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Risk of Herpes Zoster Prior to and Following Cancer Diagnosis and Treatment: A Population-Based Prospective Cohort Study

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Background. Information on the risks of herpes zoster (zoster) preceding a cancer diagnosis and the role of cancer treatment on risk is limited.

Methods. This was a prospective cohort of 241497 adults, with mean age 62.0 years at recruitment (2006–2009), linked to health datasets from 2006 to 2015. The relation between cancer diagnosis, treatment, and zoster risk was analyzed using time-varying proportional hazards models.

Results. Over 1760 481 person-years of follow-up, 20 286 new cancer diagnoses and 16 350 zoster events occurred. Participants with hematological and solid cancer had higher relative risks of zoster than those without cancer (adjusted hazard ratio [aHR], 3.74 [95% confidence interval {CI}, 3.11–4.51] and 1.30 [95% CI, 1.21–1.40], respectively). Compared to those without cancer, zoster risk was also elevated prior to a hematological cancer diagnosis (aHR for 1–2 years prior, 2.01 [95% CI, 1.31–3.09]), but this was not the case for solid cancers (aHR for 1–2 years prior, 0.90 [95% CI, .75–1.07]). Compared to those without cancer, zoster risk among participants with solid cancers receiving chemotherapy was greater than in those without a chemotherapy record (aHR, 1.83 [95% CI, 1.60–2.09] and 1.16 [95% CI, 1.06–1.26], respectively).

Conclusions. For hematological cancer, increases in zoster risk are apparent in the 2 years preceding diagnosis and treatment; for solid organ cancers, the increased risk appears to be largely associated with receipt of chemotherapy.

Keywords. herpes zoster; neoplasm; cancer; chemotherapy.

Herpes zoster (zoster) is a neurocutaneous disease caused by the reactivation of latent varicella zoster virus (VZV) [1]. The most well-recognized risk factors for zoster include increasing age and immunosuppression, but any factor that has an impact on VZV-specific or general cell-mediated immunity may affect the risk [2]. Previous studies have demonstrated that a cancer diagnosis is associated with zoster [3–7], with the association strongest among those with hematological cancers [3, 5, 6]. Possible explanations for the association between cancer and subsequent zoster could be the immune system dysfunction caused by the cancer itself, which is likely in hematological cancers, or the immunocompromising effects of treatments that cancer patients receive [3, 4].

Previous studies have reported zoster among cancer patients following chemotherapy [4, 8–11]. However, there are few studies that attempt to separate the risk associated with the cancer itself from the receipt of cancer treatment, particularly chemotherapy [4]. Clinical guidelines recommend antivirals for zoster prevention in patients with hematological cancer receiving specific chemotherapies; however, they are less clear for solid organ cancer patients receiving conventional chemotherapy [12, 13]. Given that a new non–live subunit zoster vaccine has been shown to be safe and immunogenic in immunocompromised patients [14, 15], better defining the factors that contribute to the increased risk of zoster in cancer patients could inform strategies for targeted prevention. To add to the limited evidence, we therefore conducted this study, aiming to examine the risks leading up to a cancer diagnosis and how the cancer itself and cancer treatment affect the risk of zoster in a large cohort of older Australian adults.

METHODS

Data Sources

The Sax Institute's 45 and Up Study is a population-based prospective cohort study that recruited >267 000 Australians aged ≥45 years in the state of New South Wales (NSW), Australia (population 7.9 million [16]). From January 2006 to December 2009, eligible residents in NSW were randomly sampled from the

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Department of Human Services (formerly Medicare Australia) enrollment database, which covers all citizens and permanent residents as well as some temporary residents and refugees. At recruitment, participants were required to complete a self-administered postal questionnaire that included information on sociodemographic, lifestyle, and health-related information. All participants consented to long-term follow up and linkage of their information to other healthcare-related administrative databases. The cohort includes approximately one-tenth of all residents in NSW in the eligible age range. Detailed information on this cohort has been published elsewhere [17].

For this study, participants' survey data was probabilistically linked to the NSW Admitted Patient Data Collection (APDC) and Registry of Births, Deaths and Marriages (RBDM) by the Centre for Health Record Linkage (http://www.cherel.org.au/), with a false-positive rate around 5 per 1000 [18], and deterministically linked to the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) by the Sax Institute (https://www.saxinstitute.org.au/), using a unique identifier provided by the Department of Human Services.

The APDC database records all hospitalizations in NSW including information on the date of admission, date of procedure, and the principal diagnosis and principal procedure undertaken during hospitalization, as well as up to 49 secondary diagnoses and procedures at each admission [19]. All diagnoses are coded according to the *International Classification of Diseases, Tenth Revision*, Australian Modification (*ICD-10-AM*) [20] and procedures are coded according to the Australian Classification of Health Interventions [21]. The national MBS database records all subsidized medical care and diagnostic services under the MBS and the date of service [22]. The national PBS database records all medications prescribed and dispensed under the PBS according to PBS item codes and the Anatomical Therapeutic Chemical (ATC) Classification System [23], as well as the date of dispensing [24]. The RBDM records the date of all births, deaths, and marriages in NSW residents [25]. Complete records for study participants from the APDC, MBS, PBS, and RBDM were available up to 31 December 2015.

All participants provided informed consent to be included in the study. Ethical approval for the 45 and Up Study was provided by the University of New South Wales Human Research Ethics Committee (number 10186), and this linkage study was approved by the NSW Population and Health Services Research Ethics Committee (HREC/10/CIPHS/97).

Study Definitions

Participants were classified as having an episode of zoster if they had a record of either a specific antiviral medication for treatment of zoster in the PBS database (PBS item codes 1052J, 8002E, 8064K, 8897G) or a hospitalization record with *ICD-10-AM* code B02 in either the principal or secondary diagnosis field in the APDC database. This method of zoster case ascertainment has been shown to provide similar estimates of disease incidence to other sources of case ascertainment [7, 26].

Participants were classified as having a cancer diagnosis if they had a hospitalization record with an *ICD-10-AM* code for cancer in the principal diagnosis field in the APDC database. All cancer codes (C00–C43, C45–C97) except nonmelanoma skin cancer (C44) were included. This method of cancer ascertainment has been demonstrated to be reliable in other studies [27, 28].

Cancer treatments were classified into chemotherapy and radiotherapy. We did not aim to examine the effect of surgical treatment. Receipt of chemotherapy was defined as participants who had records with either chemotherapy procedures in the APDC, or cytotoxic chemotherapy in the MBS, or a record of antineoplastic agents (ATC code L01) in the PBS recorded at a date on or following the date of cancer diagnosis. Receipt of radiotherapy was defined as participants who had records of either radiotherapy procedures in the APDC or radiotherapy treatment in the MBS. Details of specific codes used for chemotherapy and radiotherapy are shown in Appendix 1. Using these records for ascertaining chemotherapy and radiotherapy has been shown to have high specificity, although sensitivity is low [29].

Potential covariates including sociodemographic, behavioral, and health-related factors were derived from the 45 and Up Study recruitment questionnaire and were based on purported risk factors for zoster from earlier studies [7, 30]: annual household pretax income in Australian dollars; marital status; area of residence; private health insurance; smoking status; ever attending breast, prostate, or bowel cancer screening programs; use of supplements; self-reported history of doctor-diagnosed cardiac disease/stroke or asthma/hay fever; and level of physical limitation based on the Medical Outcomes Study–Physical Functioning Score [31].

Analysis

Participants were excluded if they met the following criteria: (1) holding a Department of Veterans Affairs card as they can receive zoster treatment through an alternate scheme to the PBS (n = 6299); (2) <45 years old at baseline (n = 7); or (3) had a record of either a zoster diagnosis (n = 5917) or a cancer diagnosis prior to their recruitment date (n = 14 420). Person-years of follow-up was calculated from study recruitment date to the first diagnosis of zoster, death, or 31 December 2015, whichever came first.

Cox proportional hazards models were used to estimate hazard ratios (HRs) for the association between a cancer diagnosis, cancer treatment, and zoster risk, adjusting for age, sex, and other factors that were significantly associated with zoster in the models. For all adjusted factors, missing data were included in the model as a separate group. Follow-up time was split into months, and age, cancer diagnosis, and cancer treatment were

treated as time-varying covariates in analyses. At the start of follow-up, all participants were initially classified as having no cancer and then contributed person-time to the categories of cancer and cancer with chemotherapy and/or with radiotherapy from the date of the first linked record of any of these events. A cancer diagnosis was considered at 3 levels: (1) any cancer; (2) solid organ or hematological cancers; and (3) specific solid organ cancers or hematological cancers. When examining the association between specific cancers and zoster, we used competing risks [32]. Unless otherwise specified, the reference group for all analyses was person-time without cancer.

Risk of zoster according to the time since cancer diagnosis (<1, 1 to <2, 2 to <3, and ≥3 years) was examined. Moreover, as herpes zoster has been reported as an indicator of occult cancer [33, 34], we also examined zoster risk in the years prior to the cancer diagnosis (<1, 1 to <2, and ≥2 years). Only for these analyses, the reference group was participants without cancer from baseline to the end of follow-up.

Sensitivity analyses were undertaken excluding any cases who had ≥3 prescriptions for antiviral medications in 1 year, as antiviral prophylaxis for at least 6–12 months (sequential prescriptions) is recommended for use in patients after stem cell transplantation [13], and thus the use of antiviral medication may not be indicative of a zoster event in these cases.

Analysis was undertaken using Stata version 14.1 software (StataCorp, College Station, Texas).

RESULTS

A total of 241 497 participants were included in analyses. At recruitment, the mean age was 62.0 (standard deviation, 10.9) years, and 54.5% were female. During 1 760 481 person-years (PY) of follow-up, 16 350 (6.8%) participants had a first incident zoster event (9.3 per 1000 PY) and 20 286 (8.4%) participants had a new cancer diagnosis (11.5 per 1000 PY).

Table 1 describes the participants who had a diagnosis of zoster or cancer during follow-up according to various characteristics measured at recruitment. Multivariable regression analyses examining characteristics associated with incident zoster showed significant associations between zoster and these factors.

The HRs of incident zoster in relation to cancer type are shown in Figure 1. The age- and sex-adjusted HR for zoster following a cancer diagnosis compared to those without cancer was 1.43 (95% confidence interval [CI], 1.34–1.53); this did not change substantially after adjustment (adjusted HR [aHR], 1.41 [95% CI, 1.32–1.52]). Compared to those without cancer, the risk of zoster was substantially higher in participants with hematological cancers (aHR, 3.74 [95% CI, 3.11–4.51]) than those with solid organ cancers (aHR, 1.30 [95% CI, 1.21–1.40]; *P* value for

Table 1. Characteristics of Participants at Recruitment and Among Those With Incident Cancer and With Incident Herpes Zoster

Category	Population (N = 241 497)	Incident Herpes Zoster (n = 16 350)	Incident Cancer (n = 20 286)
Mean age, y (SD)	62.02 (10.9)	64.04 (10.6)	66.44 (10.3)
Age group, y			
45–54	74 839 (31.0)	3705 (22.7)	3009 (14.8)
55–64	79 475 (32.9)	5387 (33.0)	6295 (31.0)
65–74	51 376 (21.3)	4383 (26.8)	6285 (31.0)
≥75	35 807 (14.8)	2875 (17.6)	4697 (23.2)
Sex			
Female	131 634 (54.5)	10 136 (62.0)	8373 (41.3)
Annual household income, AUD			
<20 000	68 777 (28.5)	5092 (31.1)	7146 (35.2)
20 000–39 999	18 976 (7.9)	1267 (7.8)	1700 (8.4)
40 000–69 999	43 704 (18.1)	2763 (16.9)	3268 (16.1)
≥70 000	58 949 (24.4)	3375 (20.6)	3783 (18.7)
Unknown/not reported	51 091 (21.2)	3853 (23.6)	4389 (21.6)
Area of residence			
Major city	125 269 (52.9)	8799 (54.8)	10 766 (54.0)
Inner regional	84 254 (35.5)	5612 (35.0)	6946 (34.8)
Outer regional/remote	27 422 (11.6)	1637 (10.2)	2233 (11.2)
Marital status			
Single	14 005 (5.8)	820 (5.0)	1144 (5.7)
Married/partner	180 371 (75.1)	12 210 (75.1)	14 836 (73.6)
Separated/divorced/widowed	45 662 (19.0)	3226 (19.8)	4168 (20.7)
Smoking			
Never	139 050 (57.9)	9678 (59.5)	10 463 (51.8)
Past	83 332 (34.7)	5726 (35.2)	8101 (40.1)
Current	17 843 (7.4)	855 (5.3)	1619 (8.0)
Attend cancer screening			
No	62 451 (26.4)	3212 (20.0)	5664 (28.5)
Yes	174 319 (73.6)	12 843 (80.0)	14 210 (71.5)
Supplement use			
No	33 987 (14.3)	1713 (10.6)	2147 (10.8)
Yes	203 755 (85.7)	14 431 (89.4)	17 811 (89.2)
Heart disease/stroke			
No	209 851 (86.9)	13 899 (85.0)	16 738 (82.5)
Yes	31 646 (13.1)	2451 (15.0)	3548 (17.5)
Asthma/hay fever			
No	189 302 (78.4)	12 530 (76.6)	16 284 (80.3)
Yes	52 195 (21.6)	3820 (23.4)	4002 (19.7)
Physical limitations			
None	74 865 (31.0)	4308 (26.4)	4811 (23.7)
Minor	38 375 (15.9)	2516 (15.4)	3089 (15.2)
Moderate	69 689 (28.9)	4995 (30.6)	6758 (33.3)
Severe	34 728 (14.4)	2833 (17.3)	3541 (17.5)
Unknown	23 840 (9.9)	1698 (10.4)	2087 (10.3)
Private health insurance			
No	86 481 (35.8)	5532 (33.8)	7612 (37.5)
Yes	155 016 (64.2)	10 818 (66.2)	12 674 (62.5)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AUD, Australian dollars; SD, standard deviation.

Cancer type (*ICD-10*)	Person-years	Zoster	Model 1 (95% CI)[a]	Model 2 (95% CI)[b]
Any cancer (c00-43,c45-96)	61 736	886	1.43 (1.34–1.53)	1.41 (1.32–1.52)
Solid organ cancers (c00-43,c45-80)	58 829	774	1.31 (1.22–1.41)	1.30 (1.21–1.40)
Hematological cancers (c81-c96)	2907	112	3.78 (3.14–4.56)	3.74 (3.11–4.51)
By solid organ cancer				
Oral (c00-06)	697	10	1.42 (.76–2.64)	1.43 (.77–2.65)
Colorectal (c18-20)	8505	116	1.20 (1.00–1.44)	1.21 (1.01–1.46)
Lung (c34)	1532	32	1.88 (1.33–2.67)	1.89 (1.33–2.67)
Melanoma (c43)	5897	67	1.07 (.84–1.36)	1.05 (.82–1.33)
Breast (female) (c50)	10 507	168	1.40 (1.20–1.63)	1.38 (1.18–1.60)
Uterus (female) (c54 -55)	1403	18	1.06 (.67–1.69)	1.05 (.66–1.68)
Prostate (male) (c61)	17 972	188	1.16 (1.00–1.34)	1.14 (.98–1.31)
Kidney (c64)	1336	12	0.89 (.51–1.57)	0.87 (.50–1.54)
Bladder (c67)	2281	30	1.17 (.82–1.67)	1.14 (.80–1.64)
CNS (c71-72)	333	-	0.97 (.31–3.00)	0.94 (.30–2.90)
Secondary malignancy (c77-79)	1951	39	1.84 (1.34–2.51)	1.82 (1.33–2.50)
By hematological cancer				
Lymphoma (c81-86)	1799	57	2.93 (2.26–3.80)	2.88 (2.22–3.73)
Myeloma (c90)	564	28	4.78 (3.30–6.93)	4.81 (3.32–6.97)
Leukemia (c91-95)	443	23	4.93 (3.28–7.43)	4.94 (3.28–7.43)
Other hematological (c88,c96)	101	-	3.36 (1.26–8.96)	3.21 (1.20–8.56)

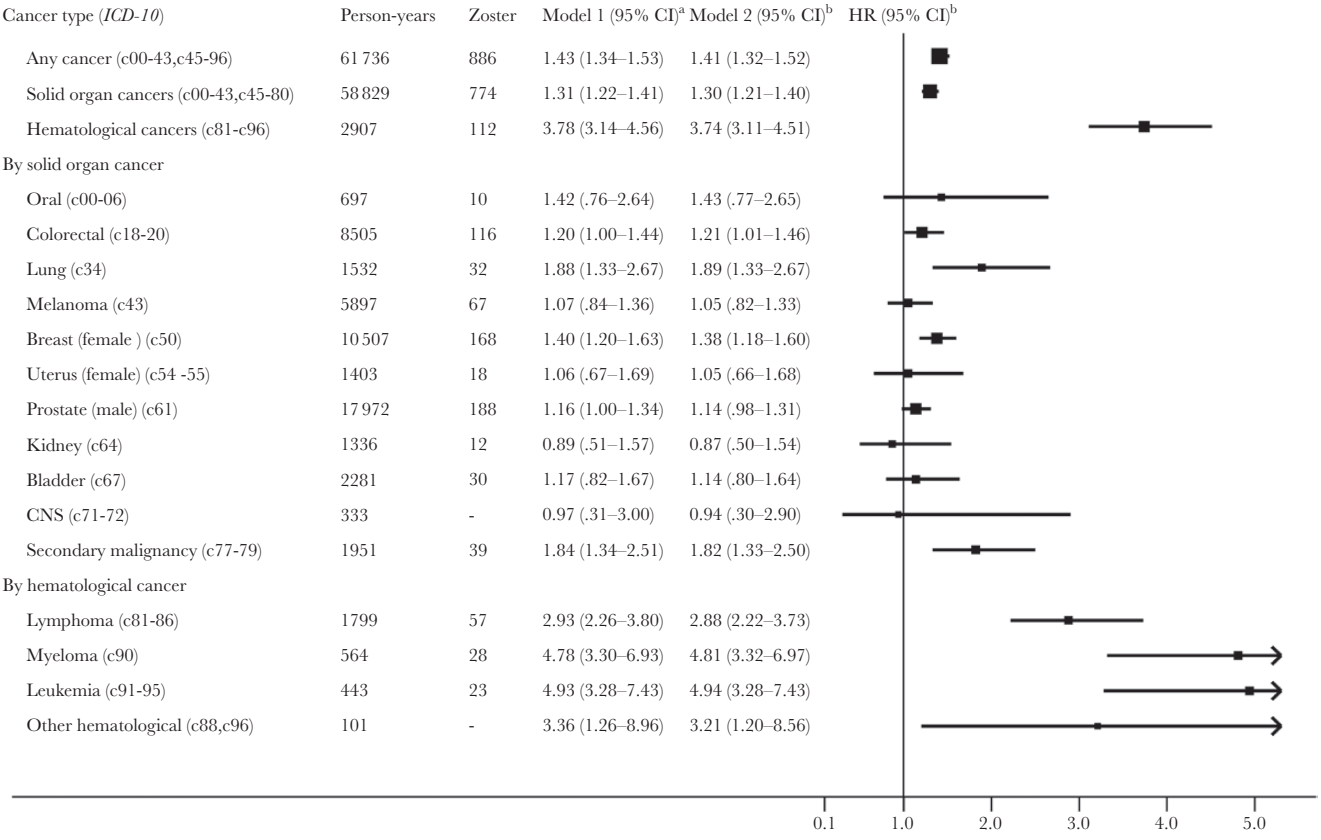

Figure 1. Adjusted hazard ratios of herpes zoster following cancer diagnosis according to cancer type. For the reference group (= 1.00), those without cancer, there were 1 698 601 person-years and 15 464 incident zoster events. For analyses for specific cancer types, this varied slightly due to use of competing risks (see Methods). Number not shown (-) is <5. [a]Adjusted for age and sex. [b]Adjusted for age, sex, income, residence, marital status, private health insurance, smoking, cancer screening, supplement use, heart disease/stroke, asthma/hay fever, and physical limitations. Abbreviations: CI, confidence interval; CNS, central nervous system; HR, hazard ratio; *ICD-10, International Classification of Diseases, Tenth Revision.*

heterogeneity <.001). The number of events was not sufficient to determine whether the magnitude of the association with zoster differed significantly according to specific cancer types.

Compared to those without cancer at end of follow-up, the risk of zoster following a cancer diagnosis was greatest within the first year following diagnosis (aHR, 5.09 [95% CI, 3.83–6.75] for hematological cancer and 1.44 [95% CI, 1.26–1.64] for solid organ cancer) and it decreased with time since diagnosis. For participants with solid organ cancers, after 3 years, risk was not significantly different to that of those without cancer, whereas for those with hematological cancers it remained elevated (aHR, 2.13 [95% CI, 1.37–3.30]) (Figure 2; Appendix 2). For participants with hematological cancers, compared to those without cancer at end of follow-up, the risk of zoster was also significantly elevated in the 2 years prior to the cancer diagnosis (within 1 year prior: aHR, 1.95 [95% CI, 1.30–2.91]; 1–2 years prior: aHR, 2.01 [95% CI, 1.31–3.09]), but this was not the case for those with solid organ cancer (within 1 year prior: aHR, 0.98 [95% CI, .84–1.14]; 1–2 years prior: 0.90 [95% CI, .75–1.07]).

As the majority of those with hematological cancer would be expected to receive chemotherapy, we focused our analyses of treatment on solid organ cancers. Of participants with a solid organ cancer, 23.4% (4453) had a record of chemotherapy receipt, 28.3% (5374) had a record of radiotherapy receipt, 11.2% (2127) had records of receiving both, and 59.5% (11 307) had records for receipt of neither (Appendix 3). Of participants who received either chemotherapy or radiotherapy, the median time to first receipt of either chemotherapy or radiotherapy following cancer diagnosis was 1.8 and 2.7 months, respectively.

Compared to those without cancer, the risk of zoster among those with solid organ cancer receiving chemotherapy (with or without radiotherapy) was an aHR of 1.83 (95% CI, 1.60–2.09), whereas the risk for solid organ cancer patients without a record of chemotherapy was significantly lower (aHR, 1.16 [95% CI, 1.06–1.26]; *P* value for heterogeneity <.001). When we subdivided those with chemotherapy according to the receipt of radiotherapy (Figure 3; Appendix 4), the relative risks of zoster were similar. Among patients with solid organ cancer receiving chemotherapy alone: aHR, 1.84 [95% CI, 1.54–2.20]; in those receiving both chemotherapy and radiotherapy: aHR, 1.81 [95% CI, 1.49–2.21]; *P* value for heterogeneity = .9. There was a significantly increased risk of zoster for solid organ cancer patients

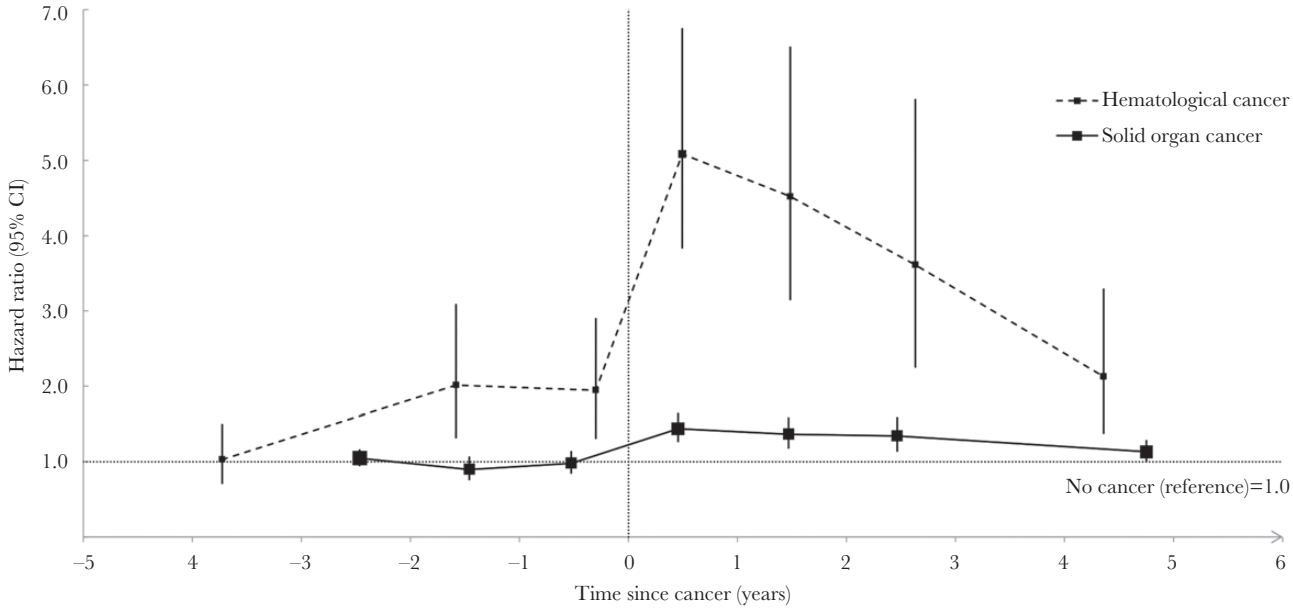

Figure 2. Adjusted hazard ratios (HRs) of herpes zoster by time before and after a cancer diagnosis. HRs are plotted according to the mean time in each category (see Methods). Person-years of reference group is 1 621 322, compared with 1 698 601 in other analyses due to follow-up time attributed to time before cancer. HRs are adjusted for age, sex, income, residence, marital status, private health insurance, smoking, cancer screening, supplement use, heart disease/stroke, asthma/hay fever, and physical limitations.

receiving radiotherapy alone (aHR, 1.38 [95% CI, 1.17–1.63]) but not for those with neither chemotherapy nor radiotherapy records (aHR, 1.10 [95% CI, .99–1.21]).

Figure 4 shows the incidence of zoster in the cohort by cancer diagnosis and treatment, adjusted for age, sex, and other factors. Among individuals without cancer, the incidence of zoster was 9.1 per 1000 PY. This compares to 34.0, 16.6, and 10.6 per 1000 PY, respectively, in the first year following a diagnosis with hematological cancer, solid organ cancer with chemotherapy, and solid organ cancer without a chemotherapy record.

In the sensitivity analyses there were 163 zoster cases (1.0% of the total) where there were at least 3 records of antiviral medications provided in a 1-year period. When we excluded these potentially misclassified cases from our analyses, it made no material difference to our results.

DISCUSSION

In this analysis of data from 240 000 older adults with over 8 years of follow-up, we found that a diagnosis of cancer was associated with about a 40% higher risk of developing zoster compared to those without cancer. The risk was substantially greater among those with hematological cancers compared to those with solid organ cancers. For both types of cancer, risks were highest in the first year following diagnosis, decreasing thereafter. The zoster risk in those with solid cancers became similar to that in those without cancer within the 3 years after diagnosis, and it remained significantly elevated in those with hematological cancers up to 3 years after diagnosis. Importantly, we also found that among those with solid organ cancers, the risk of zoster was substantially higher among those receiving chemotherapy compared to those not receiving chemotherapy, and among those with hematological cancers, there appeared to be an increased risk of zoster in the 2 years prior to the cancer diagnosis.

The findings from our study build on earlier reports regarding the risks of zoster related to a cancer diagnosis and cancer treatment. Our findings regarding the magnitude of zoster risk following hematological and solid organ cancers are consistent with a UK study of >190 000 cancer cases and 730 000 controls, which estimated odds ratios for zoster of 2.46 (95% CI, 2.33–2.60) and 1.19 (95% CI, 1.17–1.22), respectively [3]. This study also reported that for most types of cancers, the risks of zoster decreased with time since diagnosis; however, the study lacked information on cancer treatment and therefore could not estimates risks associated with chemotherapy or radiotherapy [3].

Studies of zoster risk following treatment in cancer patients have focused primarily on hematopoietic stem cell transplant (HSCT) or specific chemotherapeutic agents [35–37]. These

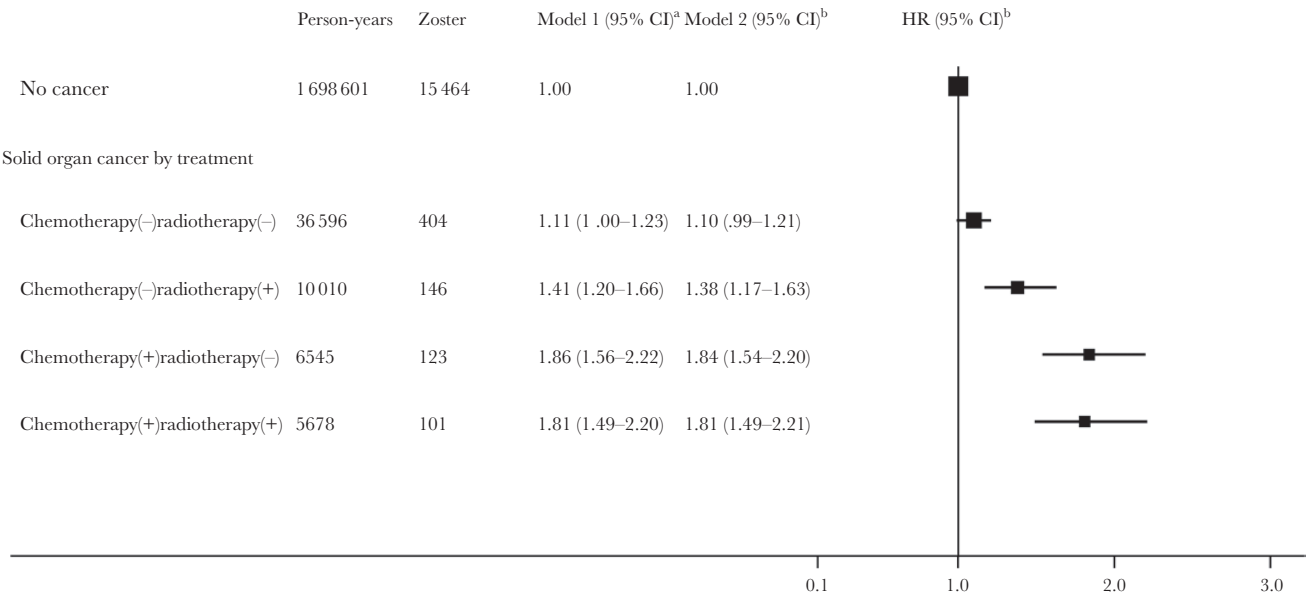

Figure 3. Adjusted hazard ratios of herpes zoster after solid organ cancer by record of chemotherapy and radiotherapy receipt. [a]Adjusted for age and sex. [b]Adjusted for age, sex, income, residence, marital status, private health insurance, smoking, cancer screening, supplement use, heart disease/stroke, asthma/hay fever, and physical limitations. Abbreviation: CI, confidence interval.

studies report zoster events in cancer patients but they include only patients with hematological cancers and do not enable comparisons of risk to be made to those with solid organ cancers or to the general population without cancer. For example, an earlier report from the United States found that the risk of zoster among cancer patients with chemotherapy was more than double that of cancer patients without [4]. However, this study only included cancer patients and lacked a representative control group without cancer; therefore the zoster risks could only be compared to the general population using age and sex standardization.

It is well known that T-cell–mediated immunity plays an important role in maintaining latent VZV in a subclinical state

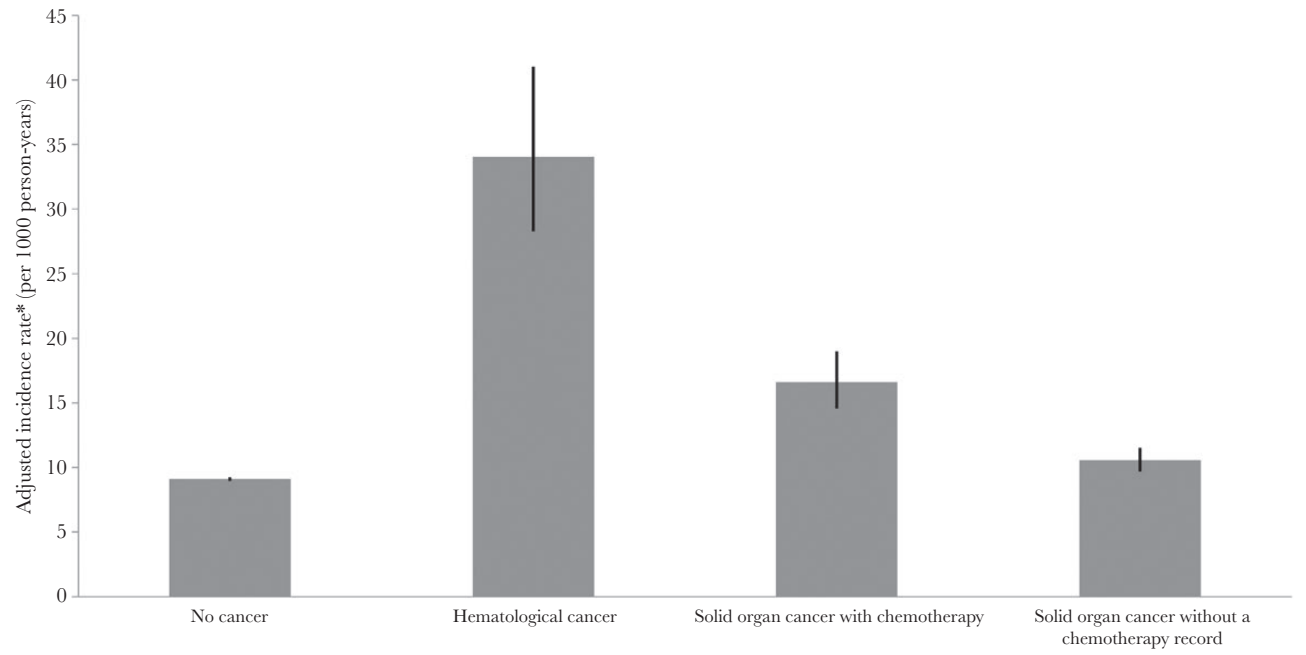

Figure 4. Incidence rate* of herpes zoster according to cancer and treatment. *Adjusted for age, sex, income, residence, marital status, private health insurance, smoking, cancer screening, supplement use, heart disease/stroke, asthma/hay fever, and physical limitations. For those with cancer, incidence rates refer to adjusted incidence rates in the first year following a cancer diagnosis.

in neural ganglia [38]. Previous reports suggest possible mechanisms for the association between cancer and zoster could be immune dysfunction caused by the cancer itself, the treatment that cancer patients receive, or a combination of both [3, 4]. Our results suggest that for those with solid organ cancers, the association of cancer with an increased risk of zoster is primarily explained by chemotherapy treatment. For those with hematological cancers, the risks of zoster are substantially higher than for solid organ cancers, but trying to disentangle the contribution of treatment from the hematological cancer itself is more difficult as the majority of those with hematological cancer would receive chemotherapy during the course of their illness. However, we found that among those with hematological cancer, the risk of zoster was elevated in the 2 years prior to their diagnosis (albeit not as high as after the diagnosis), presumably before they received treatment. This finding suggests that the immune dysfunction from the hematological cancer itself can lead to zoster activation, although we also observed a substantial rise in risk after diagnosis (Figure 2), supporting a major role for subsequent treatment in further increasing the risk.

The strengths of our study include the population-based prospective study design with a long follow-up period, large sample size, independent ascertainment of zoster records from those of cancer and treatment, and the ability to report the absolute rates of zoster following cancer diagnoses in different clinical groups. The latter is considered of particular relevance for interventions such as vaccination or prophylactic antiviral use that require estimates of absolute risk to support cost-effectiveness assessments. Our study included individuals with and without cancer, including participants with a range of cancer types. The longitudinal design and use of incident solid and hematological cancer diagnoses as the main exposure allowed examination of zoster risk before and after a diagnosis. This has not, to our knowledge, been done before and provides insights of etiological, clinical, and preventive relevance.

Limitations include the fact that information on the stage of cancer was not available in our study. It is possible that later stages of certain solid organ cancers may be associated with greater levels of immunosuppression from the cancer itself and that the stage of a solid organ cancer would also be correlated with the likelihood of receiving chemotherapy. However, an earlier study with information on cancer stage suggested that there is no significant difference in zoster risk comparing cancer patients with localized, regional, and distantly spread cancers [4].

Validation studies have demonstrated that although our ascertainment of chemotherapy and radiotherapy has high specificity (96%), sensitivity is low (30%–36%) [29]; thus, a proportion of those classified as having no record of chemotherapy or radiotherapy may have actually had it. This is reflected in the low proportion of patients in our study with hematological cancers with a record of chemotherapy (49.3%; Appendix 3). However, for our analyses, the reference group was those without cancer, so it is likely that the relative risk estimates for those classified with a solid organ cancer and chemotherapy would not be affected by this misclassification. However, this misclassification may explain why the point estimate for those with solid organ cancer but no chemotherapy was slightly elevated. Incident cancer in this study was ascertained using hospital admission records. This has been shown to be accurate in cancers such as breast, colorectal, and lung, compared with cancer registrations [28, 29]. Although most cancers require either day-case or overnight hospitalization for diagnosis or therapy such as surgery, chemotherapy, radiotherapy, and palliative care—captured by our study—individuals with indolent cancers may not be hospitalized [39]. Finally, we may have missed capturing all zoster cases [26], particularly milder ones, as we defined the outcome based on hospitalization and/or specific antiviral medication records. This could potentially bias our results if, for example, those with cancer were more likely to be diagnosed with zoster or to have severe zoster requiring hospitalization or antiviral treatment than those without. However our outcome is more likely to capture more severe cases, which is important from the perspective of prevention.

Clinical guidelines recommend that antiviral medications should be considered for preventing zoster in patients after HSCT and for patients with hematological cancer receiving specific therapies such as fludarabine and alemtuzumab, but recommendations are less clear for solid organ cancer patients undergoing conventional chemotherapy [12, 13]. A live attenuated herpes zoster vaccine has been available worldwide for more than a decade but is not indicated for use in immunocompromised people, such as those with cancer. In this study, we estimated that, in the year following a hematological cancer diagnosis, the annual incidence of zoster was considerable, at 3.4% (34 per 1000 PY), and 1.7% (17 per 1000 PY) in those with solid organ cancers receiving chemotherapy. While this is lower than the estimated annual attack rate of symptomatic seasonal influenza among unvaccinated adults aged >65 years (7.2%) who are targeted for influenza vaccination [40], the risks are still substantial and morbidity is high. Furthermore, as immunocompromised patients usually experience more severe complications of zoster [41], cancer patients, especially those receiving chemotherapy, may not only have higher risk of zoster but also more complications. Given that a new recombinant vaccine for herpes zoster (HZ/su vaccine) has been reported to be safe and immunogenic in those with human immunodeficiency virus and in autologous HSCT recipients in phase 1/2 trials [14, 15], and another non–live vaccine to prevent zoster is being developed that is safe and efficacious in immunocompromised patients [42], zoster vaccination now holds promise as a preventive strategy considered for cancer patients, particularly those expected to receive chemotherapy.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to

benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Gross G, Schöfer H, Wassilew S, et al. Herpes zoster guideline of the German Dermatology Society (DDG). J Clin Virol **2003**; 26:277–89; discussion 291–3.
2. Forbes HJ, Thomas SL, Langan SM. The epidemiology and prevention of herpes zoster. Curr Dermatol Rep **2012**; 1:39–47.
3. Hansson E, Forbes HJ, Langan SM, Smeeth L, Bhaskaran K. Herpes zoster risk after 21 specific cancers: population-based case-control study. Br J Cancer **2017**; 116:1643–51.
4. Habel LA, Ray GT, Silverberg MJ, et al. The epidemiology of herpes zoster in patients with newly diagnosed cancer. Cancer Epidemiol Biomarkers Prev **2013**; 22:82–90.
5. Yenikomshian MA, Guignard AP, Haguinet F, et al. The epidemiology of herpes zoster and its complications in Medicare cancer patients. BMC Infect Dis **2015**; 15:106.
6. Rusthoven JJ, Ahlgren P, Elhakim T, et al. Varicella-zoster infection in adult cancer patients. A population study. Arch Intern Med **1988**; 148:1561–6.
7. Liu B, Heywood AE, Reekie J, et al. Risk factors for herpes zoster in a large cohort of unvaccinated older adults: a prospective cohort study. Epidemiol Infect **2015**; 143:2871–81.
8. Bermúdez A, Marco F, Conde E, Mazo E, Recio M, Zubizarreta A. Fatal visceral varicella-zoster infection following rituximab and chemotherapy treatment in a patient with follicular lymphoma. Haematologica **2000**; 85:894–5.
9. Bilgrami S, Chakraborty NG, Rodriguez-Pinero F, et al. Varicella zoster virus infection associated with high-dose chemotherapy and autologous stem-cell rescue. Bone Marrow Transplant **1999**; 23:469–74.
10. Kim ST, Park KH, Oh SC, et al. Varicella zoster virus infection during chemotherapy in solid cancer patients. Oncology **2012**; 82:126–30.
11. Gopalan V, Nair RG, Pillai S, Oberholzer T. Genital herpes zoster as a consequence of cancer chemotherapy-induced immunosuppression: report of a case. J Infect Chemother **2012**; 18:955–7.
12. Sandherr M, Hentrich M, von Lilienfeld-Toal M, et al. Antiviral prophylaxis in patients with solid tumours and haematological malignancies—update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Ann Hematol **2015**; 94:1441–50.
13. Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, version 2.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw **2016**; 14:882–913.
14. Stadtmauer EA, Sullivan KM, Marty FM, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit candidate vaccine in adult autologous hematopoietic stem-cell transplant recipients. Blood **2014**; 124:2921–9.
15. Berkowitz EM, Moyle G, Stellbrink HJ, et al; Zoster-015 HZ/su Study Group. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. J Infect Dis **2015**; 211:1279–87.
16. Australian Bureau of Statistics. Australian demographic statistics. http://www.abs.gov.au/ausstats/abs@.nsf/mf/3101.0. Accessed 10 August 2018.
17. 45 and Up Study Collaborators. Cohort profile: the 45 and Up Study. Int J Epidemiol **2008**; 37:941–7.
18. Centre for Health Record Linkage. Quality assurance. http://www.cherel.org.au/quality-assurance. Accessed 22 October 2018.
19. Centre for Health Record Linkage. Data dictionaries—NSW Admitted Patient Data Collection (APDC). http://www.cherel.org.au/data-dictionaries#section1. Accessed 10 August 2018.

20. National Center for Classification in Health. The *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification* (*ICD-10-AM*), 2nd ed. Lidcombe, NSW: National Centre for Classification in Health, **2000**.
21. Best L. Australian classification of health interventions—adapted for international use (ACHI-I). Health Inf Manag **2003**; 31:14–7.
22. Sax Institute. Data books—Medicare benefits schedule (MBS) data dictionary. https://www.saxinstitute.org.au/wp-content/uploads/MBS-Data-Dictionary-January-2017.pdf. Accessed 10 August 2018.
23. World Health Organization. Anatomical therapeutic chemical (ATC) classification index with defined daily doses (DDDs). Oslo: WHO Collaborating Centre for Drug Statistics Methodology, **2000**.
24. Sax Institute. Data books—pharmaceutical benefits scheme (PBS) data dictionary. https://www.saxinstitute.org.au/wp-content/uploads/PBS-Data-Dictionary-January-2017.pdf. Accessed 10 August 2018.
25. Centre for Health Record Linkage. Data dictionaries—NSW mortality data. http://www.cherel.org.au/data-dictionaries#section1. Accessed 10 August 2018.
26. MacIntyre R, Stein A, Harrison C, Britt H, Mahimbo A, Cunningham A. Increasing trends of herpes zoster in Australia. PLoS One **2015**; 10:e0125025.
27. Goldsbury D, Weber M, Yap S, Banks E, O'Connell DL, Canfell K. Identifying incident colorectal and lung cancer cases in health service utilisation databases in Australia: a validation study. BMC Med Inform Decis Mak **2017**; 17:23.
28. Kemp A, Preen DB, Saunders C, et al. Ascertaining invasive breast cancer cases; the validity of administrative and self-reported data sources in Australia. BMC Med Res Methodol **2013**; 13:17.
29. Goldsbury DE, Armstrong K, Simonella L, Armstrong BK, O'Connell DL. Using administrative health data to describe colorectal and lung cancer care in New South Wales, Australia: a validation study. BMC Health Serv Res **2012**; 12:387.
30. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis **2004**; 4:26–33.
31. Hays RD, Liu H, Spritzer K, Cella D. Item response theory analyses of physical functioning items in the medical outcomes study. Med Care **2007**; 45:S32–8.
32. Gichangi A, Vach W. The analysis of competing risks data: a guided tour. Stat Med **2005**; 132:1–41.
33. Iglar K, Kopp A, Glazier RH. Herpes zoster as a marker of underlying malignancy. Open Med **2013**; 7:e68–73.
34. Schmidt SA, Mor A, Schønheyder HC, Sørensen HT, Dekkers OM, Cronin-Fenton D. Herpes zoster as a marker of occult cancer: a systematic review and meta-analysis. J Infect **2017**; 74:215–35.
35. Leung AY, Yuen KY, Cheng VC, Lie AK, Liang R, Kwong YL. Clinical characteristics of and risk factors for herpes zoster after hematopoietic stem cell transplantation. Haematologica **2002**; 87:444–6.
36. Sahoo F, Hill JA, Xie H, et al. Herpes zoster in autologous hematopoietic cell transplant recipients in the era of acyclovir or valacyclovir prophylaxis and novel treatment and maintenance therapies. Biol Blood Marrow Transplant **2017**; 23:505–11.
37. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol **2008**; 26:4784–90.
38. Weinberg A, Levin MJ. VZV T cell-mediated immunity. Curr Top Microbiol Immunol **2010**; 342:341–57.
39. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood **2008**; 111:5446–56.
40. Somes MP, Turner RM, Dwyer LJ, Newall AT. Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: a systematic review and meta-analysis. Vaccine **2018**; 36:3199–207.
41. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med **2000**; 342:635–45.
42. Mullane KM, Winston DJ, Wertheim MS, et al. Safety and immunogenicity of heat-treated zoster vaccine (ZVHT) in immunocompromised adults. J Infect Dis **2013**; 208:1375–85.