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Family history of zoster and risk of developing herpes zoster

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ABSTRACT

Background: Studies have investigated a possible association between family history of HZ and the occurrence of HZ. However, the results were inconclusive and susceptible to bias. We evaluated this association in an elderly population.
Methods: The matched case-control study conducted at Kaiser Permanente Southern California in 2012-2015 included 656 incident HZ patients ≥60 whose skin lesion tested positive for varicella zoster virus by polymerase chain reaction. Half of the HZ patients were vaccinated with zoster vaccine as achieved by stratified sampling. The controls were randomly selected and 1:1 matched to the cases on sex, age (±1 year), and zoster vaccination (±3 months of the case's vaccination date). Conditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI).
Results: Having any blood relative with a history of HZ was associated with a slightly increased risk of HZ (adjusted OR = 1.37, 95% CI 1.05–1.79). The adjusted OR associated with having one and two categories of first-degree blood relatives with a history of HZ was 1.30 (95% CI: 0.97–1.73) and 2.53 (95% CI: 1.17–5.44), respectively.
Conclusions: Our results suggested a weak association between the development of HZ and a positive family history of HZ among the elderly population.

Background

Herpes zoster (HZ), or shingles, is a painful vesicular rash, usually unilateral, caused by the varicella zoster virus (VZV). The pain and potential long-term effects associated with HZ, including post-herpetic neuralgia (PHN) and cranial nerve damage, can be debilitating, with a serious impact on quality of life. In 2006, the zoster vaccine received Food and Drug Administration (FDA) approval for use in healthy adults aged 60 and older. Zoster vaccine can increase cell-mediated immunity to VZV and reduce the risk of HZ (Tseng et al., 2011; Oxman et al., 2005).

Better understanding of risk factors for HZ can provide information about which patients are at an increased risk of HZ and could benefit most from vaccination. It can also provide insights regarding the pathophysiology of HZ and VZV reactivation. Multiple factors have been proposed as possibly associated with the risk of developing HZ. These include age, sex, race, genetics, immune disorders, physical trauma, psychological stress, toxin exposure, depression, and anxiety (Thomas and Hall, 2004; Schmader et al., 1990). Except for advanced age and immunosuppression, other risk factors for HZ are less clear. Family history has also been proposed as a potential risk factor for HZ, however, the findings are inconsistent (Ansar et al., 2014; Lasserre et al., 2012; Hernandez et al., 2011; Gatti et al., 2010; Hicks et al., 2008). Results from studies investigating genetic susceptibility to HZ have also been inconclusive (Crosslin et al., 2015; Wozniak et al., 2007; Cho et al., 2007; Opdal, 2004; Meenagh et al., 2002; Haanpaa et al., 2002).

Previous studies were prone to errors due to small sample size, unclear HZ case diagnosis, imprecise measurement of family history, differential recall between cases and controls, referral bias, and use of non-contemporaneous controls. To address these

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concerns, we conducted a prospective matched case-control study in a large health care organization in the United States.

Objectives

The aim of this study was to evaluate the association between a family history of HZ and the risk of developing HZ.

Study design

Setting

This study was conducted at Kaiser Permanente Southern California (KPSC), an integrated healthcare organization that provides prepaid comprehensive health care. KPSC serves more than 4.2 million members who are both racially and socio-economically diverse. The demographic makeup of the KPSC membership closely mirrors the Southern California population (Derose et al., 2013; Koebnick et al., 2012). Members receive medical care in KPSC-owned facilities and contracted facilities. Electronic health records store medical information such as socio-demographics, diagnoses, utilization (outpatient, emergency department, and inpatient encounters), procedures, laboratory tests, pharmacy utilization, vaccination records, membership history, and death.

Study population

The matched case-control study included incident HZ cases recruited from KPSC members, either with a history of vaccination with the HZ vaccine or without. An algorithm for recruitment was developed to achieve the matching. The algorithm started with identifying a vaccinated HZ case first, followed by an age (±2 years), and sex-matched unvaccinated HZ case, and then a vaccinated control matched to the vaccinated HZ case on age (±1 year), sex, and date of HZ vaccination (±3 months), and then an unvaccinated control age- (±1 year) and sex-matched to the unvaccinated case. The algorithm ensured an equal number of vaccinated and unvaccinated HZ cases in the case group that were 1:1 matched with vaccinated and unvaccinated control subjects. The number of cases and controls in the study was set to allow detection of an odds ratio associated with a family history of HZ as small as 1.5 with 80% power and a 5% type I error rate assuming 15% of control subjects reported a family history of HZ. The study was approved by KPSC Institutional Review Board and informed consent was obtained during the face-to-face visit for cases or during phone interviews for controls.

Cases

First, beginning from January 1, 2012, incident HZ patients at KPSC were identified prospectively every day by an ICD-9 code of 053.xx from outpatient and emergency department encounters. Patients with a zoster vaccine vaccination record (age $\geq$ 60 years at vaccination) between January 1, 2007 and June 30, 2014 and prior to HZ diagnosis were defined as the vaccinated HZ cases. On the same day or the day after the encounter with the HZ diagnosis, a trained research associate began contacting the vaccinated HZ patients by phone only to verify their HZ diagnosis and to arrange a face-to-face interview within 5 days of diagnosis and to obtain at least two separate skin lesion samples for testing. Up to 10 phone call attempts within 4 days after diagnosis per patient were made before the patient was considered ineligible. After obtaining informed consent, skin specimens were obtained according to the protocol prepared by the National VZV lab at the Centers for Disease Control and Prevention (CDC), which performed the standard polymerase chain reaction (PCR) test to confirm the presence of VZV from the skin specimens. Additional inclusion criteria to address feasibility concerns included selecting patients who were able to competently answer interview questions in English or Spanish, patients who resided in a safe and accessible area where the research associate could arrive in less than 3 hours of driving, and patients whose rash location was in an accessible area for specimen collection. A patient would not be included if he or she expressed concerns about being interviewed alone.

When the diagnosis of a vaccinated HZ case was confirmed by PCR at the CDC, a clinically diagnosed HZ case of the same sex and age (±2 year) with no record of zoster vaccination was identified from the daily list of HZ patients. The recruitment and inclusion criteria were identical to those of the vaccinated cases. If this unvaccinated case tested negative for VZV by PCR, then the process of identifying an unvaccinated matched HZ case would be repeated again until a positive one was found.

Controls

A vaccinated control subject was selected randomly from a list of KPSC members matched to a vaccinated HZ case on age (±1 year), sex, and date of zoster vaccine vaccination (±3 months) once the diagnosis of HZ of a vaccinated patient was confirmed by a PCR test. A control subject was considered eligible if the subject had never been clinically diagnosed with HZ. Up to 8 possible controls were identified to each case. Control subjects were contacted by a trained research associate for a telephone interview. Usually, the interview was conducted within 1 week after the eligibility was determined. Similarly, an unvaccinated control subject was selected randomly from a list to match to an unvaccinated HZ case on age (±1 year) and sex. Up to 3 phone call attempts per potential control were made before the next eligible control was considered.

Measurement

The cases received a face-to-face interview using a standardized questionnaire to obtain information on socio-demographic characteristics, family history of HZ, lifestyle factors, and comorbidities. The controls were interviewed by phone with the same structured questionnaire. For family history of HZ, the subjects were asked whether there were categories of relatives (parents, siblings, grandparents, children, grandchildren, uncle or aunt, cousin, and spouse) with a history of HZ and whether the relatives were blood related or non-blood related. The number of relatives in each relative category was not measured as this could significantly increase the difficulty of answering these questions among elderly patients and affect the validity.

The relatives with HZ were grouped into blood relative with HZ and non-blood relative with HZ. The number of subjects in the blood relative with HZ group included those who reported blood-related parents, siblings, grandparents, grandchildren, or uncle/aunt/cousin with a history of HZ. Furthermore, the blood relatives with HZ were also grouped by the number of subjects having 0, 1, 2, or 3 first order relative categories (parent, sibling, and children) with a history of HZ and by the number of subjects reporting any relatives other than first order (uncle/aunt, grandparent, grandchildren, cousin) with a history of HZ. The number of subjects who reported non-blood relative with a history of HZ included the ones having relatives who were not blood related (i.e. by marriage or by adoption) with a history of HZ, except for spouses with a history of HZ who were reported separately. The two non-blood relative categories were analyzed separately and served as "negative control" groups for interpretation of association.

Statistical analysis

Descriptive statistics for cases and controls were calculated. Conditional logistic regression models were used to estimate the matched odds ratio (OR) and 95% confidence interval (CI), corresponding to the association between having relatives with a history of HZ and the risk of developing HZ. The matched odds ratios were further adjusted by including covariates in the multivariate conditional logistic regression model. Variables were included in the initial model if they had a bivariate p-value of less than 0.2 for the association with HZ disease outcome. The covariates were retained in the model by a stepwise procedure if the p-value was less than 0.15 in the model. The estimated odds ratios were stratified by HZ vaccination status to evaluate potential effect modification by vaccination status. The analyses were performed using SAS Enterprise 5.1 (SAS Institute Inc, Cary, North Carolina).

Results

The study population included a total of 1112 participants, 556 lab-confirmed HZ cases and 556 matched controls. The participation rate among the unvaccinated and vaccinated cases was 53.9% of those that we contacted. The remaining 46.1% of the unvaccinated and vaccinated cases declined to participate when contacted and eligibility could not be determined. The participation rate for vaccinated and unvaccinated controls was 61.3% of those that we contacted. The remaining 38.7% of the vaccinated and unvaccinated controls declined to participate when contacted and again eligibility could not be determined.

The male to female ratio of participants was 4:6. The median age was 72.0 years for cases and 72.0 years for controls. The demographic distribution for cases and controls is presented in Table 1. The racial distribution was significantly different between the cases and the controls. Marital status, education level, and employment status were similar between groups.

Table 2 presents the distribution of body mass index, health behavior variables, and selected potential risk factors for HZ. A significantly higher proportion of cases reported having a weakened immune system as told by doctors (11.1% vs. 5.55% in controls) and having a sudden stressful life event in the past 3 months (48.9% vs. 29.9% in controls). There was a slight difference between cases and controls in the distribution of surgery during the past 3 months and contact with chickenpox in the past year. The distributions of body mass index, physical activity, cigarette smoking, alcohol drinking, and recent trauma were similar between groups.

Table 3 presents the distribution of comorbidities that the participants had at the time of the interview or within the 6 months prior to their interview. The distributions for most of the comorbidities were similar between the cases and the controls except a smaller proportion of the cases reported having cancer or autoimmune disorders other than systemic lupus erythematosus and rheumatoid arthritis.

Table 1
Distribution of Demographic Variables Between Herpes Zoster Cases and Their Matched Controls.

Characteristics	Cases (n = 656) Number (%)	Controls (n = 656) Number (%)	P-Value
Age at baseline, years[a]			0.93
60–69 year old	210 (32.0)	215 (32.8)	
70–79 year old	319 (48.6)	312 (47.6)	
≥80 year old	127 (19.4)	129 (19.7)	
Mean (Standard deviation)	73.3 (±6.8)	73.3 (±6.8)	
Median	72.0	72.0	
Sex[a]			1
Female	396 (60.4)	396 (60.4)	
Male	260 (39.6)	260 (39.6)	
Vaccination status[a]			1
Vaccinated	328 (50.0)	328 (50.0)	
Unvaccinated	328 (50.0)	328 (50.0)	
Race/ethnicity			<0.01
Asian	70 (10.7)	23 (3.5)	
Black	46 (7.0)	63 (9.6)	
Hispanic	132 (20.1)	70 (10.7)	
Other/Multiple/Unknown	12 (1.8)	12 (1.8)	
White	396 (60.4)	488 (74.4)	
Marital Status			0.27
Married/Living with partner	445 (67.9)	414 (63.6)	
Never married	21 (3.2)	21 (3.2)	
Separated or divorced	90 (13.7)	92 (14.1)	
Widowed	98 (15)	124 (19.0)	
Education			0.61
Some high school or less	57 (8.7)	55 (8.4)	
High school/Tech school	161 (24.6)	146 (22.4)	
Some college and above	437 (66.7)	452 (69.2)	
Employment			0.58
Not employed	15 (2.3)	10 (1.5)	
Retired	517 (78.9)	516 (78.9)	
Currently employed	123 (18.8)	128 (19.6)	

[a] Matching variables.

Table 2
Distribution of Health Behaviors and Other Risk Factors for Herpes Zoster Cases and Their Matched Controls.

Variables	Cases (n = 656) Number (%)	Controls (n = 656) Number (%)	P-value
Body mass index			0.29
<21	55 (8.4)	63 (9.6)	
21–25	226 (34.6)	255 (39.0)	
26–30	215 (32.9)	197 (30.1)	
≥31	158 (24.2)	139 (21.3)	
Vigorous physical activity, days per week			0.12
No	501 (76.5)	498 (75.9)	
1–2 days	37 (5.6)	28 (4.3)	
3–4 days	59 (9.0)	50 (7.6)	
5–7 days	58 (8.9)	80 (12.2)	
Moderate physical activity, days per week			0.33
No	204 (31.1)	184 (28.2)	
1-2 days	75 (11.5)	72 (11.0)	
3-4 days	143 (21.8)	131 (20.1)	
5-7 days	233 (35.6)	265 (40.6)	
Cigarette smoking			0.12
No	347 (53.1)	357 (54.5)	
Yes, Ever	285 (43.6)	261 (39.8)	
Yes, Current	21 (3.2)	37 (5.6)	
Alcohol drinking			0.54
No	291 (44.5)	286 (43.6)	
Yes	363 (55.5)	370 (56.4)	
Any contact with chickenpox patients in the past year			0.06
Don't Know	2 (0.3)	5 (0.8)	
No	646 (98.5)	633 (96.5)	
Yes	8 (1.2)	18 (2.7)	
Have a weakened immune system as told by doctors			<0.01
No	583 (88.9)	620 (94.5)	
Yes	73 (11.1)	36 (5.5)	
Trauma during the past 3 months			0.07
No	611 (93.1)	626 (95.4)	
Yes	45 (6.9)	30 (4.6)	
Surgery during the past 3 months			0.08
No	597 (91.0)	614 (93.6)	
Yes	59 (9.0)	42 (6.4)	
Sudden stressful event during the past 3 months			<0.01
No	335 (51.1)	460 (70.1)	
Yes	321 (48.9)	196 (29.9)	

The distribution of family history of HZ reported by cases and controls is presented in Table 4. Having any blood relative with a history of HZ was associated with a slightly increased risk of HZ after adjusting for race/ethnicity, contact with chickenpox in the past year, weakened immune system, surgery in the past 3 months, sudden stressful event in the past 3 months, liver disease within past 6 months, and cancer within past 6 months (adjusted OR = 1.37, 95% CI 1.05–1.79). Similar number of cases and controls reported any parent having a history of HZ (13.3% and 13.1% respectively in both groups, adjusted OR = 1.17, 95% CI 0.82–1.65). Neither cases nor controls reported having grandchildren with a history of HZ. The adjusted OR associated with having one and two categories of first order blood relatives with a history of HZ was 1.30 (95% CI: 0.97–1.73) and 2.53 (95% CI: 1.17–5.44), respectively. No one reported having all three categories of first order relative with a history of HZ. The association was stronger in the vaccinated group. Interestingly, the adjusted OR associated with having a non-blood relative with a history of HZ was also elevated, particularly among the group vaccinated with HZ vaccine (adjusted OR = 4.43, 95% CI 1.01–19.5 in the vaccinated group versus 0.79, 95% CI 0.29–2.19 in the unvaccinated group).

Discussion

We conducted a prospective, matched case-control study to investigate the possible association between family history of HZ and development of HZ among subjects 60 years and older. The HZ cases in the study were all incident cases and confirmed by PCR testing. The controls were concurrently identified from those who never developed HZ prior to the study and matched to the cases on age, sex, and HZ vaccination status. Our study is one of the largest to date to assess family history as a risk factor for HZ. We obtained detailed information on history of HZ for different categories of relatives, and also included non-blood relatives to serve as negative controls and to help dissect the role of differential recall as a source of bias in our results. Our study found a weak but significant association of family history as a risk factor for developing HZ. The consistent finding of a slightly increased risk of HZ associated with different relative categories could be explained by differential recall that is inherent in the case-control study design.

There have been a few studies from the United States (Hernandez et al., 2011; Hicks et al., 2008; Marin et al., 2016),

Table 3
Distribution of Comorbidities within past 6 Months for Herpes Zoster Cases and Their Matched Controls.

Comorbidities	Cases (n = 656) Number (%)	Controls (n = 656) Number (%)	P-value
Systemic lupus erythematosus (SLE)			1
No	652 (99.4%)	652 (99.4%)	
Yes	4 (0.6%)	4 (0.6%)	
Rheumatoid arthritis (RA)			0.78
No	631 (96.2%)	629 (95.9%)	
Yes	25 (3.8%)	27 (4.1%)	
Other autoimmune disorders, other than SLE or RA			0.02
No	655 (99.8%)	648 (98.8%)	
Yes	1 (0.2%)	8 (1.2%)	
Diabetes			0.12
No	506 (77.1%)	529 (80.6%)	
Yes	150 (22.9%)	127 (19.4%)	
Asthma			0.25
No	590 (89.9%)	602 (91.8%)	
Yes	66 (10.1%)	54 (8.2%)	
Skin allergy			0.19
No	562 (85.7%)	578 (88.1%)	
Yes	94 (14.3%)	78 (11.9%)	
Heart attack			0.54
No	642 (97.9%)	645 (98.3%)	
Yes	14 (2.1%)	11 (1.7%)	
Stroke			0.56
No	649 (98.9%)	651 (99.2%)	
Yes	7 (1.1%)	5 (0.8%)	
Crohn's disease			0.76
No	650 (99.1%)	651 (99.2%)	
Yes	6 (0.9%)	5 (0.8%)	
Depression			0.93
No	576 (87.8%)	577 (88.0%)	
Yes	80 (12.2%)	79 (12.0%)	
Kidney disease			0.71
No	594 (90.5%)	598 (91.2%)	
Yes	62 (9.5%)	58 (8.8%)	
Liver disease			0.09
No	649 (98.9%)	641 (97.7%)	
Yes	7 (1.1%)	15 (2.3%)	
Lung disease			0.58
No	614 (93.6%)	609 (92.8%)	
Yes	42 (6.4%)	47 (7.2%)	
Stomach disease			0.93
No	591 (90.1%)	590 (89.9%)	
Yes	65 (9.9%)	66 (10.1%)	
Cancer			0.03
No	608 (92.7%)	586 (89.3%)	
Yes	48 (7.3%)	70 (10.7%)	

Iran (Ansar et al., 2014), France (Lasserre et al., 2012), and Italy (Gatti et al., 2010), that investigated the possible association between family history of HZ and the risk of developing HZ. Hicks et al. first reported that cases were more likely than controls to report blood relatives with a history of HZ (39% vs. 11%, respectively). The authors also found a more than 13-fold increased risk associated with having multiple blood relatives and a 4.5-fold increase with having single blood relatives with a history of HZ. Less than 50% of the cases in the study were more than 60 years of age (Hicks et al., 2008). Subsequently, Hernandez et al. reported similar results with an OR of 4.44 for having a first degree relative with a history of HZ and an increased risk with multiple blood relatives. More than 43% of the HZ cases in that study reported having blood relatives with a history of HZ, compared to only 10.5% in the controls. The median age of the cases was 51.7 years (Hernandez et al., 2011). Ansar et al. conducted a similar study in Iran among subjects with an average age of 50 years and reached similar conclusions. More than 46% of the cases reported having relatives with a history of HZ, compared to only 12% reported by the controls (Ansar et al., 2014). The study by Lasserre et al. in

Table 4
Odds Ratio Estimations by Conditional Logistic Regression for Family History of Herpes Zoster, By Vaccination Status.

Categories	Vaccinated with HZ vaccine				Not vaccinated with HZ vaccine				Total population			
	Cases (328)	Controls (328)	Matched Odds Ratio[a]		Cases (328)	Controls (328)	Matched Odds Ratio[a]		Cases (656)	Controls (656)	Matched Odds Ratio[a]	
	Number (%)	Number (%)	Unadjusted	Adjusted[b]	Number (%)	Number (%)	Unadjusted	Adjusted[b]	Number (%)	Number (%)	Unadjusted	Adjusted[b]
Blood relative with zoster												
No	215 (65.5%)	226 (68.9%)	1	1	234 (71.3%)	257 (78.4%)	1	1	449 (68.4%)	483 (73.6%)	1	1
Yes	113 (34.5%)	102 (31.1%)	1.16 (0.84–1.60)	1.26 (0.86–1.83)	94 (28.7%)	71 (21.6%)	1.48 (1.03–2.13)	1.60 (1.05–2.45)	207 (31.6%)	173 (26.4%)	1.30 (1.02–1.66)	1.37 (1.05–1.79)
Parents												
No	269 (82%)	269 (82%)	1	1	300 (91.5%)	301 (91.8%)	1	1	569 (86.7%)	570 (86.9%)	1	1
Yes	59 (18%)	59 (18%)	1.00 (0.68–1.46)	1.29 (0.82–2.03)	28 (8.5%)	27 (8.2%)	1.04 (0.61–1.78)	1.08 (0.59–1.98)	87 (13.3%)	86 (13.1%)	1.01 (0.74–1.39)	1.17 (0.82–1.65)
Siblings												
No	290 (88.4%)	310 (94.5%)	1	1	297 (90.5%)	305 (93%)	1	1	587 (89.5%)	615 (93.8%)	1	1
Yes	38 (11.6%)	18 (5.5%)	2.25 (1.25–4.05)	2.54 (1.28–5.04)	31 (9.5%)	23 (7%)	1.36 (0.79–2.36)	1.42 (0.75–2.69)	69 (10.5%)	41 (6.3%)	1.78 (1.19–2.67)	1.80 (1.16–2.79)
Grandparents												
No	322 (98.2%)	321 (97.9%)	1	1	326 (99.4%)	320 (97.6%)	1	1	648 (98.8%)	641 (97.7%)	1	1
Yes	6 (1.8%)	7 (2.1%)	0.86 (0.29–2.55)	1.03 (0.31–3.46)	2 (0.6%)	8 (2.4%)	0.14 (0.02–1.16)	0.24 (0.02–2.46)	8 (1.2%)	15 (2.3%)	0.52 (0.22–1.25)	0.57 (0.23–1.45)
Children												
No	308 (93.9%)	312 (95.1%)	1	1	304 (92.7%)	316 (96.3%)	1	1	612 (93.3%)	628 (95.7%)	1	1
Yes	20 (6.1%)	16 (4.9%)	1.27 (0.64–2.49)	0.85 (0.40–1.84)	24 (7.3%)	12 (3.7%)	2.00 (1.00–4.00)	2.14 (0.95–4.79)	44 (6.7%)	28 (4.3%)	1.61 (0.99–2.61)	1.52 (0.90–2.57)
Uncle/Aunt/Cousin												
No	319 (97.3%)	318 (97%)	1	1	320 (97.6%)	319 (97.3%)	1	1	639 (97.4%)	637 (97.1%)	1	1
Yes	9 (2.7%)	10 (3%)	0.86 (0.29–2.55)	1.29 (0.36–4.61)	8 (2.4%)	9 (2.7%)	0.89 (0.34–2.30)	0.72 (0.24–2.18)	17 (2.6%)	19 (2.9%)	0.89 (0.45–1.74)	0.89 (0.43–1.84)
Number of categories of first order relative												
0	227 (69.2%)	241 (73.5%)	1	1	251 (76.5%)	272 (82.9%)	1	1	478 (72.9%)	513 (78.2%)	1	1
1	85 (25.9%)	81 (24.7%)	1.10 (0.78–1.55)	1.09 (0.73–1.63)	71 (21.6%)	50 (15.2%)	1.51 (1.02–2.24)	1.58 (1.01–2.47)	156 (23.8%)	131 (20%)	1.28 (0.98–1.67)	1.30 (0.97–1.73)
2	16 (4.9%)	6 (1.8%)	2.73 (1.06–6.99)	4.39 (1.48–13.1)	6 (1.8%)	6 (1.8%)	1.03 (0.33–3.22)	0.97 (0.25–3.82)	22 (3.4%)	12 (1.8%)	1.92 (0.95–3.89)	2.53 (1.17–5.44)
Any second order relative												
No	313 (95.4%)	312 (95.1%)	1	1	318 (97%)	312 (95.1%)	1	1	631 (96.2%)	624 (95.1%)	1	1
Yes	15 (4.6%)	16 (4.9%)	0.92 (0.40–2.08)	1.31 (0.51–3.34)	10 (3%)	16 (4.9%)	0.60 (0.26–1.37)	0.60 (0.22–1.60)	25 (3.8%)	32 (4.9%)	0.77 (0.45–1.32)	0.80 (0.45–1.43)
Non-blood relative with zoster												
No	316 (96.3%)	324 (98.8%)	1	1	319 (97.3%)	319 (97.3%)	1	1	635 (96.8%)	643 (98%)	1	1
Yes	12 (3.7%)	4 (1.2%)	3.67 (1.02–13.1)	4.43 (1.01–19.5)	9 (2.7%)	9 (2.7%)	1.00 (0.40–2.52)	0.79 (0.29–2.19)	21 (3.2%)	13 (2%)	1.63 (0.81–3.28)	1.30 (0.61–2.79)
Spouse with zoster												
No	298 (90.9%)	293 (89.3%)	1	1	305 (93%)	293 (89.3%)	1	1	603 (91.9%)	586 (89.3%)	1	1
Yes	30 (9.1%)	35 (10.7%)	0.85 (0.51–1.40)	0.80 (0.45–1.44)	23 (7%)	35 (10.7%)	0.65 (0.38–1.11)	0.65 (0.34–1.21)	53 (8.1%)	70 (10.7%)	0.74 (0.51–1.07)	0.74 (0.49–1.10)

[a] Matched on age (±1 year), sex, and date of vaccination (±3 months).
[b] Adjusted for race/ethnicity, contact with chickenpox in the past year, weakened immune system, surgery in the past 3 months, sudden stressful event in the past 3 months, liver disease within past 6 months, and cancer within past 6 months.

France found a positive association of HZ with family history with an OR of 3.7. The median age of the cases in the study was 67 years. About 37% of the cases and 20.4% of the controls reported having at least one relative with a history of HZ (Lasserre et al., 2012). On the other hand, Gatti et al., who used PHN cases in their study, reported no evidence of family history as a risk factor for HZ, as a considerable proportion of the cases (28.4%) and a similar percentage of the controls (29.6%) reported a family history of HZ. The average age of the subjects in the study was about 72 years (Gatti et al., 2010).

The proportion of cases reporting having a family history of HZ in previous studies ranged from around 28% to 46% for cases and from 10% to 35% for controls. The wide variation, especially in controls, could partially be explained by the age distribution of the study participants. The younger the participants were, the lower the proportion of having a family history of HZ, which is plausible as many of their relatives were also younger and at a lower risk for HZ. The mean age of cases and controls in our study was 73.3 years old. About 32% of the cases and 27% of the controls reported having blood relatives with a history of HZ. Compared to previous studies that reported a positive association, our study had a much higher proportion of controls who reported a family history of HZ because our participants were older. The proportion of cases reporting a family history of HZ in our study was lower than those from previous studies, even though the cases in our study were much older than those from previous studies. Besides recall bias, an alternative explanation for these inconsistent estimations is that the association between a family history of HZ and the development of HZ is age-dependent, i.e., early onset HZ may be more likely to be associated with a family history. Furthermore, the fraction of HZ attributable to any risk factor, including family history, likely declines with increasing decade of life since age is such a strong risk factor for HZ.

If family history of HZ is really a strong risk factor for HZ biologically, one would expect the OR to be greater for first order than second order relatives. In our study, the adjusted OR was 1.30 (95% CI: 0.97–1.73) and 2.53 (95% CI: 1.17–5.44) for having one and two categories of first order blood relatives with a history of HZ, and was 0.80 (95% CI 0.45–1.43) for having any other non-first order blood relatives with such a history. Similar to our study, Marin et al.'s study (mean age 65) estimated a modest odds ratio of 1.65, with a dose response trend (OR for having first and second order relatives with HZ was 1.87 and 0.81, respectively) (Marin et al., 2016). On the other hand, three previous studies reported similar high OR for having first and second order relatives with HZ (Ansar et al., 2014; Hernandez et al., 2011; Hicks et al., 2008), which is not consistent with biological plausibility. It is conceivable that some biases contributed to their estimations.

There were some potential limitations in our study. First, our cases were confirmed by PCR and interviewed face-to-face during the acute phase of the disease, while our controls were interviewed by phone. As such, cases likely had better recall about family history, while controls may have under-reported their family history. This could have inflated the odds ratio estimates. We conducted a post-hoc analysis to explore this possibility by breaking our matches and evaluating the association of the subset of zoster cases reporting family members who had zoster persisting at least 1 month. We expected that there would be less error in recalling family history in this subgroup, and indeed, we found no evidence of family history as a risk factor in this analysis. Second, we had differential participation between cases and controls which may have led to selection bias, especially among the vaccinated group. A family history of HZ is likely associated with getting vaccinated. There could be participation bias if those who had a family history of HZ, were vaccinated, and developed HZ were more likely to participate. This could possibly explain some high odds ratios we observed in the vaccinated group. Third, although family history of HZ is presumably associated with the number of relatives, we did not attempt to collect information regarding the number of relatives by category. However, it was unlikely that the family size would be significantly different between cases and controls. Finally, using the number of categories of first order relatives with a history of HZ as a proxy for estimating the total number of first order relatives with such history could potentially underestimate the association.

In conclusion, with a large number of HZ cases confirmed by PCR in this study, our results suggested only a weak association between the development of HZ and a positive family history of HZ among the elderly population.

Conflict of interest

Hung Fu Tseng and Steven Jacobsen report receiving research support from Novartis Vaccines and GSK. Others report no conflict of interest

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Disclaimer

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