Risk Factors for Herpes Zoster Among Adults

Mona Marin, Rafael Harpaz, John Zhang, Peter C. Wollan, Stephanie R. Bialek, and Barbara P. Yawn

1National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; 2Department of Research, Olmsted Medical Center, Rochester, Minnesota

Background. The causes of varicella-zoster virus reactivation and herpes zoster (HZ) are largely unknown. We assessed potential risk factors for HZ, the data for which cannot be obtained from the medical sector.

Methods. We conducted a matched case-control study. We established active surveillance in Olmsted County, Minnesota to identify HZ occurring among persons age ≥50 years during 2010–2011. Cases were confirmed by medical record review. Herpes zoster-free controls were age- and sex-matched to cases. Risk factor data were obtained by telephone interview.

Results. We enrolled 389 HZ case patients and 511 matched controls; the median age was 65 and 66 years, respectively. Herpes zoster was associated with family history of HZ (adjusted odds ratio [aOR] = 1.65); association was highest with first-degree or multiple relatives (aOR = 1.87 and 3.08, respectively). Herpes zoster was also associated with prior HZ episodes (aOR = 1.82), sleep disturbance (aOR = 2.52), depression (aOR = 3.81), and recent weight loss (aOR = 1.95). Stress was a risk factor for HZ (aOR = 2.80), whereas a dose-response relationship was not noted. All associations indicated were statistically significant (P < .05). Herpes zoster was not associated with trauma, smoking, tonsillectomy, diet, or reported exposure to pesticides or herbicides (P > .1).

Conclusions. We identified several important risk factors for HZ; however, the key attributable causes of HZ remain unknown.

Keywords. family history; herpes zoster; risk factors; shingles.

Herpes zoster (HZ) is caused by the reactivation of varicella-zoster virus (VZV) that establishes latency in sensory ganglia after initial infection as varicella. Herpes zoster is a painful and debilitating illness that affects approximately 1 in 3 persons during their lifetime [1]; its morbidity and impacts on quality of life increase with age [2–4]. Although it affects a large number of persons, with an estimated 1 million HZ cases annually in the United States, the causes of VZV reactivation and HZ are not completely known. Older age and immunosuppression are well documented risk factors, attributed to diminished VZV-specific cell-mediated immunity, but they cannot fully explain the epidemiology of HZ [5]. Several other potential risk factors have been evaluated but are unconfirmed or of insufficient prevalence to explain most episodes [5, 6]. Since 2006, a vaccine to prevent HZ has been available and recommended in the United States for use in immune-competent adults age ≥60 years [7, 8]. Other HZ vaccines are currently undergoing development.

An understanding of risk factors for HZ is vitally important. Improved awareness of epidemiological risk factors could help inform mechanistic understanding of VZV reactivation and HZ disease. In the context of HZ vaccines, observational studies of HZ vaccine performance cannot be properly evaluated without recognizing key risk factors to know whether their prevalence is balanced in vaccine recipients and nonrecipients. Furthermore, for unknown reasons, HZ rates have been increasing in the United States for decades [1, 9, 10]. These increases make it impossible to interpret HZ vaccine impact; indeed, HZ increase has made it challenging to interpret long-range clinical vaccine trials because these trials generally use historic controls for long-range follow up [11, 12]. Recognition of key risk factors for HZ could thus make trends interpretable and allow for better assessment of vaccine impact. In addition, a better understanding of these factors may suggest new approaches for prevention and treatment of HZ.

Although there is an enormous amount of literature relating to HZ risk factors, most studies have explored factors that can be assessed using medical records or administrative data [5, 8]. However, there are many plausible risk factors for HZ for which information would not typically be available in the medical sector. Given the important unknowns relating to HZ risk, we attempt to fill this gap by conducting an analysis of a large array of potential risk factors for HZ that are based on patient self-report.

METHODS

Study
We used a matched case-control study design. Herpes zoster cases were identified through active surveillance among residents of Olmsted County, aged ≥50 years, who had healthcare encounters for HZ with onset of HZ between January 1, 2010 and October 12, 2011. As previously reported [13], cases were identified within 72 hours of diagnosis, based on the International Classification of Diseases, Ninth Revision (ICD-9) codes of 053 using the Rochester Epidemiology Project (REP). The REP uses administrative data to link the diagnostic codes with
visits dates, basic demographic and procedure information for persons visiting clinics and hospitals associated with the healthcare providers in the County: ie, Olmsted Medical Center, Mayo Clinic, and Rochester Family Medical Clinic. All cases were confirmed by trained researchers who conducted medical record reviews, applying strict criteria to identify evidence of HZ: ie, documentation of a physician diagnosis of either acute HZ or acute HZ complication accompanied by a description of an acute onset of dermatomal pain and vesicular rash not attributed to other causes.

Controls were selected using ICD-9 codes from REP for residents of Olmsted County who sought non-HZ-related medical care at the same clinic and at the closest time before the HZ-related visit date in the matching case [13]. Controls were matched to case patients by date of birth (<1 year) and sex; intended matching was at least 1:1. Potential controls whose medical records showed evidence of HZ within 3 years of the rash onset date in the matching cases were excluded.

For both case patients and controls, data on potential HZ risk factors were collected by telephone interview conducted at approximately 21 days after rash onset (case patients) or within 6 months of the rash onset in the matching case (controls) and complemented with medical record review for vaccination status and medical history data, including immune status. When data on HZ vaccination were not found in the medical record or a participant reported vaccination not confirmed by medical record review, information from the Southeast Minnesota Immunization registry was considered the gold standard. This registry contains adult immunization data from all clinics and all large pharmacies in Southeast Minnesota and is estimated to include >96% of all adult immunizations in Olmsted County.

Potential risk factors were selected based on theoretical plausibility or on suggestive but controversial or inadequately verified prior work. They include the following: family history, previous episode of HZ, stress, injury/trauma, tonsillectomy, pesticide/herbicide exposure, smoking and secondhand smoking, diet, and weight loss (questions listed in Appendix). We also collected data on emotional functioning using the 8-item Patient Health Questionnaire depression scale (PHQ-8), an established valid diagnostic and severity measure for depressive disorders [14].

Analysis
Analyses were performed in SAS (version 9.3; SAS Institute Inc., Cary, NC). To evaluate the association between HZ and potential risk factors, we computed adjusted odds ratio (aOR) and confidence intervals using conditional regression for matched pair analysis controlling for age, sex, immune compromise, and vaccination status. Index date for controls was the rash onset date in the matching case. Immunocompromised were patients who, at the time of HZ onset/index date, had the following: hematological malignancies; hematopoietic or solid organ transplant within the 12 months before HZ onset/index date; acquired immune deficiency syndrome; treatments associated with immune compromise within 3 months of the onset of HZ (chemotherapy, radiation therapy, systemic immune-suppressive therapy, including chronic systemic use of ≥10 mg prednisone/day). Only persons who had received HZ vaccine >30 days before onset/index date were considered to be vaccinated.

For family history of HZ, we defined first-degree relatives as parents, siblings, and children; we defined nonfirst-degree relatives as grandparents, grandchildren, aunts, uncles, and cousins. If a participant indicated a first-degree and a nonfirst-degree relative, the participant was classified as having first-degree relatives. To assess the influence of different levels of stress, a “severe” stress category was created based on participants’ description of new or increased stress in the 3 months before HZ and included death, divorce, separation, major personal illness, major illness in a first-degree relative, and death of a close family member. To assess depression, a total score of 10 or greater for PHQ-8 was considered indicative of clinically significant depressive symptoms, as previously classified in the literature [14].

Human Subjects
The study was approved by the Institutional Review Boards at Olmsted Medical Center, Mayo Clinic, and the Centers for Disease Control and Prevention (Atlanta, GA). Consent was obtained from all participants; in addition, only persons with previous consent to participate in REP (>93% of all Olmsted County residents) were eligible to be controls.

RESULTS
A total of 389 case patients aged ≥50 years with confirmed HZ and 511 matched controls were included in the analysis. Median age of participants was 65 and 66 years for case patients and controls, respectively; more than half were female (Table 1).

Case patients were significantly more likely than controls to report blood relatives with a history of HZ (45% vs 35%; aOR = 1.65) (Table 2). When family history was further analyzed by degree of blood relation and number of relatives with HZ, we found a dose-response relationship (P < .001), with the risk being greatest for participants who reported first-degree relatives with HZ or multiple blood relatives with HZ. A family history of HZ did not appear to influence the likelihood of HZ vaccination among either case patients (16% of those with family history vs 22% of those without a family history were vaccinated), controls (34% vs 32%), or the total study population (25% vs 28%) (P > .1).

Case patients were significantly more likely than controls to report a previous episode of HZ (13% vs 9%; aOR = 1.82) (Table 2). Most commonly, participants had >20-year interval from the previous HZ episode (40% of case patients and 64% of controls) and were age ≥20 years at the previous HZ episode (90% of case patients and 95% of controls); for these 2 characteristics, differences between case patients and controls were not statistically
significant. Of the case patients who indicated site of previous HZ (39 of 51 case patients with previous HZ), 44% (17 of 39) reported same site for the current and previous HZ episodes. A similar proportion of participants with and without a reported previous episode of HZ received HZ vaccination (23% and 27%, respectively; P = .4). Both family history and a previous episode of HZ remained significantly associated with HZ when included together in a model, with basically no differences in the strength of the association compared with the univariable analysis results reported above.

Case patients were also significantly more likely than controls to report new or increased stress in the 3 months before HZ (54% vs 28%; aOR = 2.80) (Table 2). Although the rates of reporting stress were different between case patients and controls, the self-reported level of stress (on a scale from 0 [no stress] to 10 [worst stress imaginable]) was not: mean was 6.6 and 6.3, respectively, median was 7 for both. There was no dose-response relationship between HZ and severity of stress.

Case patients were significantly more likely than controls to report major changes in sleep—with resulting lack of sleep in the 3 months before HZ—recent weight loss, or depression (P < .0001). Because of the potential association of these factors with stress, we ran a model that included all 4 factors; all remained significant (Table 2).

We found no association between HZ and injury/trauma in the 3 months before HZ, neither any trauma nor trauma requiring medical attention (Table 2). In addition, we did not find a difference in the frequency of trauma specifically at the site of HZ (for case patients) or the body site where HZ occurred in case patients (for controls); 76% for each of the 74 case patients and 115 controls with trauma/injury in the past 3 months provided answers that allowed us to determine the site of trauma, and 36% (20 of 56) of case patients and 29% (25 of 86) of controls indicated trauma at the site of HZ or on the body site where HZ occurred in case patients (P = .380). We also found no association between HZ and recognition or diagnosis of new health conditions in the 3 months before HZ, tonsillectomy, self-assessed exposure to pesticides/herbicides, diet, or smoking. Exposure to secondhand smoke in the past 3 years was associated with HZ risk, but no dose relationship with the intensity of exposure was found.

**DISCUSSION**

We conducted an extensive analysis of plausible risk factors for HZ that are not readily studied using information routinely captured by the medical sector or documented in medical records. We found that both personal and family history of HZ, stress, sleep disturbance, depression, and recent weight loss were risk factors for HZ.

Personal history of previous HZ as a risk factor for current HZ is usually ignored, and recurrence of HZ is considered uncommon. Our results suggest otherwise, confirming the results of a higher rate of recurrent HZ reported by a previous publication in the same general study population [15], and they have policy implications. The Advisory Committee on Immunization Practices recommends vaccination of persons with prior history [8]. Our results suggest that persons with prior HZ remain at elevated risk and may indeed benefit from vaccination.

The role of family history as a risk factor is particularly important to understand to properly interpret HZ vaccine effectiveness. For instance, HZ vaccine uptake to date has been relatively modest in the United States. If persons with a family history, ie, personal experience with HZ, are especially motivated to receive the vaccine, this would lead to a higher HZ risk among persons receiving the vaccine, resulting in an underestimate of vaccine effectiveness. However, we also found no evidence in our study that persons with a family history of HZ were more likely to receive the vaccine, suggesting less of a concern for vaccine effectiveness evaluation. On the other hand, our findings suggest that physicians should focus particular attention for HZ vaccination of their patients who have a family history of HZ.

### Table 1. Characteristics of Participants

| Characteristic                                      | HZ Case patients (N = 389) | Controlsb (N = 511) | P Valuea |
|-----------------------------------------------------|----------------------------|---------------------|----------|
| Age at HZ diagnosis/index date (years)              | n (%)                      | n (%)               |          |
| Median (range)                                      | 65 (50–93)                 | 66 (50–94)          | .177     |
| 50–54                                               | 56 (14.4)                  | 66 (12.9)           |          |
| 55–59                                               | 67 (17.2)                  | 76 (14.9)           |          |
| 60–64                                               | 67 (17.2)                  | 89 (17.4)           |          |
| 65–69                                               | 55 (14.1)                  | 68 (13.3)           |          |
| 70–74                                               | 60 (15.4)                  | 88 (17.2)           |          |
| 75–79                                               | 32 (8.2)                   | 52 (10.2)           |          |
| 80–84                                               | 31 (8.0)                   | 43 (8.4)            |          |
| 85+                                                 | 21 (5.4)                   | 29 (5.7)            |          |
| Sex                                                  |                            |                     |          |
| Male                                                | 146 (37.5)                 | 179 (35.0)          | .179     |
| Female                                              | 243 (62.5)                 | 332 (65.0)          |          |
| Race                                                 |                            |                     |          |
| White                                               | 371 (95.8)                 | 480 (95.6)          | .687     |
| Immunocompromised at time of HZ diagnosis/index date |                            |                     |          |
| Yes                                                  | 36 (9.3)                   | 16 (3.1)            | <.0001   |
| No                                                   | 352 (90.7)                 | 494 (96.9)          |          |
| HZ vaccine                                           |                            |                     |          |
| Yes                                                  | 74 (19.1)                  | 166 (32.6)          | <.0001   |
| Noa                                                  | 313 (80.9)                 | 344 (67.4)          |          |

Abbreviations: HZ, herpes zoster.

a Not all participants responded to every question; therefore, the number of participants by characteristics does not always add to the total.

b The case-to-control ratio in the study population was as follows: 1:1 for 286 pairs, 1:2 for 85 pairs, 1:3 for 17 pairs, and 1:4 for 1 pair.

c P values calculated by Cochrane-Mantel-Haenszel test and matched pair analysis unless otherwise indicated.

d P value calculated by Wilcoxon rank-sum test.

e Includes participants vaccinated after HZ onset/index date: 15 case patients and 11 controls.
Table 2. Distribution of Case Patients and Controls According to Potential Risk Factors Examined and the Strength of the Associationa

| Characteristic                                      | Case Patients (N = 352) (n, %) | Controls (N = 494) (n, %) | aORb (95% CI) | P Value |
|-----------------------------------------------------|--------------------------------|---------------------------|---------------|---------|
| **Family history of HZ**                            |                                |                           |               |         |
| No                                                  | 206 (55.1)                     | 324 (64.8)                |               |         |
| Yes                                                 | 168 (44.9)                     | 176 (35.2)                | 1.65 (1.21–2.24) | .0015   |
| **Degree of blood relationc**                       |                                |                           |               |         |
| No family history                                   | 206 (55.1)                     | 324 (64.8)                | Ref           |         |
| Non-1st degree                                      | 17 (4.6)                       | 32 (6.4)                  | 0.81 (0.41–1.61) | .559    |
| 1st degree                                          | 151 (40.4)                     | 144 (28.8)                | 1.87 (1.34–2.60) | .0002   |
| **Single vs multiple relatives with HZd**           |                                |                           |               |         |
| No family history                                   | 206 (55.1)                     | 324 (64.8)                | Ref           |         |
| 1                                                   | 115 (30.8)                     | 145 (29.0)                | 1.39 (1.00–1.93) | .054    |
| ≥2                                                  | 53 (14.2)                      | 31 (6.2)                  | 3.08 (1.80–5.27) | <.0001  |
| **Previous episode of HZ**                          |                                |                           |               |         |
| No                                                  | 333 (86.7)                     | 464 (91.3)                |               |         |
| Yes                                                 | 51 (13.3)                      | 44 (8.7)                  | 1.82 (1.12–2.95) | .016    |
| **New/increased stress in the 3 mo before HZ**      |                                |                           |               |         |
| No                                                  | 178 (46.3)                     | 369 (72.2)                |               |         |
| Yes                                                 | 206 (53.7)                     | 142 (27.8)                | 2.80 (2.06–3.80)* | <.0001  |
| **New/increased severe stress in the 3 mo before HZ**|                                |                           |               |         |
| No                                                  | 330 (89.9)                     | 468 (94.5)                |               |         |
| Yes                                                 | 37 (10.1)                      | 27 (5.5)                  | 1.89 (1.09–3.28) | .024    |
| **New health conditions diagnosed or recognized in the 3 mo before HZ** |                                |                           |               |         |
| No                                                  | 288 (75.2)                     | 411 (80.8)                |               |         |
| Yes                                                 | 96 (24.8)                      | 98 (19.2)                 | 1.28 (0.91–1.81) | .159    |
| **Major changes in sleep with resulting lack of sleep in the 3 mo before HZ** |                                |                           |               |         |
| No                                                  | 305 (78.6)                     | 448 (88.2)                |               |         |
| Yes                                                 | 83 (21.4)                      | 60 (11.8)                 | 2.52 (1.67–3.83)* | <.0001  |
| **Depression (Personal Health Questionnaire [PHQ-8 depression score >10]** |                                |                           |               |         |
| No                                                  | 341 (88.1)                     | 492 (96.7)                |               |         |
| Yes                                                 | 46 (11.9)                      | 17 (3.3)                  | 3.81 (2.80–6.98)* | <.0001  |
| **Injury/trauma in the 3 mo before HZ**              |                                |                           |               |         |
| No                                                  | 311 (80.8)                     | 396 (77.5)                |               |         |
| Yes                                                 | 74 (19.2)                      | 115 (22.5)                | 0.82 (0.59–1.16) | .265    |
| **Injury/trauma requiring medical attention in the 3 mo before HZ** |                                |                           |               |         |
| No                                                  | 336 (92.3)                     | 470 (94.2)                |               |         |
| Yes                                                 | 28 (7.7)                       | 29 (5.8)                  | 1.21 (0.68–2.15) | .517    |
| **Ever smoked >100 cigarettes**                     |                                |                           |               |         |
| No                                                  | 207 (53.8)                     | 274 (53.8)                |               |         |
| Yes                                                 | 178 (46.2)                     | 235 (46.2)                | 1.05 (0.78–1.40) | .760    |
| **Number of years smoked**                          | Median (Q1, Q3)                | 20 (10, 30)               | 20 (10, 35) |         |
| Exposure to secondhand smoke in the past 3 y       |                                |                           |               |         |
| No                                                  | 254 (66.3)                     | 374 (74.1)                |               |         |
| Yes                                                 | 129 (33.7)                     | 131 (25.9)                | 1.44 (1.03–2.00) | .033    |
| Intensity of exposure to secondhand smokef         |                                |                           |               |         |
| No exposure                                         | 254 (67.2)                     | 374 (74.8)                | Ref           |         |
| Light                                               | 79 (20.9)                      | 80 (16.0)                 | 1.45 (0.98–2.14) | .063    |
| Moderate                                            | 20 (5.3)                       | 23 (4.6)                  | 1.41 (0.69–2.85) | .346    |
| Heavy                                               | 25 (6.6)                       | 23 (4.6)                  | 1.79 (.88–3.65) | .111    |
| **Ever exposure to pesticides/herbicides**         |                                |                           |               |         |
| No                                                  | 239 (61.6)                     | 316 (62.3)                |               |         |
| Yes                                                 | 149 (38.4)                     | 191 (37.7)                | 0.97 (.71–1.31) | .829    |
| **Tonsillectomy**                                   |                                |                           |               |         |
| No                                                  | 198 (60.2)                     | 305 (62.9)                |               |         |
| Yes                                                 | 131 (39.8)                     | 180 (37.1)                | 1.14 (.84–1.56) | .405    |
| **Description of diet before HZ**                   |                                |                           |               |         |
| Fair/Poor                                           | 123 (31.9)                     | 155 (30.5)                |               |         |
| Very good/Good                                      | 263 (68.1)                     | 354 (69.5)                | 1.03 (.76–1.40) | .842    |
Four of 5 previous studies (2 in the United States and 1 each in France, Iran, and Italy) that explored the relationship between family history and HZ consistently reported an association; however, the associations were stronger than what we report [16–19]. The different effect size across studies is to be expected because these studies are affected by recall bias and family structure (eg, for a large family the denominator will be larger, or if one lives close to most of the family the ascertainment may be better). Compared with the previous studies, we found a much higher proportion of controls that reported a family history of HZ (35% vs 10.5%–20%), whereas the proportion of case patients with a family history of HZ was within the range reported previously (45% vs 37%–48%). A dose-effect relationship was reported previously between risk for HZ and number of blood relatives with a history of HZ (classified as single vs multiple) [16, 17]. We found the same relationship but also documented a dose-effect relationship based on the closeness of the blood relation, whereby persons who have first degree relatives with HZ have a higher risk for HZ than persons who have nonfirst-degree relatives with HZ—a finding that heightens the role of family history in a person’s risk for HZ. The 1 study that did not find family history a risk factor for HZ included patients who reported with postherpetic neuralgia within 1 year from onset of acute HZ rather than patients presenting with HZ [20]. Postherpetic neuralgia adds an element of “noise,” whether due to less accurate ascertainment or different type of genetic predisposition, so it may be more likely to miss an association. In addition, age is a factor: the older the median age, the lower the attributable impact of genetics because of the increased importance of age as a risk factor. In the studies that found an association HZ-family history, the median age of case patients ranged from 52 to 67 years (including our study in which the median age was 65 years), whereas in the study that did not find an association, the median age of case patients was 72 years. Taken together, our findings regarding personal and family history as risk factors for HZ support the possibility (1) that genetics may play an important role in HZ risk [21, 22] and (2) that genetic analyses of HZ risk might be productive. On the other hand, genetics alone cannot explain the current epidemiology of HZ nor why rates appear to have been increasing over time [1, 9, 10].

Less consistency can be found in the literature regarding stress as a risk factor for HZ [18, 23–26]. We found stress in the 3 months before HZ to be a risk factor, but there was no evidence of a dose response (assuming that severe stress was more likely a risk factor than mild stress). Differences between studies may be due to recall bias and subjectivity in defining stress and levels of stress. Using a novel analysis method (self-controlled case series) and more specific criteria for stress (a catastrophic health event or death occurring to a spouse), validated by showing increased mental health visits, a recent study found no evidence that psychological stress triggers HZ [26]. Depressions as a risk factor for HZ warrants further investigation. In our study, depression was the factor with the strongest association with HZ risk. Studies suggested that depression may be influencing HZ risk through the same mechanism of decreasing the cell mediated immunity; depression was found to be associated with decline in VZV-specific cell-mediated immunity as measured by the VZV responder cell frequency [27, 28]. The negative findings also are instructive. We were not able to replicate the results of a previous study that reported a strong association (8- to 12-fold increased risk) between physical trauma at the same site as the rash and HZ [29]. Cigarettes, chemicals, pesticides, and fruit intake have been associated with HZ in some previous studies [5, 30], but we did not find an association in our study. We investigated tonsillectomy because the tonsils seem to be important in the natural history of primary varicella infection based on animal models [31, 32], and tonsillectomy was a common childhood procedure. We speculated

---

| Characteristic               | Case Patients (N = 352) (n, %) | Controls (N = 494) (n, %) | aOR\(^b\) (95% CI) | \(P\) Value |
|-----------------------------|-------------------------------|---------------------------|---------------------|------------|
| Servings of vegetables/day  |                               |                           |                     |            |
| Median (Q1, Q3)             | 2 (1, 3)                      | 2 (1, 3)                  |                     |            |
| Servings of fruits/day      |                               |                           |                     |            |
| Median (Q1, Q3)             | 2 (1, 3)                      | 2 (1, 3)                  |                     |            |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HZ, herpes zoster; Q1, lower quartile; Q3, upper quartile; Ref, Reference.

\(^{a}\) Not all participants responded to every question; therefore, the number of participants by characteristics does not always add to the total.

\(^{b}\) Calculated using conditional regression for matched pair analysis controlling for age, sex, vaccination status, and immune compromise.
that tonsillectomy might therefore modify patterns of VZV latency and subsequent development of HZ. We found no association; however, if tonsillectomy occurred after the varicella had occurred, it should no longer influence HZ.

Although the use of survey methods allowed us to explore a large array of factors that could not be assessed using other methods, self-reported data come with limitations. In particular, recall bias or misclassification were possible, especially for events that may have occurred many years ago. Differential bias between case patients and controls was possible regarding recall of or even knowing about blood relatives with a history of HZ or other factors because case patients are usually more motivated to try and recall exposure that could explain their condition. In addition, several factors involved subjectivity in assessment of exposure. We considered depression as a risk factor for HZ rather than a consequence because the survey asked about its presence upon or soon after rash onset. We controlled for immune compromise in analysis. However, we performed a sensitivity analysis without immunocompromised participants included, and the aORs were generally ±10% of those presented. The community where we conducted the study is predominantly white, with many working in the health sector, and this raises questions on generalizability. However, in the context of assessing risk factors, homogeneity is a benefit (assuming no biological interaction) because there is less possibility of confounding. The fairly high age in our study might have led to a lower effect size or reduced our ability to identify nonage risk factors.

CONCLUSIONS

We conducted a hypothesis-generating scan of a large range of self-reported potential risk factors for HZ, and we were able to study several unexplored factors that now seem less likely to play a prominent role in the development of HZ. We also identified several factors that do seem important and that warrant additional exploration. Nonetheless, it is unlikely that any of the factors that we identified account for an important portion of the burden of HZ in the general population. The factors that distinguish the large number of immunocompetent persons who develop HZ during their lives from those who do not remain unknown.

Acknowledgments

We thank Marge Kurland, Linda Paradise, Karen Isthiani, and Dr. Christine Pilon for their work in collecting data and interviewing participants, the staff at the Rochester Epidemiology Project for identifying and matching controls, and all participants for responding to interview questions.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Financial support. This study was funded by the Centers for Disease Control and Prevention with funds from the American Recovery and Reinvestment Act of 2009. In addition, the study used the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health.

Potential conflicts of interest. B. P. Y. has served in the Advisory committees related to herpes zoster vaccines for both Merck and GSK and has received research grants from Merck. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Yawn BP, Saddier P, Wollan PC, et al. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc 2007; 82:1341–9.
2. Yawn BP, Inzler RE, Wollan PC, et al. Health care utilization and cost burden of herpes zoster in a community population. Mayo Clin Proc 2009; 84:787–94.
3. Stein AN, Britt H, Harrison C, et al. Herpes zoster burden of illness and health care resource utilisation in the Australian population aged 50 years and older. Vaccine 2009; 27:520–9.
4. Drolet M, Brisson M, Schmader KE, et al. The impact of herpes zoster and post-herpetic neuralgia on health-related quality of life: a prospective study. CMAJ 2010; 182:1731–6.
5. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis 2004; 4:26–33.
6. Joesoef RM, Harpaz R, Leung J, Bialek SR. Chronic medical conditions as risk factors for herpes zoster. Mayo Clin Proc 2012; 87:961–7.
7. Ozman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005; 352:271–84.
8. Harpaz R, Ortega-Sanchez IR, Seward JE. Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57:1–30; quiz CE2–4.
9. Leung J, Harpaz R, Molinari NA, et al. Herpes zoster incidence among insured persons in the United States, 1993–2006: evaluation of impact of varicella vaccination. Clin Infect Dis 2011; 52:332–40.
10. Ragozzino MW, Melton Ll III, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore) 1982; 61:310–6.
11. Merck Sharp & Dohme Corp. Zostavax [European public assessment reports–product information]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000674/WC500053462. pdf. Accessed 16 June 2016.
12. Hales CM, Harpaz R, Ortega-Sanchez IR, et al. Update on recommendations for use of herpes zoster vaccine. MMWR Morb Mortal Wkly Rep 2014; 63:729–31.
13. Marin M, Yawn BP, Hales CM, et al. Herpes zoster vaccine effectiveness and manifestations of herpes zoster and associated pain by vaccination status. Hum Vacc Immunother 2015; 11:1157–64.
14. Kroenke K, Strine TW, Spitzer RL, et al. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2008; 114:635–43.
15. Yawn BP, Wollan PC, Kurland MJ, et al. Herpes zoster recurrences more frequent than previously reported. Mayo Clin Proc 2011; 86:88–93.
16. Hicks LD, Cook-Norris RH, Mendoza N, et al. Family history as a risk factor for herpes zoster: a case-control study. Arch Dermatol 2008; 144:603–8.
17. Hernandez PO, Javed S, Mendoza N, et al. Family history and herpes zoster risk in the era of shingles vaccination. J Clin Virol 2011; 52:344–8.
18. Lasserre A, Blazeeza F, Gorwood P, et al. Herpes zoster: family history and psychological stress-case-control study. J Clin Virol 2012; 55:153–7.
19. Ansar A, Farschvian M, Ghasemzadeh M, Sobhan MR. Association between family history and herpes zoster: a case-control study. J Res Health Sci 2014; 14:111–4.
20. Gatti A, Pica P, Boccia MT, et al. No evidence of family history as a risk factor for herpes zoster in patients with post-herpetic neuralgia. J Med Virol 2010; 82:1007–11.
21. Hampa M, Nurmakko T, Hurme M. Polymorphism of the IL-10 gene is associated with susceptibility to herpes zoster. Scand J Infect Dis 2002; 34:112–4.
22. Cho JW, Shin DH, Lee KS. Polymorphism of the IL-10 gene is associated with susceptibility to herpes zoster in Korea. J Dermatol Sci 2007; 45:213–5.
23. Schmader K, George LK, Burchett BM, et al. Race and stress in the incidence of herpes zoster in older adults. J Am Geriatr Soc 1998; 46:973–7.
24. Schmader K, George LK, Burchett BM, Pieper CF. Racial and psychosocial risk factors for herpes zoster in the elderly. J Infect Dis 1998; 178(suppl 1):567–70.
25. Schmader K, Studenski S, MacMillan J, et al. A stressful life event modifies risk factors for herpes zoster? J Am Geriatr Soc 1990; 38:1188–94.
26. Harpaz R, Leung JW, Brown CJ, Zhou FJ. Psychological stress as a trigger for herpes zoster: might the conventional wisdom be wrong? Clin Infect Dis 2015; 60:781–5.
27. Irwin MR, Levin MJ, Carrillo C, et al. Major depressive disorder and immunity to varicella-zoster virus in the elderly. Brain Behav Immun 2011; 25:599–66.
28. Irwin M, Costlow C, Williams H, et al. Cellular immunity to varicella-zoster virus in patients with major depression. J Infect Dis 1998; 178(suppl 1):S104–8.
Questions asked to inquire about potential risk factors for herpes zoster

1. Ever family history of shingles? Yes No
   If yes, who (relationship) _____________

2. Ever previous episode of herpes zoster? Yes No
   If yes, describe where on body ________________
   When __________

3. In the past 3 months, new or increased stress? Yes No
   If yes, describe ________________
   Level of stress 3 months before shingles: 0=no stress to 10=worst stress imaginable __________

4. In the past 3 months, new conditions diagnosed or recognized? Yes No
   If yes, describe ________________

5. In the past 3 months, major changes in sleep with resulting lack of sleep? Yes No
   If yes, describe ________________

6. In the past 3 months, injury or trauma that left bruises or lumps, marks or scars? Yes No
   If yes, describe site (location by body part and side) ________________
   When __________

7. In the past 3 months did any of these injuries or trauma require medical attention? Yes No
   If yes, describe site (location by body part and side) ________________
   When __________

8. Have you ever smoked more than 100 cigarettes? Yes No
   # of years smoked __________

9. Exposure to secondhand smoke in the past 3 years? Yes No
   If yes, overall would you consider it: Light Moderate Heavy

10. Ever exposure to pesticides or herbicides? Yes No
    If yes, thinking about of the times you were exposed, would you say that your total exposures was: Light Moderate Heavy

11. Have you ever had your tonsils removed? Yes No

12. Thinking about before you got the shingles, how would a dietitian describe your diet?
    (a) Very good Good Fair Poor
    (b) How many servings of vegetables a day ______
    (c) How many servings of fruits a day ______

13. Have you lost weight recently? Yes No
    If yes, before your shingles? Yes No