Herpes zoster as a marker of an underlying malignancy

Running title: Herpes zoster marker of malignancy

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Abstract

Background: Both herpes zoster and malignancy are associated with an immunosuppressed state. However, the association between herpes zoster and the subsequent development of a malignancy is unclear. This study aimed to assess if a diagnosis of herpes zoster is a risk factor for subsequent malignancy.

Methods: Utilizing a physician billing database, individuals 18 years of age and older with a diagnosis of herpes zoster and without a prior cancer diagnosis or human immunodeficiency virus infection were included in the study. Individuals with a herpes zoster diagnosis were matched one-to-one to those without a herpes zoster diagnosis, and both were examined for the development of cancer.

Results: There were 542,575 individuals diagnosed with herpes zoster. Compared with controls, they were more likely ($p< 0.001$) to have a history of myocardial infarction, asthma, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and hypertension. The incidence of cancer was significantly greater in individuals with herpes zoster compared to those without in both men and women and across all time intervals studied. The greatest adjusted hazard ratio was seen 180 days after a herpes zoster diagnosis (1.19, CI 1.12-1.25); this decreased as the time from herpes zoster diagnosis increased. The greatest relative increase in cancer incidence following a herpes zoster diagnosis occurred in individuals diagnosed with lymphoma.

Interpretation: There is a risk of developing a malignancy following an episode of herpes zoster in both men and women and in all age groups 18 years and over. The risk is greatest in the first 180 days following a herpes zoster diagnosis.

Introduction:

Herpes zoster presents as a painful vesicular rash in a dermatomal distribution resulting from the reactivation of the varicella zoster virus in the dorsal root ganglia.[1,2] The rash is self-limited and resolves in 2 to 4 weeks.[3] Age appears to be the key risk factor for the development of herpes zoster.[4] A decrease in cell-mediated immunity is thought to be responsible for the increased incidence of varicella-zoster virus reactivation seen in older individuals.[5] Patients with conditions resulting in impaired cell-mediated immunity such as lymphoma, human immunodeficiency virus (HIV) infection and those receiving chemotherapy and steroids[6] are at increased risk of developing herpes zoster.

Although it is known that both herpes zoster and malignancy are associated with an immunosuppressed state[7], studies examining the association between herpes zoster and a subsequent diagnosis of cancer have shown discordant results[8-13]. Two studies showing an association were those examining the risk of hematological malignancies following herpes zoster[8,9]. A study by Buntinx et al examining a database of over 300,000 patients found an increased incidence of cancer following a herpes zoster diagnosis in patients over 65 years of age overall and in females older than 65 years of age but not in males[12]. There was no difference in the incidence in the first year after herpes zoster diagnosis which was interpreted that a diagnosis of herpes zoster was not a marker of undiagnosed malignancy. Hence, the authors recommended against screening patients with herpes zoster for an underlying malignancy. A recent retrospective cohort study by Wang et al found no difference in overall cancer incidence in patients with herpes zoster when compared to expected rates in a population[13].

This article will report on the largest study to date to examine whether a diagnosis of herpes zoster is a risk factor for a subsequent cancer diagnosis. It will describe the risk of cancer following a herpes zoster diagnosis based on age, sex and type of malignancy.

Methods:

A matched cohort design was used to study the development of cancer in patients with a diagnosis of herpes zoster. Exposed subjects had herpes zoster and unexposed controls did not. Study control subjects were matched by age and sex. Multivariate Cox proportional hazards models were used to compare rates of cancer between study groups while controlling for potential confounders. Cases were identified from April 1st, 1993 to March 31st, 2010 and cancer outcomes were identified until December 31st, 2010.

Patients 18 years of age and older were included in the study. However, patients with a history of human immunodeficiency virus (HIV) infection and pre-existing cancer were excluded from the analysis.

Data relating to a diagnosis of herpes zoster was derived from the physician billings database in the universal Ontario Health Insurance Plan (OHIP) and obtained through a comprehensive research agreement with the Ontario Ministry of Health and Long-Term Care. The OHIP covers physician and hospital services for Ontario residents and includes approximately 94% of ambulatory physician visits in the province. The diagnosis of herpes zoster has a unique diagnostic code in the OHIP billing system (053). The exposed subjects were those individuals

for whom a first billing code for herpes zoster was submitted, while the unexposed controls were those individuals for whom a billing code for herpes zoster was not submitted.

The Ontario Cancer Registry (OCR) was used to determine which patients were diagnosed with cancer and if the same patient also had a diagnosis of herpes zoster whether the cancer diagnosis preceded or followed the herpes zoster diagnosis. The process of cancer registration in Ontario relies on records collected for other purposes including hospital discharge and day surgery summaries which include a diagnosis of cancer; pathology reports with any mention of cancer; records of patients referred to eight regional cancer centres or the Princess Margaret Hospital, the specialized institutions treating cancer patients in Ontario; and death certificates with cancer recorded as the underlying cause of death. Approximately 400, 000 records are submitted to OCR each year.

Simple proportions and means were used to compare the characteristics of exposed subjects and unexposed controls. Time periods of 180 days, 1 year, 2 years, 3 years, 4 years and 5 years were used to examine the relationship between cases and controls for the outcome of a cancer diagnosis using Cox proportional hazard models that controlled for urban-rural setting, area-level income and co-morbidities including acute myocardial infarction[14], asthma[15], congestive heart failure[16], chronic obstructive pulmonary disease[17], diabetes mellitus[18] and hypertension[19].

The study was approved by the Research Ethics Boards of St. Michael's Hospital and Sunnybrook Health Sciences Centre in Toronto.

Results:

Table 1 shows the demographics of the exposed subjects and unexposed controls studied. There were 542,575 individuals diagnosed with herpes zoster from 1993 to 2010 and included in the study. The mean age of cases was 54.08 years with the majority of cases (59.7%) occurring after age 50. The two groups were very similar in terms of urban/ rural location of residence and income quintiles. Even though they reached statistical significance, the differences were very small. The cases were slightly more likely to have a history of myocardial infarction, asthma, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and hypertension ($p< 0.001$).

Table 2 shows the cumulative incidence and unadjusted and adjusted hazard ratios for cancer from the time of diagnosis of herpes zoster in the exposed subjects. The incidence of cancer was significantly greater in exposed subjects when compared to unexposed controls across all of the time intervals studied. The greatest adjusted hazard ratio at 1.19 (CI 1.12-1.25) was seen at 180 days after a herpes zoster diagnosis. It tended to decrease as the time from herpes zoster diagnosis increased.

There was an increase in the number of malignancies in both males and females who had a prior diagnosis of herpes zoster. There was also an increased risk of malignancy in individuals who had a prior episode of herpes zoster across all age ranges studied (data not shown).

Table 3 shows the number and types of cancers per 1000 years of person time from the time of diagnosis of herpes zoster in exposed subjects and unexposed controls. There were more cancers diagnosed per 1000 years of person time in all of the time intervals and all cancer types except

colorectal cancer at 180 days, 4 years and overall. The greatest relative increase in cancer incidence (68%) following a herpes zoster diagnosis occurred in those individuals diagnosed with lymphoma. This risk was greatest (112%) at 180 days. The greatest absolute increases in risk of malignancy following a herpes zoster diagnosis occurred for 'Other' cancer types followed by lymphoma, lung, prostate and leukemia.

Interpretation:

This matched cohort study examining the risk of malignancy following a diagnosis of herpes zoster is the largest published to date. The results demonstrate an association between herpes zoster and subsequent development of a malignancy in both men and women as well as across all age categories studied. The greatest adjusted and unadjusted hazard ratios for cancer diagnosis following herpes zoster was seen at 180 days with a persisting but declining ratio over subsequent years. There was an 18.6% increase in adjusted cancer risk following a herpes zoster diagnosis within the first 180 days and an 11.4% adjusted increase at one year. Although a risk is demonstrated, the absolute increase in risk is modest at 1.34 per 1000 years of person time at 1 year and 0.84 per 1000 years of person time at 5 years. The greatest relative increase in specific cancer types was in lymphoma and leukemia.

Our study also noted an association between the development of herpes zoster and the presence of co-morbidities, namely, myocardial infarction, congestive heart failure, chronic obstructive lung disease (COPD), asthma, diabetes and hypertension. This finding had been noted in previously conducted studies for diabetes[20, 21] hypertension[21] and COPD[22]. Another study[23] found

an increased risk of undiagnosed diabetes mellitus (OR 2.28 CI 1.28-4.06) in patients presenting with a herpes zoster infection.

A review of the literature has revealed three studies documenting an association between a diagnosis of herpes zoster and a subsequent diagnosis of a malignancy. Sorensen et al[24] compared the incidence of malignancy in patients hospitalized with herpes zoster to the expected rate. The relative risk was reported to be 1.2 (CI 1.1-1.2) with the risk being substantially elevated during the first year of follow-up (1.3, CI 1.1-1.5) and especially for hematological cancers (3.4, CI 2.3-4.9), namely non- Hodgkin's lymphoma, multiple myeloma and leukemia.
Buntinx et al[12] conducted a retrospective cohort study utilizing a patient registry of 37 general practices in Belgium and found a statistically significant increase in cancer risk following a herpes zoster diagnosis in all patients over the age of 65 with a relative risk of 1.85 (CI 1.18-2.90). When the data were stratified by sex, the increase was only significant for females (2.65, CI 1.43- 4.90). There was no increased risk in the first year following a herpes zoster diagnosis (1.75, CI 0.82- 3.75). Another retrospective cohort study[25] examined the risk of malignancy following an episode of herpes zoster ophthalmicus and found a 9.25 fold increase (CI 5.51-15.55) in malignancy risk within the first year of a diagnosis of herpes zoster ophthalmicus. There was no significant difference in cancer type demonstrated.

A recent retrospective cohort study[13] utilizing a National Health Insurance Research Database in Taiwan examined the incidence of cancer in 35,871 patients with herpes zoster. Patients with cancer were identified through an application for a catastrophic illness certificate and the rates of cancer in the study population were compared to national incidence rates of cancer. The study concluded that a diagnosis of herpes zoster does not increase the risk of cancer overall (0.99 CI

0.93- 1.06) but did increase the risk of multiple myeloma (2.03, CI 1.01- 3.63) and bone and soft tissue cancers (2.03, CI 1.11- 3.41).

Our study is among the first to use a population-based approach. It supports previous work showing that cancer occurs early after herpes zoster and that hematological cancers are most implicated. Unlike other previous work, it did not find sex differences in cancer occurrence. This study was able to examine a five year period; although the risk diminished over time, it persisted up to five years after herpes zoster.

There are limitations to this research. The data used in this study were collected for purposes other than research and the diagnostic code for shingles has not been validated. However, the Ontario cancer registry has undergone extensive validation.[26] The large number of exposed subjects and controls means that statistical significance may have been found even for small absolute differences. The main results do show clinically important increases in cancer risk following herpes zoster infection.

In conclusion, there is a risk of developing a malignancy following an episode of herpes zoster which is present in both men and women and in all age groups 18 years and over. The risk is greatest in the first 180 days following a herpes zoster diagnosis but persists for at least five years. Clinicians are encouraged to be vigilant for malignancy in patients presenting with herpes zoster; however, screening cannot be recommended due to the modest increase in risk and lack of specificity with respect to cancer type.

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Table 1: Demographic characteristics of individuals with a Herpes Zoster diagnosis and controls.

Variable		Patients with Herpes Zoster	Patients without Herpes Zoster
Sex	**Female**	319,935 (59.0%)	319,935 (59.0%)
	Male	222,640 (41.0%)	222,640 (41.0%)
Total		542, 575	542, 575
Age	**Years (mean)**	54.08	54.08
Age Group	**18-49**	218,530 (40.3%)	218,530 (40.3%)
	50-64	148,897 (27.4%)	148,897 (27.4%)
	65-74	91,847 (16.9%)	91,847 (16.9%)
	75+	83,301 (15.4%)	83,301 (15.4%)
Setting	**Rural**	70,863 (13.1%)	73,229 (13.5%)
	Urban	465,755 (85.8%)	467,947 (86.2%)
	Unknown	5,957 (1.1%)	1,399 (0.3%)
Income Quintile	**1 (Low)**	107,049 (19.7%)	101,181 (18.6%)
	2	109,277 (20.1%)	109,404 (20.2%)
	3	106,163 (19.6%)	108,457 (20.0%)
	4	104,872 (19.3%)	108,879 (20.1%)
	5 (High)	107,338 (19.8%)	111,611 (20.6%)
	Unknown	7,876 (1.5%)	3,043 (0.6%)
Co-morbidities	**Acute myocardial infarction**	10,027 (1.8%)	8,597 (1.6%)
	Asthma	61,734 (11.4%)	47,245 (8.7%)
	Congestive Heart Failure	22,138 (4.1%)	18,390 (3.4%)
	Chronic Obstructive Pulmonary Disease	54,989 (10.1%)	45,808 (8.4%)
	Diabetes Mellitus	82,200 (15.1%)	78,461 (14.5%)
	Hypertension	171,769 (31.7%)	158,849 (29.3%)

Table 2: Cumulative incidence of cancer from time of diagnosis of Herpes Zoster in affected subjects and unaffected controls.

Time from Diagnosis of Herpes Zoster	Cancer Diagnosis in Patients with herpes zoster	Cancer Diagnosis in Patients without herpes zoster	Unadjusted Hazard Ratio (Confidence Interval)	Adjusted Hazard Ratio* (Confidence Interval)	P-Value
180 days	2,875 (0.5%)	2,403 (0.4%)	1.203 (1.139- 1.271)	1.186 (1.122- 1.253)	<0.001
1 year	5,615 (1.0%)	4,911 (0.9%)	1.154 (1.110- 1.199)	1.114 (1.096- 1.185)	<0.001
2 years	10,546 (1.9%)	9,439 (1.7%)	1.128 (1.096- 1.160)	1.114 (1.082- 1.146)	<0.001
3 years	15,166 (2.8%)	13,818 (2.5%)	1.110 (1.084- 1.136)	1.095 (1.069- 1.122)	<0.001
4 years	19,472 (3.6%)	17,812 (3.3%)	1.104 (1.081- 1.128)	1.092 (1.069- 1.115)	<0.001
5 years	23,225 (4.3%)	21,419 (3.9%)	1.094 (1.073- 1.115)	1.082 (1.061- 1.103)	<0.001

*Cox proportional hazard models controlled for urban-rural setting, area-level income and co-morbidities including acute myocardial infarction, asthma, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus and hypertension.

Table 3: Number and types of cancers per 1000 years of person time from time of diagnosis of Herpes Zoster in affected subjects and unaffected controls.

Cancer Type/ Time from herpes zoster diagnosis		Lung	Breast	Colorectal	Prostate	Leukemia	Lymphoma	Other	Total
180 days	Subject	1,47	1.39	1.22	1.54	0.35	0.70	4.15	10.82
	Control	1.25	1.27	1.33	1.36	0.22	0.33	3.26	9.02
	Ratio	1.18	1.09	0.92	1.13	1.59	2.12	1.27	1.20
1 year	Subject	1.38	1.36	1.25	1.50	0.34	0.66	4.02	10.51
	Control	1.26	1.28	1.21	1.41	0.24	0.34	3.43	9.17
	Ratio	1.10	1.06	1.03	1.06	1.42	1.94	1.17	1.15
2 years	Subject	1.42	1.33	1.26	1.49	0.33	0.61	3,90	10.34
	Control	1.31	1.29	1.24	1.35	0.23	0.37	3.45	9.24
	Ratio	1.08	1.03	1.02	1.10	1.43	1.65	1.13	1.12
3 years	Subject	1.40	1.33	1.29	1.47	0.31	0.59	3.90	10.29
	Control	1.32	1.29	1.27	1.36	0.22	0.39	3.50	9.35
	Ratio	1.06	1.03	1.02	1.08	1.41	1.51	1.11	1.10
4 years	Subject	1,42	1.34	1.29	1.48	0.32	0.59	3.89	10.33
	Control	1.34	1.29	1.29	1.38	0.23	0.39	3.51	9.43
	Ratio	1.06	1.04	1.00	1.07	1.39	1.51	1.11	1.10
5 years	Subject	1.42	1.33	1.31	1.48	0.31	0.57	3.89	10.31
	Control	1.35	1.30	1.30	1.39	0.23	0.39	3.51	9.47
	Ratio	1.05	1.02	1.01	1.06	1.35	1.46	1.11	1.09