

## The Epidemiology of Herpes Zoster in Patients with Newly Diagnosed Cancer

Laurel A. Habel<sup>1</sup>, Gary Thomas Ray<sup>1</sup>, Michael J. Silverberg<sup>1</sup>, Michael A. Horberg<sup>3</sup>, Barbara P. Yawn<sup>4</sup>, Adrienne L. Castillo<sup>1</sup>, Charles P. Quesenberry, Jr<sup>1</sup>, Yan Li<sup>2</sup>, Patricia Sadier<sup>5</sup>, and Trung N. Tran<sup>5</sup>

### Abstract

**Background:** Given the limited literature, we conducted a study to examine the epidemiology of herpes zoster (HZ) among newly diagnosed cancer patients.

**Methods:** We identified adult health plan members of Kaiser Permanente Northern California diagnosed with invasive cancer from 2001 to 2005. Electronic health records with inpatient and outpatient diagnoses, laboratory tests, and antiviral medications were used to identify HZ diagnoses from 2001 to 2006. HZ diagnoses and associated complications were confirmed by medical chart review. Treatment with chemotherapy and corticosteroids was used to classify patients by immunosuppression level.

**Results:** Among 14,670 cancer patients, 424 were diagnosed with HZ during follow-up (median 22 months). The incidence of HZ was 31/1,000 person-year (PY) in patients with hematologic malignancies and 12/1,000 PY in patients with solid tumors. The corresponding 2-year cumulative incidence of HZ was approximately 6% and 2%, respectively. Compared with incidence rates of HZ reported in a general US population, the age- and sex-standardized rates of HZ were 4.8 times higher [95% confidence interval (CI), 4.0–5.6] in patients with hematologic malignancies and 1.9 times higher (95% CI, 1.7–2.1) in those with solid tumors. HZ risk increased with increasing level of immunosuppression. Among HZ cases, 19% with hematologic malignancies and 14% with solid tumors had HZ-associated pain for at least 30 days. The corresponding numbers for nonpain-related complications were 30% and 18%, respectively.

**Conclusions:** Cancer patients are at substantially increased risk of HZ and among those with HZ, complications are relatively common.

**Impact:** Better HZ prevention and treatment options for cancer patients are needed. *Cancer Epidemiol Biomarkers Prev*; 22(1): 82–90. ©2012 AACR.

### Introduction

A history of primary infection with varicella zoster virus (VZV), which causes chicken pox, is almost universal in adult populations in North America and Europe. As with other  $\alpha$ -herpes viruses, VZV establishes latency in cells of the dorsal root ganglia after primary infection (1). Reactivation of latent VZV occurs in approximately 20% to 30% of individuals and causes herpes zoster (HZ), also known as shingles (2, 3). This reactivation typically results

in a unilateral vesicular rash in 1 or 2 adjacent dermatomes; thoracic, cervical, and ophthalmic involvements are the most common (4). The rash is often preceded by pain, which becomes more acute with the appearance of vesicles (1).

In immunocompetent individuals, HZ usually clears in two to three weeks and recurs at a low rate [approximately 4% within 4 years of a first episode (3)]. Involvement of motor nerves may cause temporary or permanent nerve palsy. HZ may be complicated by postherpetic neuralgia (PHN), which is HZ-associated pain that may last from months to years following the initial HZ episode, or more rarely with meningitis or other severe complications (1, 2).

VZV is believed to be maintained in its latent form by VZV-specific cell-mediated immunity (5) and patients who are immunosuppressed are at greater risk of HZ (3). In addition, patients with impaired cell-mediated immunity appear to have a greater tendency to have PHN and to have severe complications (1, 2, 6).

While cancer patients are often immunocompromised because of their disease or their treatment (7–10), the literature on the epidemiology and natural history of HZ among patients with cancer, especially with solid tumor

**Authors' Affiliations:** <sup>1</sup>Division of Research, and <sup>2</sup>Department of Oncology, Kaiser Permanente, Northern California, Oakland, California; <sup>3</sup>Mid-Atlantic Permanente Research Institute, Kaiser Permanente, Rockville, Maryland; <sup>4</sup>Olmsted Medical Center, Department of Research, Rochester, Minnesota; and <sup>5</sup>Merck Research Laboratories, Epidemiology Department, MRL, Merck Sharp and Dohme, Corporation, Whitehouse Station, New Jersey

**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>)

**Corresponding Author:** Laurel A. Habel, 2000 Broadway, Oakland, CA 94612. Phone: 510-891-3715; Fax: 510-891-3898; E-mail: [laurel.habel@kp.org](mailto:laurel.habel@kp.org)

**doi:** 10.1158/1055-9965.EPI-12-0815

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malignancies, is extremely limited. Several studies have been conducted among patients with Hodgkin and other types of lymphoma (9–19), but mostly decades ago. Limited data are available for patients with other types of hematologic malignancies or among those receiving current chemotherapeutic regimens.

Thus, the aim of this study was to describe the epidemiology and natural history of HZ and its complications among a large, community-based cohort of adult patients newly diagnosed with hematologic or solid tumor malignancies. We also examined estimated level of immunosuppression and other potential risk factors for HZ in cancer patients.

## Materials and Methods

### Study population and design

We conducted a retrospective cohort study of members of Kaiser Permanente Northern California (KPNC) newly diagnosed with invasive cancer. KPNC is a nonprofit, prepaid integrated health plan providing comprehensive care for more than 3.2 million members at its own hospitals and outpatient clinics. Inpatient and outpatient diagnoses, laboratory tests, and pharmacy dispensations are archived in electronic databases. Records from different databases are readily linked using the patient's unique medical record number. The KPNC membership is racially and ethnically diverse and is demographically similar to the general population of northern California, although it underrepresents the extremes of the socioeconomic spectrum (20). The study was approved by the KPNC Institutional Review Board.

The KPNC cancer registry was used to identify all health plan members aged 18 years or older diagnosed with a first invasive cancer between January 1, 2001 and December 31, 2005 ( $n = 66,446$ ). Medical facilities in California, including KPNC facilities, are required by law to report all newly diagnosed cases of cancer to the California Cancer Registry, which also reports to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program of cancer registries. As with SEER registries, the quality control and auditing of case reporting completeness for the KPNC cancer registry are ongoing processes and occur at all levels of cancer registration and reporting. The cancer registry provided information on diagnosis date, cancer type and stage, patient's age at diagnosis, and race/ethnicity.

We included only cancer patients who were continuous members of KPNC in the 240 days before their cancer diagnosis date and who had not undergone bone marrow or organ transplant and had no evidence of HZ diagnosis or treatment during that period ( $n = 61,272$ ). Although KPNC has complete historical data on outpatient pharmacy fills covering the entire time period of this study, patient-level data on medications administered in infusion clinics were not available for all infusion clinics for the entire study period. We, therefore, only considered those cancer patients who were diagnosed after the time

complete infusion medication data were available at their treating facility. There were 2,715 patients with hematologic malignancies and 29,543 patients with solid tumors. Lymphomas, which fall into both cancer groups, were included among hematologic malignancies only. As we did not have resources to adjudicate potential HZ cases among all patients, we maximized study efficiency and the power to examine patients with hematologic malignancies and solid tumors separately by including all patients with a hematologic malignancy ( $n = 2,715$ ) and a 40% random sample of the patients with solid tumors ( $n = 11,955$ ).

### Identification of potential HZ cases

Potential cases of HZ were identified by extracting records on all inpatient and outpatient encounters occurring between January 1, 2001 and December 31, 2006 at which a diagnosis code of HZ was listed (ICD9 053xx), there was a positive laboratory test for VZV (viral culture or PCR), or there was a pharmacy prescription for selected antiviral medications at doses consistent with treatment of HZ, including valacyclovir ( $\geq 3,000$  mg/d), acyclovir ( $\geq 4,000$  mg/d), or famciclovir (any dose; ref. 21). Because these antivirals are also commonly used for herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) infection, we excluded any fills that occurred within 90 days before or after a diagnosis of herpes simplex (ICD9 054.x).

### Confirmation of HZ diagnoses and complications

Medical charts of all potential HZ cases were reviewed and data on disease presentation and course were abstracted and recorded onto standardized forms. The forms and photocopied notes and laboratory results were reviewed by a study clinician (author M.A. Horberg or B. Yawn) and each potential case was classified into one of four categories: (i) definite case, (ii) probable case, (iii) possible case, or (iv) no indication of HZ. "Definite" cases were those with a description of a typical HZ rash (clustered blisters) or with prodromal pain, limited to a dermatome that was clearly described plus a physician diagnosis or a physician diagnosis of possible or rule out HZ with a positive PCR or viral culture. "Probable" cases were those with typical rash or with a rash localized to an area that would be consistent with a dermatome but with the dermatome not explicitly mentioned, plus notation of prodromal symptoms. "Possible" cases were those with a rash that might be atypical but in a region that was listed as consistent with a dermatome and no prodromal symptoms and no complications. Patients classified as "no indication of HZ" were those with either no recorded episode that suggested consideration of HZ, a rule out diagnosis of HZ, or possible HZ where viral culture or PCR was negative for VZV or was positive for HSV-1/HSV-2 and not VZV. Primary analyses included zoster cases classified as "definite" or "probable." Patients identified by chart review as having prevalent rather than incident HZ were excluded from the cohort.

HZ episode duration was defined as the number of days from the episode's index date to the last medical contact with an indication of HZ plus 30 days. Patients could have more than 1 episode of HZ during follow-up. A patient with a HZ diagnosis was considered to have a new episode when there was a visit for HZ-related symptoms or treatment with no chart indication of HZ in the prior 180 days.

The chart abstraction and clinical review also included the identification and confirmation of complications of HZ. Complications were categorized into 2 broad categories as pain-related and nonpain related. Pain-related complications included PHN, HZ-associated pain, and other pain associated with a HZ episode. Nonpain-related complications were classified as skin-related, neurologic-related, ocular/eye-related, and disseminated HZ.

Additional chart reviews were conducted on patients who received antivirals at doses lower than that recommended for treatment. Patients who received antivirals in the absence of any signs, symptoms or diagnosis for HZ were considered to have received them for prophylaxis.

#### Level of immunosuppression

Level of immunosuppression was considered an important potential predictor of HZ risk. Before any data analyses, an expert panel of 7 hematologists and oncologists developed an algorithm to classify patients' level of immunosuppression into either none/low, moderate, or high, using data available in electronic databases. Details of this algorithm were presented previously (ref. 22; see Supplementary Material). Briefly, the algorithm was based on: (i) specific chemotherapy agents and/or corticosteroids, (ii) current, and time since last, chemotherapy/corticosteroid treatment, and (iii) if hematologic malignancy, specific type. No other causes of immunosuppression were considered. Chemotherapy agents were classified into levels of immunosuppression, irrespective of dose. Corticosteroid therapy was classified into levels of immunosuppression based on dose and duration of treatment. Immunosuppression levels were allowed to change monthly to reflect the chemotherapy agents used, the dose and duration of corticosteroid if any, and time since the last immunocompromising treatment. The patient's immunosuppression level was assumed to stay at an assigned level while on therapy and for 6 months after last treatment, and then move to the next lower level for an additional 6 months. For example, if a solid cancer patient received a course of infliximab, a drug considered highly immunocompromising, their immunosuppression level was categorized as "high" during treatment and for the 6 months after treatment completion and as "moderate" for an additional 6 months. In another example, a patient with acute leukemia, a hematologic malignancy associated with severe immunosuppression, was categorized as "high" regardless of treatments received.

HIV infection was not included in the algorithm, but it was very uncommon. Less than 1% of the study cohort (88

of 14,670) was known to be infected with HIV. Among the 424 HZ cases, there were only 2 patients known to be infected with HIV (both had a hematologic malignancy).

#### Statistical analyses

Follow-up began at the date of cancer diagnosis and ended at date of first HZ episode; death; bone marrow, stem cell, or organ transplant; end of health plan membership; or December 31, 2006; whichever occurred first. For time-varying characteristics (age, immunosuppression level, and current use of immunocompromising therapy), at risk person-time and HZ events were allocated such that study subjects moved in and out of strata during follow-up. Incidence rates of HZ were calculated as the number of diagnoses of HZ divided by the person-time accrued for all cancer patients under follow-up. Confidence intervals for incidence rates were calculated assuming the events followed the Poisson distribution. Standardized incidence ratios (SIR) were calculated comparing the observed number of HZ cases to those expected in the general population using community based age- and sex-specific HZ rates in Olmsted County, MN (23). These population rates were chosen for comparison, as the Olmstead study had a similar design and HZ cases were also confirmed by medical chart review. The cumulative incidence of HZ was calculated using a nonparametric approach that takes competing risks (i.e., death) into account (24). Proportional hazard regression was used to generate HRs for HZ associated with potential risk factors, while adjusting for other variables.

#### Results

##### Description of study cohort

The final study cohort of 14,670 cancer patients included 2,715 patients diagnosed with a hematologic malignancy and 11,955 patients diagnosed with a solid tumor (Table 1). Although fewer of the solid tumor patients were young at their cancer diagnosis, the age and gender distribution of follow-up time was fairly similar to that for patients with hematologic malignancies. In both cancer groups, there were more males than females and approximately 70% were aged 60 years or older. Compared with patients with solid tumors, those with hematologic malignancies more frequently were receiving chemotherapy and, based on our algorithm, were classified as moderately or highly immunosuppressed during more of their follow-up time.

##### Incidence of HZ

During a median follow-up of 22 months (maximum 72 months), 590 potential cases of HZ were identified. Of these potential HZ cases, 424 (69%) were clinically adjudicated as "definite" ( $n = 379$ ) or "probable" ( $n = 45$ ). This included 140 definite or probable HZ cases among patients with a hematologic malignancy and 284 among patients with a solid tumor. In sensitivity analyses restricted to HZ cases adjudicated as "definite" results did not

**Table 1.** Patient characteristics and HZ rates

Characteristic	Cancer type							
	Hematologic malignancy				Solid tumor			
	Number of patients	Number HZ cases	Person-years	Rate/1,000 person-yr (95% CI)	Number of patients	Number HZ cases	Person-years	Rate/1,000 person-years (95% CI)
All subjects	2,715	140	4,465	31.4 (26.2,36.5)	11,955	284	23,072	12.3 (10.9,13.7)
Sex								
Female	1,248	67	2,040	32.8 (25.0,40.7)	5,784	161	11,298	14.2 (12.0,16.5)
Male	1,467	73	2,425	30.1 (23.2,37.0)	6,171	123	11,774	10.4 (8.6,12.3)
Age group (years)								
18–49	415	21	733	28.6 (16.4,40.9)	1,348	26	3,063	8.5 (5.2,11.7)
50–59	452	27	848	31.8 (19.8,43.8)	2,305	56	5,033	11.1 (8.2,14.0)
60–69	604	34	1,079	31.5 (20.9,42.1)	3,151	80	6,383	12.5 (9.8,15.3)
70–79	729	44	1,143	38.5 (27.1,49.9)	3,293	78	5,994	13.0 (10.1,15.9)
80+	515	14	661	21.2 (10.1,32.3)	1,858	44	2,599	16.9 (11.9,21.9)
Race/ethnicity								
Asian	249	15	371	40.4 (20.0,60.9)	1,096	36	2,145	16.8 (11.3,22.3)
Black	211	12	374	32.1 (13.9,50.3)	1,161	29	2,341	12.4 (7.9,16.9)
Hispanic	267	10	447	22.4 (8.5,36.2)	938	17	1,794	9.5 (5.0,14.0)
Other/unknown	92	5	174	28.7 (3.5,53.8)	408	12	808	14.9 (6.5,23.3)
White	1,896	98	3,099	31.6 (25.4,37.9)	8,352	190	15,984	11.9 (10.2,13.6)
Immunosuppression <sup>a</sup>								
None/low	NA	15	1,131	13.3 (6.6,20.0)	NA	171	17,276	9.9 (8.4,11.4)
Moderate	NA	39	1,535	25.4 (17.4,33.4)	NA	37	1,843	20.1 (13.6,26.5)
High/very high	NA	86	1,799	47.8 (37.7,57.9)	NA	76	3,953	19.2 (14.9,23.5)
Chemotherapy <sup>a</sup>								
Currently on	NA	99	2,066	47.9 (38.5,57.4)	NA	120	5,214	23.0 (18.9,27.1)
Currently off	NA	41	2,399	17.1 (11.9,22.3)	NA	164	17,858	9.2 (7.8,10.6)

<sup>a</sup>Classification treated as time varying, with patients moving in and out of categories during follow-up.

meaningfully change and hereafter both definite and probable HZ cases are referred to as confirmed cases. The percentage of potential cases confirmed as HZ was slightly higher for patients with solid tumors (74%) than for patients with hematologic malignancies (68%). Among cases originally identified by a clinical diagnosis or laboratory test, 81% were confirmed by chart review. Among cases originally identified by high-dose antiviral therapy, 27% were confirmed by chart review.

Median duration of an HZ episode was 44 days (mean = 80) for patients with hematologic malignancies and 31 days (mean = 75) for those with solid tumors. Virtually all HZ cases presented with rash (99% in both cancer groups), and most presented with pain symptoms (67% and 69% of the hematologic malignancy and solid tumor patients, respectively). Eight patients had more than one episode of HZ (i.e., recurrence) during follow-up (5 of the 140 patients with a hematologic malignancy and 3 of the 284 patients with a solid tumor). There were 372 HZ patients (88% of all HZ cases) who received antiviral medication (acyclovir, famciclovir, or valacyclovir). An additional 11 patients without an HZ diagnosis appeared to receive antiviral medications for HZ prophylaxis.

The incidence of HZ was 31/1,000 person-years (PY) for patients with hematologic malignancies [95% confidence interval (CI), 26–37/1,000 PY] and 12/1,000 PY for patients with solid tumors (95% CI, 11–14/1,000 PY; Table 1). The incidence of HZ was higher in females than in males and increased with increasing age among the solid tumor patients. The association with age was less consistent among patients with hematologic malignancies. In both cancer groups, HZ incidence was higher among those currently treated with chemotherapy and increased with increasing level of immunosuppression. Rates appeared to differ by specific type of solid or hematologic cancer (Table 2).

The 2-year cumulative incidence of HZ after cancer diagnosis was approximately 2% for patients with solid tumors and 6% for patients with hematologic malignancies. At 5 years, the cumulative incidence was 5% and 12%, respectively (Fig. 1). Cumulative incidence of HZ appeared to increase fairly steadily over time for both cancer groups.

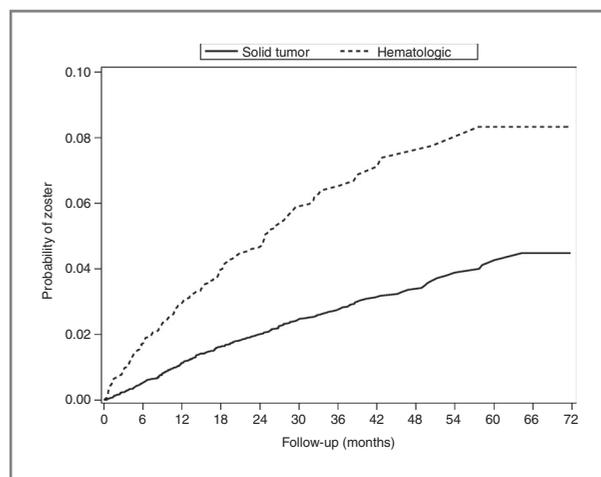
#### Comparisons of rates of HZ in cancer patients and general population

Compared with HZ incidence rates reported in a general US population (23), the age- and sex-standardized

**Table 2.** HZ rates in cancer patients, by cancer site

Cancer type	Number of patients	Person-years	Number HZ Cases	Rate/1,000 person-years (95% CI)
<b>Hematologic</b>				
Hodgkin lymphoma	154	295	15	50.8 (25.1,76.5)
Lymphocytic leukemia	325	661	19	28.8 (15.8,41.7)
Monocytic leukemia	22	12	1	81.7 (0.0,242)
Multiple myeloma	416	573	32	55.8 (36.5,75.2)
Myeloid leukemia	319	262	6	22.9 (4.6,41.2)
Non-Hodgkin lymphoma	1,442	2,640	67	25.4 (19.3,31.5)
Other leukemia	37	21	0	0.0 (0.0,0.0)
<b>Solid tumor</b>				
Brain	152	150	5	33.4 (4.1,62.6)
Breast	2,198	5,428	79	14.6 (11.3,17.8)
Colon excluding rectum	1,002	1,975	16	8.1 (4.1,12.1)
Corpus uteri	268	673	5	7.4 (0.9,13.9)
Kidney/renal pelvis	377	704	9	12.8 (4.4,21.1)
Liver/intrahepatic bile duct	171	111	0	0.0 (0.0,0.0)
Lung/bronchus	1,599	1,621	34	21.0 (13.9,28.0)
Melanoma	644	1,494	14	9.4 (4.5,14.3)
Ovary	133	190	6	31.5 (6.3,56.8)
Pancreas	309	167	0	0.0 (0.0,0.0)
Prostate	2,442	6,055	60	9.9 (7.4,12.4)
Rectum/rectosigmoid	363	741	8	10.8 (3.3,18.3)
Stomach	221	228	9	39.5 (13.7,65.2)
Thyroid	194	449	3	6.7 (0.0,14.3)
Urinary bladder	324	627	5	8.0 (1.0,15.0)
Other	1,558	2,459	31	12.6 (8.2,17.0)

incidence rates of HZ were nearly 5 times higher in patients with hematologic malignancies and nearly 2 times higher in those with solid tumors (Table 3). In both cancer groups, SIR were higher among those less than 60 years of age and among patients currently on immun-



**Figure 1.** Cumulative probability of zoster by month after cancer diagnosis.

compromising therapy or among patients categorized with higher levels of immunosuppression.

### Complications of HZ

The most commonly noted complication among patients with HZ was pain. Of the 390 patients with at least 30 days of follow-up after their HZ, 18.9% of those with hematologic malignancies, and 14.0% of those with solid tumors, had pain for 30 or more days after an HZ diagnosis. Among the 355 HZ patients with at least 90 days of follow-up, 5.7% of patients with hematologic malignancies and 8.6% of those with solid tumors had PHN for 90 days or more. Disseminated rash (defined as  $\geq 2$  dermatomes) was the most common nonpain-related complication in the HZ cases, occurring in 19.3% of those with hematologic malignancies and 8.5% of those with solid tumors. Among HZ cases with hematologic malignancies, the proportion of other nonpain-related complications including other skin-related, neurologic, and eye-related complications were 7.9%, 2.9%, and 3.6%, respectively. For those with solid tumors, it was 7.7%, 0.4%, and 3.2%, respectively. Overall, 30% of HZ cases among those with hematologic malignancies and 18% among those with solid tumors had at least 1 nonpain-related complication recorded in the medical record.

**Table 3.** Age and gender-standardized incidence ratios<sup>a</sup> of hematologic and solid tumor malignancies, by selected patient factors

Characteristic	Cancer type	
	Hematologic malignancy SIR (95% CI)	Solid tumor SIR (95% CI)
All subjects	4.8 (4.0,5.6)	1.9 (1.7,2.1)
Age group		
<60 years	9.0 (6.4,12.2)	3.0 (2.4,3.8)
60+ years	4.0 (3.3,4.9)	1.7 (1.4,1.9)
Immunosuppression		
None/Low	1.8 (1.0,3.0)	1.5 (1.3,1.7)
Moderate	3.8 (2.7,5.3)	3.2 (2.3,4.4)
High/Very High	7.7 (6.2,9.6)	3.1 (2.4,3.9)
Chemotherapy		
Currently on	7.8 (6.3,9.4)	3.7 (3.1,4.5)
Currently off	2.6 (1.8,3.5)	1.5 (1.3,1.7)

<sup>a</sup>SIR were calculated comparing the observed HZ cases to those expected based on age and gender-specific HZ rates from a study of adults in Olmsted County, MN (23).

### Risk factors for HZ

HRs of HZ associated with selected patient and clinical factors are presented in Table 4. In multivariable models, increasing age was associated with increasing risk of HZ among patients with solid tumors, but this pattern was less consistent among patients with hematologic malignancies. Similarly, the suggestion of a slightly increased risk observed for females seemed to be largely confined to patients with solid tumors. Among those with solid tumors, there was a suggestion that Asian patients may be at higher risk for HZ than white patients. Higher level of immunosuppression was associated with an increased risk of HZ in those with hematologic and solid tumor malignancies.

### Discussion

Our study is one of the first to estimate incidence rates of and examine risk factors and complications of HZ in cancer patients. Among more than 14,000 patients diagnosed with invasive cancer in the community setting, the 2-year cumulative incidence of HZ was 2% for patients with solid tumors and 6% for patients with hematologic malignancies. Among patients with HZ, complications were common, especially among patients with hematologic malignancies. Estimated immunosuppression level, based on cancer type, chemotherapy, and corticosteroid dose, was associated with rates of HZ in both cancer subgroups.

Our study had several limitations. Although our cohort was drawn from the membership of a large and ethnically diverse health plan, the results may not be generalizable to cancer patients in all geographic regions or community

health care settings. We clinically adjudicated all potential HZ cases identified from the electronic medical record, but we may have missed some cases. The general KPNC membership would have been the preferred comparison population for our SIR estimates; however, we did not have confirmed HZ cases on the full membership. Thus, despite potential differences in population characteristics, the HZ rates from Olmsted County, Minnesota, which were based on similarly confirmed cases (23), appeared to be the best available general population estimates. Of note, as the zoster vaccine was only licensed in 2006, none of the study subjects could have been vaccinated before cancer diagnosis (4). We did not exclude patients with HIV infection, but the prevalence was extremely low and thus should have had minimal impact on results. Finally, our median follow-time was approximately 2 years, thus reducing our ability to examine risk of and risk factors for HZ more than 2 years after cancer diagnosis.

The literature on the risk of HZ among patients with solid tumor malignancies is quite limited, especially for patients diagnosed in recent years (25–34). The reported percentage developing HZ has ranged from approximately 1.5% to 12%. Although there have been more studies in patients with hematologic malignancies, mostly in patients with Hodgkin or non-Hodgkin lymphoma, these also were mostly conducted in the 1970s and 1980s (9–19, 35) and were often small. The reported percentage of patients with hematologic malignancies developing HZ differed by age, stage, and treatment, and ranged from 2% to 27%. Few studies in patients with either solid tumor or hematologic malignancies have provided incidence rates for specific time intervals after cancer diagnosis.

Our results are consistent with a recent study of approximately 10,000 cancer patients in Japan that found that a higher risk of HZ in persons with than without cancer (36). As in our study, the relative increase was substantially greater among patients with hematologic malignancies than among those with solid tumors.

To our knowledge, our study is the first to categorize cancer patients into levels of immunosuppression, based on type of chemotherapy and dose of corticosteroids, and to examine level of immunosuppression and risk of HZ among cancer patients. Our findings in cancer patients are consistent with previous reports of a high risk of HZ among individuals who are immunocompromised, such as patients infected with HIV (37–39), patients receiving hematopoietic stem cell transplant or solid organ transplant, or patients with autoimmune diseases treated by immunosuppressing therapies (40–47).

Compared with patients with solid tumors, those with hematologic malignancies more commonly had earlier HZ diagnoses, episodes with longer duration, and HZ-related complications. In our study, approximately 30% of HZ patients with hematologic malignancies and 18% of those with solid tumors had at least one nonpain-related complication. These were higher than the corresponding rate of 10% reported previously in the general population (23). Our findings on HZ complications are also consistent

**Table 4.** Hazard ratios<sup>a</sup> of HZ associated with selected patient and clinical factors

<b>Risk factor</b>	<b>All cancer patients HR<sup>a</sup> (95% CI)</b>	<b>Hematologic malignancies HR<sup>a</sup> (95% CI)</b>	<b>Solid tumor malignancies HR<sup>a</sup> (95% CI)</b>
Age, y			
<50	1.0 (reference)	1.0 (reference)	1.0 (reference)
50 to <60	1.3 (0.9,1.9)	1.3 (0.7,2.3)	1.5 (0.9,2.4)
60 to <70	1.4 (1.0,2.1)	1.2 (0.7,2.1)	1.8 (1.1,2.9)
70 to <80	1.6 (1.2,2.3)	1.5 (0.8,2.7)	1.9 (1.2,3.1)
80+	1.7 (1.1,2.5)	0.9 (0.4,1.9)	2.7 (1.6,4.6)
Sex			
Male	1.0 (reference)	1.0 (reference)	1.0 (reference)
Female	1.2 (1.0,1.5)	1.1 (0.8,1.5)	1.3 (0.9,1.8)
Race			
White	1.0 (reference)	1.0 (reference)	1.0 (reference)
Asian	1.4 (1.0,1.8)	1.3 (0.7,2.2)	1.5 (1.0,2.1)
Black	1.1 (0.8,1.5)	0.9 (0.5,1.7)	1.1 (0.8,1.7)
Hispanic	0.8 (0.5,1.2)	0.6 (0.3,1.2)	0.9 (0.5,1.5)
Other/unknown	1.3 (0.8,2.2)	1.0 (0.4,2.4)	1.5 (0.8,2.7)
Cancer stage			
Localized	0.8 (0.6,1.1)	0.8 (0.5,1.4)	0.8 (0.5,1.2)
Regional	1.1 (0.8,1.4)	1.4 (0.8,2.4)	1.1 (0.7,1.6)
Distant	1.0 (reference)	1.0 (reference)	1.0 (reference)
Immunosuppression			
None/low	1.0 (reference)	1.0 (reference)	1.0 (reference)
Moderate	1.6 (1.2,2.2)	2.0 (1.1,3.8)	1.9 (1.3,2.8)
High/very high	2.2 (1.7,2.8)	3.3 (1.8,5.8)	1.9 (1.4,2.5)
Cancer type			
Solid tumor	1.0 (reference)	N/A	N/A
Hematologic malignancy	1.8 (1.4,2.3)	N/A	N/A
Cancer site			
Non-Hodgkins	N/A	1.0 (reference)	N/A
Hodgkin lymphoma	N/A	1.8 (0.9,3.3)	N/A
Lymphocytic leukemia	N/A	1.4 (0.8,2.6)	N/A
Multiple myeloma	N/A	1.9 (1.2,3.1)	N/A
Myeloid leukemia	N/A	0.8 (0.3,1.9)	N/A
Other	N/A	0.8 (0.1,5.9)	N/A
Lung/bronchus	N/A	N/A	1.0 (reference)
Breast	N/A	N/A	0.9 (0.6,1.4)
Colon excl rectum	N/A	N/A	0.4 (0.2,0.8)
Melanoma	N/A	N/A	0.9 (0.4,1.7)
Prostate	N/A	N/A	0.9 (0.5,1.5)

<sup>a</sup>HRs adjusted for all variables in table plus cancer site; each column represents the results of a separate model.

with previous reports of a more extensive local rash in immunocompromised than in immunocompetent individuals [reviewed in ref. (1)]. However, the rates of HZ-related pain that lasted for at least 30 days in our cohort of cancer patients (i.e., 19% for patients with hematologic malignancies and 14% for patients with solid tumors) were similar to that reported for patients in a general population (i.e., 18%; ref. 23).

Nearly 90% of HZ cases in our cohort were treated with antiviral medications. While most episodes of HZ can be treated successfully (1), many patients seek medical attention more than 72 hours after appearance of skin lesions

when efficacy of antiviral treatment is less clear (48). Only a small percentage of the patients in our cohort were treated prophylactically, and treatment appeared to be more frequent among those with hematologic malignancies, which is consistent with National Comprehensive Cancer Network recommendations first issued in 2007 (49). Antiviral therapy is currently recommended for patients with various hematologic malignancies during prolonged neutropenia and for those receiving specific therapies (e.g., T-cell depleting agents, bortezomib; ref. 50). Our study period preceded these recommendations and it is possible that high-risk cancer patients are

now more commonly treated with prophylactic therapy within Kaiser, and elsewhere, and have lower rates of HZ.

Few studies have examined risk factors for HZ in cancer patients. We found that older age, Asian race/ethnicity, and higher level of immunosuppression were associated with increased risk of HZ in patients with solid tumors. In patients with hematologic malignancies, only higher level of immunosuppression was clearly associated with increased risk of HZ. In prior studies in the general population, factors associated with increased risk of HZ have included older age, disease, and drug-related suppression of cellular immunity, and to a lesser extent female gender (1, 48, 51). Data are more limited on the association between race/ethnicity and risk of HZ among otherwise healthy adults, with 2 studies finding that blacks were at lower risk than whites (5, 52), and one study finding that HZ was less common among Hispanics than among non-Hispanic whites (53). The reason we observed a clear increase in HZ risk with increasing age among patients with solid tumors but not hematologic malignancies is unclear. It may in part be due to patients with hematologic malignancies being generally more immunocompromised, both by the type of cancer they have and the aggressive treatment they receive, and that high levels of immunosuppression overwhelm much of the influence of age.

In conclusion, cancer patients appear to be at substantially increased risk of HZ and, among those with HZ, complications are common. The risk of HZ is greatest for patients who are the most immunosuppressed, as estimated by treatment with chemotherapy or corticosteroids, highlighting the importance of closely monitoring these patients so that prompt and adequate treatment can be offered. While prophylactic treatment with acyclovir, or other antiviral agents, has been shown to reduce development of HZ, HZ may occur once antiviral medications are discontinued (8). The only currently available HZ vaccine is a live, attenuated virus that is contraindicated in immunocompromised patients. Given the higher risk

and morbidity of HZ in cancer patients, better prevention and treatment options are needed.

### Disclosure of Potential Conflicts of Interest

The study was funded by Merck & Co., Inc. Dr. Trung Tran is a former employee and Dr. Patricia Saddier is a current employee of Merck.

L.A. Habel has a commercial research grant from Merck. G.T. Ray has a commercial research grant from GlaxoSmithKline Pharmaceuticals, Pfizer Pharmaceuticals, and Merck Pharmaceuticals. B.P. Yawn has commercial research support from Merck. No potential conflicts of interest were disclosed by the other authors.

### Authors' Contributions

**Conception and design:** L.A. Habel, Y. Li, P. Saddier, T.N. Tran  
**Development of methodology:** L.A. Habel, G.T. Ray, M.J. Silverberg, M. Horberg, A. Castillo, C.P. Quesenberry, Jr, P. Saddier, T.N. Tran  
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** L.A. Habel, G.T. Ray, M. Horberg, A. Castillo  
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** L.A. Habel, G.T. Ray, M.J. Silverberg, M. Horberg, B.P. Yawn, A. Castillo, C.P. Quesenberry, Jr, T.N. Tran  
**Writing, review, and/or revision of the manuscript:** L.A. Habel, G.T. Ray, M.J. Silverberg, M. Horberg, B.P. Yawn, A. Castillo, C.P. Quesenberry, Jr, P. Saddier, T.N. Tran  
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** L.A. Habel, G.T. Ray, A. Castillo  
**Study supervision:** L.A. Habel, A. Castillo, P. Saddier, T.N. Tran

### Acknowledgments

The authors thank Dr. Paula Annunziato for her significant input in the design of the medical abstraction form and the overall conduct of the study. The authors thank Drs. Ralph Raasch, David Weber, Jonathan Serody, Anthony Stein, David Rizzieri, David Neil Hayes, and David Wohl for their contribution in the creation of the algorithm to classify patients into levels of immunosuppression based on chemotherapy and treatment with corticosteroids. The authors also thank Dr. Michael Trigg for his input in applying this algorithm to our data.

### Grant Support

This work was supported by Merck & Company; Michael J. Silverberg was supported by a grant from NIAID (K01AI071725).

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Received July 19, 2012; revised October 23, 2012; accepted October 24, 2012; published OnlineFirst November 1, 2012.

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