<td>8,909 (0.8%)</td>
<td>439 (0.4%)</td>
<td></td>
</tr>
</tbody>
</table>

^aFrequency matching was conducted on sex, age, and year of selection.

^bMedicare coverage and physician claims were calculated excluding the 12-month period immediately before cancer diagnosis/control selection.

1.17; 95% CI, 1.03–1.34), and lung adenocarcinoma (aOR, 1.13; 95% CI, 1.03–1.24; Table 2). The non-melanoma skin cancers did not include basal cell or squamous cell carcinomas (SCCs), because these are not captured in cancer registries. Among the skin cancers, we observed an association between HZ and cutaneous sarcomas (not including Kaposi’s sarcoma, which was evaluated separately; aOR, 1.71; 95% CI, 1.12–2.61; Table 2). There was also a borderline association with appendageal skin cancers (aOR 1.47; 95% CI, 0.99–2.16; P = 0.0542).

In a sensitivity analysis, we excluded HIV-infected individuals. As the prevalence of HIV was very low, the ORs associating HZ and cancer were similar after this exclusion (data not shown).

Among solid cancers, HZ was mostly associated with tumors that had regional or distant stage at diagnosis (Table 3). Significant associations were observed for regional stage colon cancer (aOR, 1.13; 95% CI, 1.02–1.24) and nonmelanoma skin cancer (aOR, 1.97; 95% CI, 1.32–2.94), and with distant stage oral cavity/pharyngeal cancer (aOR, 1.74; 95% CI, 1.17–2.59) and lung cancer (aOR, 1.17; 95% CI, 1.07–1.27). Associations were not significant for any localized stage cancers (Table 3).

The associations with HZ were significant when it was diagnosed 13 to 35 months before cancer diagnosis/control selection for the majority of cancers (Table 4). HZ was significantly associated with the following cancers at a latency of 36 to 59 months: lung cancer (aOR, 1.16; 95% CI, 1.02–2.32), non-melanoma skin cancer (aOR, 1.78; 95% CI, 1.23–2.57), myeloma (aOR, 1.66; 95% CI, 1.32–2.09), and CLL/SLL (aOR, 1.37; 95% CI, 1.06–1.76). Notably, only lymphoplasmacytic lymphoma was strongly associated with HZ for the longest latency of 60+ months (aOR, 1.99; 95% CI, 1.25–3.14). The association appeared strongest at short latency intervals for a number of cancers, and this trend was significant for lung cancer, myeloma, and CLL/SLL (Table 4).

Discussion

Because HZ may be a marker of immunosuppression among older adults, we examined its association with cancer risk in the present study. Notably, HZ was not associated with an increased risk for the great majority of cancers. Instead, our results support that a diagnosis of HZ is associated with increased risk only of certain cancers, particularly hematologic malignancies.

There are at least two mechanisms by which an association between HZ and risk of cancer might be explained. Firstly, age-related immune system disorders may lead to reactivation of VZV (8, 26), and at the same time, compromise effective immune surveillance for cancer. However, the best evidence for a role of immune surveillance in preventing the development of cancer is for those malignancies caused by oncogenic viruses (e.g., Kaposi’s sarcoma and anogenital cancers) and a few additional malignancies (e.g., melanoma; 27, 28), and the absence of associations between HZ and most of these cancers argues against this explanation for the associations we observed. Second, cancers may exist in a preclinical or undetectable stage for several months or years before they manifest clinically. Immune system dysfunction caused by such pre-cancers or early cancers may lead to HZ that manifests before the cancer is clinically apparent (26, 29). This mechanism would be a type of reverse causation, in that the cancer or its precursor caused an immunosuppressed state leading to HZ.

The associations between HZ and hematologic malignancies have been noted previously, including with CLL/SLL (30, 31), multiple myeloma (32, 33), lymphoplasmacytic lymphoma (14), and DLBCL (34). We observed that the associations for most of these malignancies were significant when zoster was assessed more than 3 to 5 years before cancer diagnosis/control selection. HZ could be an early marker of immune dysfunction that leads to the development of DLBCL, because DLBCL is strongly associated with immunosuppressive states such as HIV (35) and solid organ transplantation (36). Epstein–Barr virus is etiologically involved in the majority of immunosuppression-associated DLBCL cases (37), but only a minority of DLBCL cases in apparently immunocompetent elderly adults (38). Exclusion of HIV-infected individuals did not change the association between HZ and DLBCL that we observed, thus ruling out confounding by HIV. Of interest, monoclonal gammopathy of undetermined significance and monoclonal B-cell lymphocytosis are asymptomatic pre-malignant conditions that can precede by several years the development of multiple myeloma (39, 40), lymphoplasmacytic lymphoma (41), and CLL/SLL (42). Thus, an alternative explanation is that HZ may be a manifestation of these precursors (i.e., reverse causation).

We also found that HZ was associated with some smoking-associated cancers such as cancers of the oral cavity/pharynx (especially gum/other mouth cancers) and lung (small cell and
Figure 1. Associations between HZ and risk of cancer. The associations with HZ are summarized for each cancer type (y-axis) as ORs with their corresponding 95% CIs on the x-axis (logarithmic scale). ORs are adjusted for age (categorized, 66–69, 70–74, 75–79, 80–84, 85–99 years), sex, year of cancer diagnosis/control selection (1992–1995, 1996–1999, 2000–2001, 2002–2003, 2004–2005), race (whites, non-whites/unknown), and number of physician claims per year.

Asterisk indicates cancers that were identified to be significantly associated with HZ after correction for multiple comparisons by the Benjamini-Hochberg method. AML, acute myeloid leukemia; CLL/SLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; DLBCL, diffuse large B-cell lymphoma; MDS, myelodysplastic syndrome.

<table>
<thead>
<tr>
<th>Cancer Category</th>
<th>Number of subjects</th>
<th>aOR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip</td>
<td>2,259</td>
<td>1.21</td>
<td>0.84, 1.73</td>
<td>0.3069</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>2,427</td>
<td>1.22</td>
<td>0.88, 1.68</td>
<td>0.2235</td>
</tr>
<tr>
<td>Oral cavity/opharynx</td>
<td>14,416</td>
<td>1.21</td>
<td>1.04, 1.42</td>
<td>0.0148*</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,164</td>
<td>1.15</td>
<td>0.96, 1.36</td>
<td>0.1262</td>
</tr>
<tr>
<td>Stomach</td>
<td>22,120</td>
<td>1.10</td>
<td>0.97, 1.25</td>
<td>0.1433</td>
</tr>
<tr>
<td>Small intestine</td>
<td>3,608</td>
<td>1.01</td>
<td>0.76, 1.34</td>
<td>0.9560</td>
</tr>
<tr>
<td>Colon</td>
<td>121,862</td>
<td>1.10</td>
<td>1.02, 1.19</td>
<td>0.0146*</td>
</tr>
<tr>
<td>Rectum</td>
<td>24,073</td>
<td>1.05</td>
<td>0.92, 1.20</td>
<td>0.4955</td>
</tr>
<tr>
<td>Anus</td>
<td>2,550</td>
<td>1.18</td>
<td>0.85, 1.63</td>
<td>0.3323</td>
</tr>
<tr>
<td>Liver</td>
<td>9,991</td>
<td>1.02</td>
<td>0.84, 1.23</td>
<td>0.8522</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>10,356</td>
<td>1.03</td>
<td>0.87, 1.23</td>
<td>0.7386</td>
</tr>
<tr>
<td>Pancreas</td>
<td>32,275</td>
<td>1.02</td>
<td>0.91, 1.14</td>
<td>0.6962</td>
</tr>
<tr>
<td>Nose/middle ear</td>
<td>1,414</td>
<td>1.27</td>
<td>0.83, 1.96</td>
<td>0.2734</td>
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<tr>
<td>Larynx</td>
<td>8,049</td>
<td>1.28</td>
<td>1.03, 1.58</td>
<td>0.0265</td>
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<tr>
<td>Lung*</td>
<td>175,531</td>
<td>1.11</td>
<td>1.03, 1.20</td>
<td>0.0048*</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>3,239</td>
<td>1.19</td>
<td>0.88, 1.61</td>
<td>0.2593</td>
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<tr>
<td>Bone/joint</td>
<td>732</td>
<td>1.58</td>
<td>0.95, 2.65</td>
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</tr>
<tr>
<td>Soft tissue</td>
<td>4,584</td>
<td>0.99</td>
<td>0.77, 1.29</td>
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<td>Melanoma</td>
<td>26,452</td>
<td>1.06</td>
<td>0.94, 1.20</td>
<td>0.3389</td>
</tr>
<tr>
<td>Other non-epithelial skin*</td>
<td>3,935</td>
<td>1.46</td>
<td>1.17, 1.82</td>
<td>0.0008*</td>
</tr>
<tr>
<td>Kaposi's sarcoma</td>
<td>632</td>
<td>1.18</td>
<td>0.64, 2.16</td>
<td>0.5932</td>
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<tr>
<td>Breast</td>
<td>130,966</td>
<td>1.04</td>
<td>0.95, 1.14</td>
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<td>Cervix</td>
<td>3,932</td>
<td>0.82</td>
<td>0.59, 1.15</td>
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<td>Uterus</td>
<td>126,843</td>
<td>0.97</td>
<td>0.85, 1.11</td>
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<td>Ovary</td>
<td>15,701</td>
<td>0.92</td>
<td>0.79, 1.08</td>
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<td>Vagina</td>
<td>905</td>
<td>0.70</td>
<td>0.37, 1.32</td>
<td>0.2696</td>
</tr>
<tr>
<td>Vulva</td>
<td>3,206</td>
<td>1.24</td>
<td>0.96, 1.61</td>
<td>0.1031</td>
</tr>
<tr>
<td>Prostate</td>
<td>209,123</td>
<td>1.09</td>
<td>0.98, 1.22</td>
<td>0.1080</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>60,204</td>
<td>1.06</td>
<td>0.96, 1.16</td>
<td>0.2202</td>
</tr>
<tr>
<td>Kidney</td>
<td>24,120</td>
<td>1.00</td>
<td>0.88, 1.14</td>
<td>0.9671</td>
</tr>
<tr>
<td>Ureter</td>
<td>1,438</td>
<td>0.83</td>
<td>0.51, 1.34</td>
<td>0.4358</td>
</tr>
<tr>
<td>Eye/orbit</td>
<td>1,435</td>
<td>1.41</td>
<td>0.95, 2.09</td>
<td>0.0900</td>
</tr>
<tr>
<td>Brain/nervous system</td>
<td>9,724</td>
<td>1.08</td>
<td>0.89, 1.31</td>
<td>0.4211</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5,813</td>
<td>0.93</td>
<td>0.73, 1.20</td>
<td>0.5656</td>
</tr>
<tr>
<td>Myeloma*</td>
<td>15,009</td>
<td>1.38</td>
<td>1.21, 1.59</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Leukemias</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>8,889</td>
<td>1.14</td>
<td>0.96, 1.35</td>
<td>0.1449</td>
</tr>
<tr>
<td>CML</td>
<td>2,192</td>
<td>1.00</td>
<td>0.70, 1.44</td>
<td>0.5676</td>
</tr>
<tr>
<td>CMML</td>
<td>1,332</td>
<td>1.25</td>
<td>0.84, 1.86</td>
<td>0.2747</td>
</tr>
<tr>
<td>MDS</td>
<td>6,019</td>
<td>1.20</td>
<td>1.00, 1.44</td>
<td>0.0548</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>1,872</td>
<td>1.46</td>
<td>1.04, 2.07</td>
<td>0.0308</td>
</tr>
<tr>
<td>Non-Hodgkin lymphomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL*</td>
<td>15,687</td>
<td>1.30</td>
<td>1.14, 1.49</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Marginal zone</td>
<td>3,166</td>
<td>1.19</td>
<td>0.91, 1.55</td>
<td>0.2061</td>
</tr>
<tr>
<td>Follicular</td>
<td>7,133</td>
<td>1.15</td>
<td>0.94, 1.41</td>
<td>0.1827</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>1,513</td>
<td>1.10</td>
<td>0.71, 1.71</td>
<td>0.6718</td>
</tr>
<tr>
<td>Lymphoplasmacytic*</td>
<td>1,668</td>
<td>1.99</td>
<td>1.47, 2.70</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>CLL/SLL*</td>
<td>14,238</td>
<td>1.55</td>
<td>1.36, 1.77</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Peripheral T-cell</td>
<td>1,317</td>
<td>1.21</td>
<td>0.79, 1.84</td>
<td>0.3786</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>735</td>
<td>1.18</td>
<td>0.65, 2.15</td>
<td>0.5925</td>
</tr>
<tr>
<td>All cancers</td>
<td>1,108,986</td>
<td>1.10</td>
<td>1.04, 1.18</td>
<td>0.0025</td>
</tr>
</tbody>
</table>
adeno
carcinoma). Smokers may have suppressed immune sta-
tus due to various immunomodulatory effects of tar
and nicotine (43), so it is important to consider that these associations
could be explained by smoking. Few studies have evalu-
ted the relationship between smoking and HZ. HZ ophthal-
mic has been reported to have an earlier age of onset in
smokers than nonsmokers (44), and post-herpetic neuralgia
is more intense among smokers (45). However, two studies that
assessed risk factors for HZ actually found an inverse associa-
tion between smoking and HZ (46, 47). One possibility is that
smokers may access healthcare less regularly than nonsmokers,
leading to underdiagnosis of HZ (46).

An interesting finding of our study was the association
between HZ and non-melanoma skin cancers, particularly
cutaneous sarcomas other than Kaposi’s sarcoma. Immunosup-
pression due to HIV infection or solid organ transplantation
leads to increased risk of melanomas and a range of non-
melanoma skin cancers (48, 49). We did not find any significant association between HZ and other cutaneous sarcomas or Kaposi’s sarcoma, and the association with appendageal skin cancers was too borderline significant.

Two previous Italian studies noted associations of soft tissue sarcomas with HZ (50, 51). Cutaneous sarcomas may also be associated with solid organ transplants (49), indicating a role of immunosuppression in their etiology. The most common cutaneous sarcomas in our study population were malignant fibrous histiocytoma and dermatofibrosarcoma. However, the number of cases for specific histological subtypes of cutaneous sarcoma was too small to evaluate their associations with HZ separately. A few case series have reported development of skin cancers at the site of previous HZ (52–54), but a direct etiologic role of HZ in causing skin cancers seems unlikely.

The strength of the associations between HZ and solid

cancers appeared stronger when cancers were diagnosed at
either regional or distant stage. In addition, the associations
for many cancers were strongest at the shortest latency inter-
vals. It is possible that immunosuppression plays an etiologic
role late in the development of these cancers, especially for
the most aggressive tumors. Alternatively, even though we
excluded assessment of HZ in the 12 months before cancer
diagnosis, some of these associations may be due to reverse
causation.

Our study has a few limitations. First, we did not have data on
potential confounders such as smoking, alcohol intake, and

socioeconomic status, or on comorbidities and immunosuppres-
sive drugs which may affect immune status. However, to the extent
that these factors have their effects on cancer risk by causing
immune impairment, we should have been able to partly capture

Table 2. Subgroup analyses to determine specific subsite/histology of cancers associated with HZ.

<table>
<thead>
<tr>
<th>Cancer group</th>
<th>Number of subjects</th>
<th>HZ, N (%)</th>
<th>aOR* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity/pharynx</td>
<td>14,416</td>
<td>192 (1.13%)</td>
<td>1.03 (0.91, 1.17)</td>
<td>0.6978</td>
</tr>
<tr>
<td>Tongue</td>
<td>4,390</td>
<td>56 (1.28%)</td>
<td>1.11 (0.84, 1.46)</td>
<td>0.4635</td>
</tr>
<tr>
<td>Floor of the mouth</td>
<td>1,384</td>
<td>19 (1.37%)</td>
<td>1.35 (0.85, 2.14)</td>
<td>0.2018</td>
</tr>
<tr>
<td>Gum/mouth</td>
<td>3,693</td>
<td>71 (1.92%)</td>
<td>1.49 (1.17, 1.91)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Other oral cavity/pharynx</td>
<td>4,949</td>
<td>46 (0.93%)</td>
<td>1.00 (0.74, 1.35)</td>
<td>0.9870</td>
</tr>
<tr>
<td>Colon</td>
<td>121,862</td>
<td>1,786 (1.47%)</td>
<td>1.17 (1.04, 1.31)</td>
<td>0.0070</td>
</tr>
<tr>
<td>Cecum/appendix</td>
<td>28,831</td>
<td>475 (1.65%)</td>
<td>1.08 (0.95, 1.23)</td>
<td>0.2446</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>20,038</td>
<td>323 (1.61%)</td>
<td>1.07 (0.79, 1.46)</td>
<td>0.3384</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>20,322</td>
<td>305 (1.50%)</td>
<td>1.05 (0.83, 1.32)</td>
<td>0.6998</td>
</tr>
<tr>
<td>Descending colon</td>
<td>6,006</td>
<td>77 (1.28%)</td>
<td>1.10 (0.99, 1.22)</td>
<td>0.0888</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>41,170</td>
<td>518 (1.26%)</td>
<td>1.10 (0.99, 1.22)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Lung</td>
<td>175,531</td>
<td>2,387 (1.36%)</td>
<td>1.17 (1.03, 1.34)</td>
<td>0.0162</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>23,422</td>
<td>306 (1.31%)</td>
<td>1.09 (0.98, 1.22)</td>
<td>0.1263</td>
</tr>
<tr>
<td>SCC</td>
<td>36,863</td>
<td>449 (1.22%)</td>
<td>1.09 (0.98, 1.22)</td>
<td>0.1263</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>61,014</td>
<td>808 (1.32%)</td>
<td>1.11 (1.03, 1.24)</td>
<td>0.0070</td>
</tr>
<tr>
<td>Other non-small cell carcinomas</td>
<td>54,232</td>
<td>824 (1.52%)</td>
<td>1.10 (1.00, 1.21)</td>
<td>0.0494</td>
</tr>
<tr>
<td>Nonmelanoma skin</td>
<td>3,935</td>
<td>91 (2.31%)</td>
<td>1.10 (0.89, 1.35)</td>
<td>0.9969</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>1,513</td>
<td>34 (2.25%)</td>
<td>1.26 (0.89, 1.78)</td>
<td>0.1969</td>
</tr>
<tr>
<td>Appendageal carcinoma</td>
<td>1,204</td>
<td>27 (2.24%)</td>
<td>1.47 (0.99, 2.16)</td>
<td>0.0542</td>
</tr>
<tr>
<td>Sarcoma (except Kaposi’s sarcoma)</td>
<td>964</td>
<td>23 (2.39%)</td>
<td>1.71 (1.33, 2.20)</td>
<td>0.0324</td>
</tr>
<tr>
<td>Other nonepithelial skin cancers</td>
<td>254</td>
<td>–b</td>
<td>1.94 (0.92, 4.15)</td>
<td>0.0879</td>
</tr>
</tbody>
</table>

NOTE: Underlined values in the table are statistically significant (P < 0.05).

bThere were fewer than 11 people with HZ. The number is suppressed in accordance with the SEER-Medicare data use agreement.

Table 3. Associations of HZ with cancer, by stage at diagnosis.

<table>
<thead>
<tr>
<th>Cancer sites/histology</th>
<th>Localized stage aOR* (95% CI)</th>
<th>Regional stage aOR* (95% CI)</th>
<th>Distant stage aOR* (95% CI)</th>
<th>Unstaged aOR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity/pharynx</td>
<td>1.28 (0.99, 1.63)</td>
<td>1.11 (0.89, 1.40)</td>
<td>1.74 (1.17, 2.59)</td>
<td>0.95 (0.55, 1.66)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.08 (0.96, 1.21)</td>
<td>1.09 (0.98, 1.21)</td>
<td>1.17 (1.07, 1.27)</td>
<td>1.04 (0.90, 1.20)</td>
</tr>
<tr>
<td>Colon</td>
<td>1.06 (0.96, 1.17)</td>
<td>1.13 (1.02, 1.24)</td>
<td>1.27 (1.06, 1.53)</td>
<td>0.98 (0.80, 1.21)</td>
</tr>
<tr>
<td>Nonmelanoma skin</td>
<td>1.29 (0.96, 1.72)</td>
<td>1.39 (1.12, 2.04)</td>
<td>1.88 (0.77, 4.93)</td>
<td>1.31 (0.70, 2.45)</td>
</tr>
</tbody>
</table>

NOTE: Underlined values in the table are statistically significant (P < 0.05).

Table 4. Associations of HZ with cancer at different latency intervals

<table>
<thead>
<tr>
<th>Cancer sites/histology</th>
<th>Zoster 13–35 months before cancer diagnosis/control selection aOR* (95% CI)</th>
<th>Zoster 36–59 months before cancer diagnosis/control selection aOR* (95% CI)</th>
<th>Zoster 60+ months before cancer diagnosis/control selection aOR* (95% CI)</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity/pharynx</td>
<td>1.46 (1.13, 1.90)</td>
<td>1.18 (0.88, 1.57)</td>
<td>1.06 (0.82, 1.37)</td>
<td>0.0855</td>
</tr>
<tr>
<td>Lung</td>
<td>1.21 (1.07, 1.38)</td>
<td>1.16 (1.02, 1.32)</td>
<td>1.01 (0.90, 1.13)</td>
<td>0.0308</td>
</tr>
<tr>
<td>Colon</td>
<td>1.20 (1.04, 1.38)</td>
<td>1.12 (0.98, 1.29)</td>
<td>1.03 (0.91, 1.16)</td>
<td>0.0892</td>
</tr>
<tr>
<td>Nonmelanoma skin</td>
<td>1.47 (0.96, 2.23)</td>
<td>1.18 (1.23, 2.57)</td>
<td>1.25 (0.88, 1.77)</td>
<td>0.4531</td>
</tr>
<tr>
<td>Myeloma</td>
<td>1.55 (1.22, 1.98)</td>
<td>1.66 (1.52, 2.09)</td>
<td>1.08 (0.86, 1.36)</td>
<td>0.0204</td>
</tr>
<tr>
<td>NHLs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large B cell</td>
<td>1.48 (1.17, 1.87)</td>
<td>1.26 (0.99, 1.61)</td>
<td>1.22 (0.99, 1.50)</td>
<td>0.2470</td>
</tr>
<tr>
<td>Lymphoplasmacytic</td>
<td>2.76 (1.71, 4.45)</td>
<td>1.29 (0.66, 2.50)</td>
<td>1.99 (1.25, 3.34)</td>
<td>0.4147</td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>2.22 (1.79, 2.73)</td>
<td>1.37 (1.06, 1.76)</td>
<td>1.23 (0.99, 1.54)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

NOTE: Underlined values in the table are statistically significant (P < 0.05).
Abbreviations: aOR, adjusted odds ratio; CI, confidence intervals; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

their influence through the ascertainment of HZ. Second, cases in our study had more physician claims per year than controls before cancer diagnosis/control selection. A greater use of the healthcare system could have increased the likelihood of being diagnosed with HZ. Although we adjusted for the number of physician visits in our analyses, the possibility of residual confounding cannot be ruled out. Third, as HZ was defined by the presence of at least two outpatient or physician claims at least 30 days apart, we were likely to miss cases who were treated and cured of HZ within 30 days after the first claim. However, we believe that the resulting reduced prevalence of HZ would have affected cancer cases and the control group equally, and that the use of this strict definition improved the accuracy of our measures of association. Finally, given the number of associations we assessed, some could be due to chance, but we utilized a multiple comparisons procedure to minimize this possibility and identify the most noteworthy findings.

The strengths of our study include our assessment of a large nationally representative sample of the U.S. elderly population. Because both HZ and cancer increase with age, the elderly are an important group in whom to assess these associations. SEER registries have strict quality control measures for cancer ascertainment which contribute to the reliability of the cancer outcomes (30). Furthermore, the availability of detailed information on cancer histology and stage allowed us to perform subgroup analyses and identify specific subtypes of cancers associated with HZ, which was not possible in previous studies. We minimized the possibility of reverse causation by excluding 12 months before cancer diagnosis for ascertainment of HZ, and by conducting subgroup analyses over longer latency periods (36–59 and 60+ months).

In conclusion, our results support that HZ is not a generalized marker of increased risk for all cancers, thus suggesting that age-related decline in immune function does not play a major role in the development of cancer among the elderly. Instead, the associations were limited to a select group of cancers, especially hematologic malignancies and advanced stage solid tumors. It seems unwise to screen broadly for cancers based on our results, because the associations that we observed were somewhat limited and modest in magnitude. Nonetheless, a diagnosis of HZ in a patient over 65 years old should prompt physicians to perform a thorough history and physical examination, with a focus on identifying immunosuppressing conditions and any early symptoms or signs of cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: P. Mahale, E.L. Yanik, E.A. Engels
Development of methodology: P. Mahale, E.L. Yanik, E.A. Engels
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P. Mahale, E.L. Yanik, E.A. Engels
Writing, review, and/or revision of the manuscript: P. Mahale, E.L. Yanik, E.A. Engels
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P. Mahale, E.L. Yanik, E.A. Engels

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References


