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REVIEW

Herpes zoster as a marker of occult cancer: A systematic review and meta-analysis

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Summary *Objectives:* Researchers have advocated for an increased awareness of occult cancer among herpes zoster patients, but there are no systematic reviews to support these claims. We therefore conducted a systematic review and meta-analysis of evidence on zoster and risk of occult cancer.
Methods: Through February 18, 2016, we searched PubMed, EMBASE and references of relevant papers for studies on zoster and risk of any cancer. One author screened retrieved papers by title and abstract; included papers were reviewed by two authors for eligibility, data extraction, and potential biases. Despite statistical heterogeneity, associations were consistently in the same direction and we therefore computed pooled relative risks using random-effects models.
Results: We identified 46 eligible studies, 10 of which considered all cancer types combined. The pooled relative risk for any cancer was 1.42 (95% confidence interval: 1.18, 1.71) overall and 1.83 (95% confidence interval: 1.17, 2.87) at one year after zoster. Considering cancer subtypes, the highest estimates were generally reported for occult hematological cancer. The absolute risk of any cancer at one year after presentation with zoster was 0.7—1.8%.
Conclusion: This study supports an association between zoster and occult cancer, but the low absolute risk of cancer limits the clinical implications.

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Introduction

Herpes zoster is characterized by a unilateral vesicular rash that is accompanied by severe neuralgia.[1,2] It is caused by reactivation of the varicella-zoster virus, which lies dormant in the sensory ganglia following the primary infection, chickenpox.[1,2] The risk of reactivation increases with age and it is estimated that up to 50% of people who live up to 85 years will develop herpes zoster.[1]

Several large population-based studies have suggested that patients with herpes zoster have an increased risk of occult cancer.[3–7] These findings have instigated discussion of whether patients with herpes zoster should be examined for cancer in order to expedite diagnosis and ultimately improve prognosis.[3,4,7–9] Although such discussions should rely on a sound evidence base, no systematic review exists of studies on the topic. In particular, the types of cancers that are most likely to be associated with reactivation of latent varicella-zoster virus are yet to be uncovered systematically.

The aim of this systematic review was to collate evidence on the association between herpes zoster and the risk of subsequent cancer diagnosis. Because the primary interest was occult cancer, the main focus was on cancer diagnosed in the first year following herpes zoster compared with persons without herpes zoster. As a secondary aim, we specifically examined which cancer types are most strongly associated with herpes zoster.

Materials and methods

Search strategy and eligibility criteria

We conducted the study according to The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[11] (Web Methods 1 and 2). We formulated the study protocol (available from study authors upon request) in accordance with PRISMA for protocols,[12,13] with slight modifications to increase applicability to the non-interventional subject under consideration.

In collaboration with a trained librarian, we performed a comprehensive literature search of the MEDLINE (PubMed) and EMBASE electronic databases to identify studies published on the association between herpes zoster and cancer before February 1, 2015 (Web Methods 3 outlines the search strings). We also searched reference lists of eligible articles to identify further potentially relevant studies. On February 18, 2016, we updated the search.

Studies were eligible for inclusion if (1) herpes zoster was included as an exposure or predictor, (2) the outcome was overall cancer or one or more specific subtypes of cancer, and (3) a control group was included, i.e., controls without cancer in case-control studies or a comparison cohort without herpes zoster or a similar reference population (e.g., a general population sample) in cohort studies. We did not consider myelodysplastic and myeloproliferative syndromes not classified as neoplasms in the 10th revision of the International Classification of Diseases by the World Health Organization. We imposed no restrictions to publication year, study population or setting (inpatients, outpatients, or general practice), design, eligibility criteria, length of follow-up, or statistical analyses applied. Besides English language papers, we aimed to include publications in other languages known by the authors or by consulting colleagues. Meeting abstracts or studies published as abstract only were not eligible.

Study selection and data extraction

One investigator (SAJS) performed the initial screening of titles and abstracts and retrieved full-text reports of potentially eligible studies. Subsequently, two investigators (SAJS, AM) performed independent eligibility assessment of the retrieved reports using the eligibility criteria listed above. The two authors also performed data extraction by using a piloted data abstraction sheet including the following data: author, journal, publication year, study design, setting, study period, eligibility criteria, study size, age and sex distribution, data source for herpes zoster, data source for cancer diagnosis, comparator group (description of standard population or comparison cohort in cohort studies or controls in case-control studies), length of follow-up, type of relative risk estimate, statistical method used (e.g., logistic regression), maximum variables controlled for, and the maximally adjusted estimate for cancer overall, cancer subtype, and time points considered. When effect estimates were unobtainable, we extracted the raw data. As a measure of precision, we obtained 95% confidence intervals (CIs). When the 95% CI for an estimate was not reported, we retrieved the standard error, the exact p-value, estimation from a figure/graph, or raw data, listed in order of priority. Any disagreements between reviewers were resolved by consensus. When data was unreported or unclear, we sought to contact the corresponding author for clarification. Where multiple overlapping publications were included after the initial eligibility assessment, we agreed to use the most recent and inclusive report.

Risk of bias assessment

There is no consensus regarding the use of scoring tools for assessing risk of bias in non-randomized studies.[11] We therefore identified key design elements that could potentially bias study estimates, including sources of potential selection bias (non-participation in case-control studies, use of hospital controls in case-control studies, and loss to follow-up in cohort studies), information bias (self- or proxy-report of herpes zoster, and potential misclassification of herpes zoster or cancer), and lack of control for age and/or sex. The two reviewers performed the risk of bias assessment independently.

Statistical analyses

We illustrated the results for individual studies graphically using forest plots for each outcome. We considered measures of relative risk (odds ratios, risk ratios, rate ratios, hazard ratios) to be equivalent. Although this assumption is suboptimal compared with pooling individual-level data (not available), we considered the measures equivalent