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The risk of a subsequent cancer diagnosis after herpes zoster infection: primary care database study

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Background: Herpes zoster and cancer are associated with immunosuppression. Zoster occurs more often in patients with an established cancer diagnosis. Current evidence suggests some risk of cancer after zoster but is inconclusive. We aimed to assess the risk of cancer following zoster and the impact of prior zoster on cancer survival.

Methods: A primary care database retrospective cohort study was undertaken. Subjects with zoster were matched to patients without zoster. Risk of cancer following zoster was assessed by generating hazard ratios using Cox regression. Time to cancer was generated from the index date of zoster diagnosis.

Results: In total, 2054 cancers were identified in 74 029 patients (13 428 zoster, 60 601 matches). The hazard ratio for cancer diagnosis after zoster was 2.42 (95% confidence interval 2.21, 2.66) and the median time to cancer diagnosis was 815 days. Hazard ratios varied between cancers, and were highest in younger patients. There were more cancers in patients with zoster than those without for all age groups and both genders. Prior immunosuppression was not associated with change in risk, and diagnosis of zoster before cancer did not affect survival.

Conclusion: This study establishes an association between zoster and future diagnosis of cancer having implications for cancer case finding after zoster diagnosis.

Herpes zoster (shingles) is the reactivation of latent varicella zoster virus, and has an incidence ranging from 1.2 to 4.8 per 1000, increasing markedly with age (Thomas and Hall, 2004). It is associated with immunosuppression, both genetic and acquired, and has been strongly associated with a known diagnosis of cancer, a future diagnosis of HIV/AIDS, (Arvin, 1996; Thomas and Hall, 2004), and stroke (Kang *et al*, 2009).

The possibility that zoster might presage a diagnosis of cancer was first suggested in 1955 (Wyburn-Mason, 1955). Subsequent studies have failed to fully establish this association (Ragozzini *et al*, 1982; Fueyo and Lookingbill, 1984; Zaha *et al*, 1993; Yamamoto *et al*, 2003). Three larger and more recent studies have suggested that there may be an association. First, Sørensen *et al* (2004) reported a relative risk for all cancer types for zoster as 1.2 and suggested that screening for cancer would have 'low efficacy'. However, this study was of patients *hospitalised* for zoster (a minority of zoster cases, and those with more severe disease), rather than those diagnosed and managed in the community. Buntinx *et al* (2005), from a primary care database study, failed to demonstrate any increase in cancer diagnoses within a year of zoster in those under 65; however, this study did report a significant difference in females over 65 years (HR 2.65). Ho *et al* (2011) from a Health Insurance Research Database in Taiwan reported that the risk of cancer after herpes zoster ophthalmicus

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was 9.25 times greater than their matched comparison cohort. Additionally, patients with zoster had lower 1 year cancer-free survival than their comparison cohort. A more recent study from Taiwan showed no increased risk of cancer after zoster compared with expected incidence rates (Wang *et al*, 2012).

It is therefore not clear whether there is an association between a previous diagnosis of zoster (in an unselected primary care population) and subsequent diagnosis of cancer. Determining the risk of cancer following zoster is important because it raises the potential for case finding to facilitate earlier cancer diagnosis. The primary aim of this study was to determine the risk of a diagnosis of any primary cancer following zoster compared with patients without zoster, using a database of a large primary care cohort of patients. Secondary aims were to assess if specific cancers were associated with a previous diagnosis of zoster, and to determine the difference in survival in patients with cancer in the data set between those who had a prior diagnosis of zoster and those who did not.

MATERIALS AND METHODS

Patient selection and matching. The General Practice Research Database (GPRD) (now renamed as CPRD) is a large UK primary care database containing the general practice information of over 3.6 million patients from >450 practices. The information available is the medical, practice nursing, and administration records of individual patients, which includes clinical diagnoses, investigation results, prescriptions, referral decisions, and referral outcomes.

The baseline population consisted of all 'up-to-standard' patients in the GPRD of 1 January 1987 to 12 December 2002 inclusive. 'Up-to-standard' is a marker that indicates when data recording by the patient's practice meet the specific quality measures defined by the UK Medicines and Healthcare products Regulatory Agency (MHRA) (CPRD, 2012).

Cases ($n = 13\,428$) were all patients 18 years or older with a recorded medical diagnosis of zoster during the period 1 January 2001 to 12 December 2002 inclusive. A medical diagnosis of zoster was defined using a list of predefined Read/OXMIS codes. Cases were matched with patients without a prior diagnosis of zoster by gender and year of birth, in a ratio of 1 : 4.5, as recommended by Smeeth *et al* (2006). Both cases and the matched subjects had >5 years of GPRD records before their date of zoster diagnosis (cases) or pseudo-diagnosis (for matches without zoster) and no documented diagnosis of cancer (excluding non-melanoma skin cancer) during this period. We chose this time period for pragmatic reasons, although it was a trade-off against trying to find relevant past exposure of cancer and immunosuppression (see later), while trying to maximise the numbers of cases and controls, especially for the survival analysis. All records in the data set were followed up until a diagnosis of any primary cancer or for a maximum of 5 years from the respective date of zoster diagnosis or pseudo-diagnosis. Records for cases and non-cases were evaluated for first recorded cancer diagnosis (excluding non-melanoma skin cancer, and whatever the level of spread at the time of diagnosis) after the zoster diagnosis. These records were then categorised for type of cancer.

Power calculation. By comparing two groups using Cox regression, the sample size can be obtained from the formula for the log-rank test given in Hsieh *et al* (2003). Buntinx *et al* (2005) found that the number of patients without cancer was 97.94% and 99.26% for the zoster and no zoster groups, respectively; this yields an estimated hazard ratio (h) of 2.7. Using this figure, the proportion of controls, a power of $\beta = 0.9$ and a significance level of $\alpha = 0.05$, STATA 10 gave $E = 43$, $N1 = 3573$, and $N2 = 785$ where E is the estimated number of cancer events, $N1$ and $N2$ are the required sample sizes for the unexposed/exposed groups, respectively. Thus, it can be seen that the study has more than sufficient number of subjects.

Analysis. The Cox proportional hazards model was used to compare the subsequent risk of cancer in patients with and without zoster. Using the index date of the matched case, the time to cancer diagnosis was generated. Subjects who did not develop cancer after 5 years of follow-up were censored at this time. To test the possibility of there being cancers diagnosed just before a diagnosis of zoster that had not been recorded in the data set until afterwards, a sensitivity analysis excluding all cancers diagnosed within 2 months of a diagnosis of zoster was done (the time duration was based upon clinical common sense; we envisaged that this would be the likely time that a pre-existing cancer would have been diagnosed within, especially as the undiagnosed cancer was responsible for the zoster). Furthermore, because the risk of zoster and cancer vary with age, this model allowed gender-stratified and age-adjusted analyses. The Cox regression was routinely assessed using Schoenfield's residual test to test the fit of the proportional hazards model (Grambsch and Therneau, 1994). To contextualise the meaning of the hazard ratios into clinical practice, we summarised the absolute numbers of cancers diagnosed within different time durations after zoster diagnosis (Table 2).

The analysis was repeated to assess whether patients exposed to immunosuppression (which may increase the risk of both conditions) changed the overall zoster hazard ratio. Subjects with and without zoster were classed as immunosuppressed if they met one of the following criteria shown in Box 1 before their cancer diagnosis. This was based upon the definition from that used by Salisbury *et al* (2006), which identifies potential severe immunosuppression such that such patients should not receive live vaccines. It was only modified to exclude malignant disease and its treatment (because these patients have been excluded already).

To fulfill the second aim to estimate the difference in survival, patients with cancer were matched where possible (by age within 5 years, gender, and cancer site) in a 1 : 1 ratio dependent upon whether they had a zoster diagnosis or not. Cases without matches were excluded. Analysis was then performed using Kaplan–Meier estimates of the time to event.

SPSS version 16 was used for handling the data and statistical analysis (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 74 029 patients were studied; 13 428 patients with zoster were matched with 60 601 patients without zoster (>1 : 4.5). The range of follow-up for both groups was 1–1825 days. The mean age of patients with zoster was 59.6 years and without zoster was 60.0 years. There were 42% males in each group. During the study period, a total of 2054 patients developed a primary cancer. Of these, 658 developed in patients with zoster and 1396 developed in patients without zoster.

Table 1 summarises the hazard ratios for patients developing cancer after a diagnosis of zoster for all cancers and by cancer site. Median times from zoster diagnosis to cancer diagnosis are also shown. For all cancers combined, the hazard ratio was 2.42 (95% confidence interval (CI) 2.21, 2.66) and the median time from zoster to cancer was 815 days. Ovarian cancer had the highest hazard ratio of 5.35 (95% CI 2.85, 10.03) and connective tissue cancers the shortest median time to cancer (657 days – interquartile range (IQR) 382, 1664). Only a small number of cancer groups (bladder, miscellaneous, hepatocellular/bile duct, and stomach) did not have hazard ratios that were significant at the 95% CI.

Table 1. Summary of hazard ratios by cancer site and for age band, and time to cancer diagnosis

	Number of cancers		Rate per 1000 person years				
Cancer site	Zoster	No zoster	Zoster	No zoster	Hazard ratio	95% CI	Median time from zoster to cancer (days) (IQR)
Combined	658	1396	12.08	5.10	2.42	2.21, 2.66	815 (387, 1309)
Ovary	20	19	0.37	0.07	5.35	2.85, 10.03	962 (349, 1392)
Connective tissue	8	10	0.15	0.04	4.46	1.75, 11.40	657 (382, 1664)
Eye, brain, and other CNS	8	9	0.15	0.03	4.00	1.49, 10.75	1003 (669, 1314)
Oesophagus	24	36	0.44	0.13	3.35	2.00, 5.61	977 (557, 1331)
Oral cavity and pharynx	7	12	0.13	0.04	3.12	1.23, 7.97	925 (582, 1555)
Haematological	70	119	1.29	0.43	3.02	2.52, 4.06	713 (416, 1130)
Lung	89	159	1.63	0.58	2.90	2.23, 3.76	741 (293, 1205)
Breast	113	212	2.75	0.78	2.74	2.18, 3.44	873 (513, 1262)
Cervix and uterus	18	35	0.33	0.13	2.66	1.51, 4.70	1114 (572, 1571)
Pancreas	20	36	0.37	0.13	2.54	1.42, 4.53	1172 (591, 1484)
Prostate	84	172	1.54	0.63	2.49	1.92, 3.24	750 (368, 1330)
Renal	16	18	0.29	0.07	2.32	1.13, 4.75	1146 (705, 1582)
Unknown primary	39	93	0.72	0.34	2.15	1.48, 3.13	1051 (566, 1435)
Melanoma	17	42	0.31	0.15	2.14	1.22, 3.77	1165 (823, 1452)
Colorectal	83	226	1.52	0.83	1.87	1.45, 2.40	938 (400, 1409)
Bladder	23	86	0.42	0.31	1.37	0.86, 2.17	938 (422, 1420)
Miscellaneous[a]	9	63	0.17	0.23	1.27	0.68, 2.39	1094 (553, 1435)
Hepatocellular/bile duct	5	24	0.09	0.09	1.12	0.42, 2.93	1105 (827, 1400)
Stomach	5	25	0.09	0.09	1.04	0.40, 2.72	1112 (623, 1431)
Age bands for all cancer types combined (years)							
18–50	42	33	2.73	0.45	6.57	4.18, 10.41	1080 (416, 1450)
51–60	93	175	7.86	2.94	2.72	2.12, 3.50	884 (513, 1424)
61–70	175	309	14.50	5.08	2.92	2.43, 3.52	847 (423, 1419)
71–80	228	591	15.05	7.41	2.07	1.77, 2.41	793 (379, 1277)
>80	120	288	26.10	11.66	2.23	1.83, 2.81	713 (290, 1147)

Abbreviations: CI = confidence interval; CNS = central nervous system; IQR = interquartile range.
[a]The miscellaneous group of cancers included very small numbers of cancers that could not be grouped elsewhere (including and described as thyroid cancer, vagina, penis, adrenal, 'genitourinary', small intestine, maxillary sinus, pelvic peritoneum, and retroperitoneal).

Repeating the analysis but excluding all cancers diagnosed within 2 months of a diagnosis of zoster reduced the hazard ratio of a patient developing cancer slightly to 2.32 (95% CI 2.11, 2.55). The median time to diagnosis was 1723 days (IQR 1460, 1800).

Of the 2054 patients with cancer, 996 were male and 1058 were female. The hazard ratio of cancer in zoster *vs* non-zoster was highest for the youngest age band (18–50 years); HR of 6.57 (95% CI 4.28, 10.41); however, the numbers of cancers were smaller with 2.73 per 1000 person years for patients with zoster and 0.45 per 1000 person years for those without zoster. The risk was less for older age bands.

Residual diagnostic tests suggested that the proportional hazard assumptions were not met for some time points (Table 2). An extended Cox model using an interaction term of time and zoster exposure was introduced to take into account the effect of drop out and follow-up time. The difference between the zoster and no zoster groups was most marked soon after zoster. After 12 months, there were proportionately four times as many cancers in the zoster group. By 5 years, almost 10% of men over 65 years who had zoster had developed cancer. The hazard ratios are highest soon after diagnosis, but the CIs are wide, reflecting the limited number of events, so caution should be applied when interpreting these values.

Box 1. Criteria for severe immunosuppression (modified from Salisbury *et al*, 2006).

- Major organ or bone marrow transplant, or a diagnosis of HIV, severe combined immunodeficiency, or Wiskott-Aldrich syndrome before the baseline date.
- Any record of prescription of an immunosuppressive drug (azathioprine, sulfasalazine, methotrexate, cyclosporine, and lefunomide) in the 6 months before baseline date.
- Any record of a steroid prescription at a defined dose or higher (dexamethasone 3 mg daily, hydrocortisone 80 mg daily, prednisolone 40 mg daily for >1 week, and cortisone 100 mg daily) in the 3 months before baseline date.

Table 2. Hazard ratios over different time points

	Percentage (*n*) with cancer after zoster				
	Within 90 days of zoster	Within 180 days of zoster	Within 1 year of zoster	Within 3 years of zoster	Within 5 years of zoster
All patients					
Zoster ($n=13\,428$)	0.3 (45)	0.6 (84)	1.2 (154)	3.2 (424)	4.9 (658)
No zoster ($n=60\,601$)	0.0 (10)	0.1 (41)	0.3 (162)	1.2 (715)	2.3 (1396)
HR (95% CI)	20.5 (10.4, 40.8)	9.4 (6.5, 13.7)	4.4 (3.6, 5.5)	2.9 (2.5, 3.3)	2.4 (2.2, 2.7)
All males					
Zoster ($n=5625$)	0.4 (21)	0.8 (43)	1.4 (77)	3.6 (200)	5.6 (307)
No zoster ($n=25\,198$)	0.0 (5)	0.1 (17)	0.3 (74)	1.3 (338)	2.7 (689)
HR (95% CI)	19.1 (7.2, 50.5)	11.6 (6.6, 20.3)	4.8 (3.5, 6.6)	2.9 (2.4, 3.4)	2.3 (2.0, 2.6)
All females					
Zoster ($n=7803$)	0.3 (24)	0.5 (41)	1.0 (77)	2.9 (224)	4.5 (351)
No zoster ($n=35\,403$)	0.0 (5)	0.1 (24)	0.3 (88)	1.1 (377)	2.0 (707)
HR (95% CI)	22.0 (8.4, 57.7)	7.9 (4.8, 13.1)	4.1 (3.0, 5.6)	2.9 (2.4, 3.4)	2.5 (2.2, 2.9)
Males >65					
Zoster ($n=2188$)	0.9 (19)	1.5 (33)	2.7 (58)	6.5 (142)	9.9 (216)
No zoster ($n=10\,090$)	0.0 (4)	0.1 (14)	0.6 (59)	2.8 (284)	5.6 (561)
HR (95% CI)	22.2 (7.6, 65.3)	11.2 (5.9, 20.8)	4.8 (3.3, 6.8)	2.5 (2.1, 3.1)	2.1 (1.8, 2.4)
Females >65					
Zoster ($n=3297$)	0.5(17)	0.9 (29)	1.6 (53)	4.8 (158)	6.9 (229)
No zoster ($n=15\,186$)	0.0 (4)	0.1 (19)	0.4 (65)	1.8 (277)	3.3 (499)
HR (95% CI)	19.9 (6.7, 59.0)	7.2 (4.0, 12.9)	3.9 (2.7, 5.6)	2.9 (2.3, 3.5)	2.4 (2.1, 2.8)

Abbreviations: CI = confidence interval; HR = hazard ratio.

According to our definition of immunosuppression (Box 1), 1054 patients were found to have been immunosuppressed before a diagnosis of zoster. Adjusting for prior exposure to immunosuppression had no significant effect on the original hazard ratio of 2.4. The analysis yielded a hazard ratio (risk of subsequent malignancy for the immunosuppressed group taking into account zoster exposure) of 1.23 (95% CI 0.89, 1.68). Hence, there was no evidence that being immunosuppressed had any significant effect on the risk of malignancy.

For the survival analysis, it was only possible to find matches for 573 patients with cancer and a prior diagnosis of zoster. There were 252 deaths in the zoster group and 231 deaths in the no zoster group. Median survival for the zoster group was 1197 days (s.e. 171.8) and median survival for the no zoster group was 1201 days (s.e. 174.8). No significant difference was found; log rank (Mantel-Cox) $X^2=0.018$, df = 1, $P=0.894$.

DISCUSSION

Summary of main findings. This is the largest study of this nature to date, and the first to show a clear association between zoster and a subsequent diagnosis of cancer. Following analysis of the primary care records of 13 248 patients with a diagnosis of zoster, this study shows that the risk of a cancer diagnosis in adults is significantly increased (HR 2.42). The magnitude of the risk varied between cancers, and was highest in younger patients. The median time from zoster to cancer was over 2 years. There were proportionally more cancers in the patients with a history of zoster compared with those without zoster for all age groups and both male and female patients. This was more marked in the first 90 days following diagnosis and in patients over the age of 65 years. A diagnosis of zoster before cancer did not affect survival, although the study was not powered to detect this. Prior immunosuppression was not associated with a change in the risk of cancer; ours being the first study to control for this.

Discussion of findings within context of literature. The studies to which ours are most comparable are those by Sørensen *et al* (2004), Buntinx *et al* (2005), and Ho *et al* (2011). Buntinx *et al* (2005), in a smaller primary care study from Belgium, demonstrated an increased risk of cancer after zoster, but only in females over the age of 65 years (HR 2.65). Our findings (HR 2.42 for both genders and all age groups) may be a reflection of a much larger sample size (13 248 patients with zoster, compared with 1211). Sørensen *et al* (2004) had a similar sized sample to ours (10 588 patients, matching 1 : 1.2), but these were patients hospitalised with zoster (and hence less comparable to our findings and those of Buntinx, and less relevant to zoster overall), who were compared with the expected rate (based on age in 10-year age bands, gender, and cancer site) derived from the Danish Cancer Registry. They found an overall relative risk for cancer (including non-melanoma skin cancers) of 1.2 with a cumulative cancer risk of 1.8% in the first year. Similarly to our findings, they found no difference in cancer survival for all cancers but were able to demonstrate a poorer survival for zoster patients with subsequent haematological cancers. Our reported risk is lower than that reported by in the Taiwanese study by Ho *et al* (2011). Their sample was much smaller and only included patients with herpes zoster ophthalmicus. Our findings differ from those from the large

population-based study of Wang *et al* (2012). This may be explained by study design; ours being a retrospective cohort with matched controls and the Taiwanese study being an unmatched cohort with expected incidence of cancer being the comparator.

It is well established that the incidence of zoster increases with age (Thomas and Hall, 2004; Weinberg, 2007) and for a variety of reasons immunocompetence also declines with age (Arvin, 2005). These facts together with the parallel increase in malignancy with age and an association of zoster with a prior diagnosis of cancer strongly suggest that the immune system is a determinant factor that may link zoster with cancer. Various mechanisms have been suggested for this:

- There may be a reduction in cell-mediated immunity allowing zoster to manifest itself and a concurrent reduction in immune surveillance for cancer (Buntinx *et al*, 2005).
- Zoster may be an early manifestation of an impaired immune system caused by occult cancer (Arvin, 1996; Thomas and Hall, 2004).
- The zoster virus may provoke an immunological mechanism that weakens immune surveillance for cancer cells allowing tumour escape (Vicari and Trinchieri, 2004; Lin and Karin, 2007), or directly causing cancer (Kuper *et al*, 2000).

Strengths and limitations. The GPRD is a well-validated primary care data set (Jick *et al,* 1991) that meets rigorous and regularly applied quality assurance standards. The data are thought to be representative of the UK population both geographically and demographically (Rodríguez and Gutthann, 1998). The size of the database has allowed us to analyse a large number of patients that more than exceeded the number required by the power calculation and is larger than previous studies. We used 5 years of patient data both pre- and post-cancer diagnosis. In the United Kingdom, nearly all zoster is diagnosed and managed within primary care, justifying the use of a primary care data set for this study. Other studies have successfully used the GPRD to identify patients with cancer (Kaye *et al*, 2002; Jones *et al*, 2007). We are aware however that the GPRD constitutes data collected in routine practice and can be vulnerable to delays, omissions, and miscoding. Such failings, however, are likely to be similar in both groups in this study. No similar study to date has included immunosuppression as a variable. Our data permitted us to do this, and this is a strength of our work, but this strength was hindered by the fact that we had to develop our own definition of immunosuppression and there are probably a small number of patients on immunosuppressant drugs that fell outside our definition.

A potential weakness of the study is the possibility of an increased diagnostic effort and heightened surveillance both by patients with zoster and by their carers for other disease. This might account for some of the early increased association with a cancer diagnosis (Sørensen *et al*, 2004), although it seems most unlikely that this would be maintained for several years after a zoster diagnosis. Further weaknesses include our inability to match by year of diagnosis, by practice, or by stage data; hence, the survival comparison between the groups may be open to confounding. Family history of zoster and cancer may also potentially confound our results; it is well established that cancers can be familial and recent evidence suggests that this may also be true for zoster (Hicks *et al*, 2008). Tobacco consumption, diabetes, and psychological distress have also been linked to immunosuppression and may be confounders. We were unable to adjust for smoking because smoking data in GPRD during the period of the study were incomplete and inaccurate; around one quarter of records have been found to lack data about smoking habits and almost two thirds of former smokers may be misclassified (Lewis and Bresinger, 2004). McDonald *et al* (2009) have shown a reduced risk of zoster in rheumatoid patients treated with tumour necrosis factor-α antagonists and an increased risk with other immune modulating drugs. Patients with rheumatoid arthritis having a two to five times greater risk of zoster than the general population; thus, this diagnosis might additionally confound our results.

We had to make several assumptions in our methods, and these may have affected the findings. These were our choice of the definition of immunosuppression; our choice of 2 months as the time period between zoster and cancer for the sensitivity analysis; and our choice of 5 years for complete GPRD records before their date of zoster diagnosis or pseudo-diagnosis.

Implications for policy, practice, and research. Previous studies have called for more efforts to detect cancer following a zoster diagnosis (Zaha *et al*, 1993; Yamamoto *et al*, 2003); while others have been more cautious (Sørensen *et al*, 2004; Buntinx *et al*, 2005). The studies by Ragozzino *et al* (1982) and Fueyo and Lookingbill (1984) have been cited in reviews of the management of zoster to support the advice that it is not a marker of occult malignancy (Smith and Fenske, 1995; Arvin, 1996; Gnann and Whitley, 2002). Our findings would suggest otherwise and challenge the findings of these previous studies. Some cancers have relatively few early symptoms and signs, and many more initially present with symptoms that are often regarded as self-limiting, or those of benign disease (Hamilton, 2009). Hence, the diagnosis of zoster should raise the index of suspicion for cancer in health-care professionals when presented with symptoms of oncological significance. However, the effect of investigations to try to identify early-stage cancers, and the potential harm caused by the subsequent raising of anxiety are unknown at present. Lastly, the immune system's response to zoster infection needs further elucidation.

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