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Risk Factors for Herpes Zoster: A Systematic Review and Meta-analysis

Kosuke Kawai, ScD, and Barbara P. Yawn, MD, MSc, MSPH

Abstract

Objective: To systematically review studies examining risk factors for herpes zoster (HZ).

Methods: We performed a literature search using PubMed, EMBASE, and Web of Science for articles published from January 1, 2003, to February 1, 2017. A random-effects model was used to summarize the risk ratio (RR) or odds ratio (OR) and 95% CI.

Results: Of the 3450 studies screened, we included 84 studies in the systematic review and conducted meta-analysis in 62 studies. Women were at increased risk of HZ compared with men (pooled adjusted RR, 1.31; 95% CI, 1.27-1.34). Black individuals had almost half the risk of HZ as white individuals (pooled RR, 0.54; 95% CI, 0.47-0.63). Family history was found to be a risk factor for HZ (pooled OR, 3.59; 95% CI, 2.39-5.40). Autoimmune diseases, including rheumatoid arthritis (pooled RR, 1.67; 95% CI, 1.41-1.98) and systemic lupus erythematosus (pooled RR, 2.10; 95% CI, 1.40-3.15), were associated with an elevated risk of HZ. Other comorbidities were associated with an increased risk of HZ, with the pooled RRs ranging from 1.25 (95% CI, 1.13-1.39) for asthma to 1.30 (95% CI, 1.17-1.45) for diabetes mellitus and 1.31 (95% CI, 1.22-1.41) for chronic obstructive pulmonary disease.

Conclusion: Our review revealed that female sex, race/ethnicity, family history, and comorbidities are risk factors for HZ. Efforts are needed to increase the uptake of zoster vaccination.

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From the Clinical Research Center, Boston Children's Hospital and Harvard Medical School, Boston, MA (K.K.); Department of Family Medicine and Community Health, University of Minnesota, Blaine, MN (B.P.Y.).

After a primary infection causing varicella (chickenpox), varicella-zoster virus (VZV) establishes latency in sensory ganglia and can reactivate later in life to cause herpes zoster (HZ) (shingles).[1] Herpes zoster causes a painful, blistering rash and can lead to postherpetic neuralgia (PHN), a persistent painful complication, particularly common in older patients.[2-4] Postherpetic neuralgia can substantially impair the physical, psychological, and social functioning aspects of patients' lives.[5] Patients with HZ can also experience other non–pain-related complications including HZ ophthalmicus with eye involvement.[6] Further, recent studies have found that HZ is associated with an increased risk of stroke in the first 3 months following shingles.[7] The incidence rate of HZ in the general population is between 3 and 5 per 1000 person-years, with a similar incidence reported in North America, Europe, and Asia-Pacific.[8] The incidence of HZ has increased over the past several decades independent of the aging demographic.[8-10] Further, the public health burden of HZ is expected to increase with the aging population across the world.

Well-recognized risk factors for HZ are age and immunocompromising conditions as cell-mediated immunity declines.[11,12] The risk of HZ is markedly increased with older age. The age-specific incidence rate is approximately 6 to 8 per 1000 person-years in adults at 60 years of age and 8 to 12 per 1000 person-years in adults at 80 years of age.[8] Further, the risk of HZ is elevated in patients with immunocompromising conditions, including bone marrow or solid organ transplant, hematologic and solid malignancies, and human immunodeficiency virus/AIDS.[12] Immunosuppressive medications, such as chemotherapy, high-dose corticosteroids, and biologic agents, are also known to increase the risk of HZ.[12] A live attenuated zoster vaccine is indicated for the prevention of HZ.[13] The US Advisory Committee on Immunization Practices currently recommends vaccination in adults ≥60 years of age and older.[12] A live attenuated zoster vaccine is contraindicated in immunocompromised patients or those

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receiving immunosuppressive therapy. A new adjuvanted zoster subunit vaccine has recently shown promising results in immunocompetent older adults and was approved by the US Food and Drug Administration.[14,15] The vaccine is also currently being evaluated in immunocompromised individuals.

Better understanding of risk factors for HZ may provide valuable information for health care professionals to identify patients at heightened risk at all ages and could help formulate appropriate policy for vaccination strategy potentially targeted by factors other than age. A previous (2004) systematic review by Thomas and Hall[11] revealed age and immunosuppression as important risk factors but highlighted a lack of general understanding about determinants of HZ. Since then, numerous studies have investigated risk factors for HZ. The objective of our study was to systematically review studies examining risk factors for HZ and discuss implications based on the updated evidence.

METHODS

Literature Search

We performed a literature search using PubMed, EMBASE, and Web of Science. We used the following search strategy using PubMed: Medical Subject Headings (MeSH) for *herpes zoster* or the title terms for *zoster* or *shingles* in combination with the MeSH terms for *risk*, *incidence*, *odds ratio*, or *proportional hazards models* or the title/abstract terms for *risk*, *odds ratio*, *proportional hazards*, *hazard ratio*, *incidence*, or *association*. We used the similar search strategy for EMBASE and Web of Science. Our study built on the prior systematic review by Thomas and Hall.[11] Thus, we searched literature published between January 1, 2003, and February 1, 2017. We also manually searched the references cited by the retrieved articles and review articles for additional references.

Inclusion and Exclusion Criteria

Two investigators (K.K. and B.P.Y.) reviewed publications and selected eligible articles. We included studies that examined risk factors for HZ and reported measure of associations. We included only studies that evaluated the incidence of HZ. Only full-text articles in English were included. We excluded studies limited to children (≤18 years of age), immunocompromised populations (eg, bone marrow or solid organ transplant, hematologic and solid malignancies, and human immunodeficiency virus/AIDS), or other specific clinical groups. Conference abstracts, review articles, case series, and animal studies were also excluded.

Data Extraction and Quality Assessment

We collected information regarding authors, publication year, settings, study design, study population, outcome definition, measures of association, and adjusted confounding factors. In order to assess the quality of included observational studies, we evaluated study design, outcome definition, and adequate adjustment of confounding factors.

Statistical Analyses

We used a random-effects model to estimate the pooled risk ratio (RR) or odds ratio (OR) and 95% CI. The natural logarithms of the RRs and their corresponding SEs from individual studies were used to compute the pooled estimates. For studies that utilized the same data set from the same period, we included only one of the studies in the meta-analysis. We also assessed the I^2 statistic, which estimates the proportion of the total variation among studies due to heterogeneity rather than chance. As a subgroup analysis, we also examined the pooled estimates by study design (ie, cohort vs case-control studies). Publication bias was assessed by inspecting the asymmetry of a funnel plot and performing the Begg rank correlation test and the Egger regression test. All statistical analyses were conducted using Stata (StataCorp) and R, version 3.1.1 (R Project for Statistical Computing) statistical software.

RESULTS

Study Characteristics

Of the 3450 studies screened, we included 84 observational studies in the systematic review and conducted meta-analysis in 62 studies (Supplemental Figure, available online at http://www.mayoclinicproceedings.org). There were 27 studies that examined sex as a risk factor for HZ (Supplemental Table, available online at http://www.mayoclinicproceedings.org).[3,10,11,16-39] The characteristics of 43 studies that examined race/ethnicity, family