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Review

The incidence of human papillomavirus infection following treatment for cervical neoplasia: A systematic review

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HIGHLIGHTS

- Women with post-treatment HPV have a higher risk of subsequent cervical precancer.
- This review of post-treatment HPV included nearly 2000 women from 25 studies.
- Post-treatment HPV incidence ranged from 0 to 47% in up to 3 years of follow-up.

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ABSTRACT

Objective. To systematically review the published literature in order to estimate the incidence and describe the variability of human papillomavirus (HPV) infection in women following treatment for cervical neoplasia.

Methods. Several scientific literature databases (e.g. PubMed, ISI Web of Science) were searched through January 31, 2012. Eligible articles provided data on (i) baseline HPV infection status within 6 months prior to or at time of treatment (pre-treatment); and (ii) HPV test results for women's first visit after treatment occurring within 36 months (post-treatment). We abstracted and summarized the post-treatment incidence of newly detected HPV genotypes that were not present at pre-treatment, overall and stratified by study and other population characteristics.

Results. A total of 25 studies were included, reporting post-treatment HPV incidence in nearly 2000 women. Mean patient age ranged from 31 to 43 years (median 36). Most studies used cervical exfoliated cell specimens to test for HPV DNA (n = 20; 80%), using polymerase chain reaction (n = 21; 84%). Cervical neoplasia treatment included loop electrical excision procedure (n = 11; 44%); laser conization (n = 2; 8%); laser ablation, surgical conization, cryotherapy, alpha-interferon (n = 1; 4% each); or multiple treatment regimens (n = 8; 32%). Follow-up times post-treatment ranged from 1.5 to 36 months (median 6). More than half of studies (n = 17; 68%) estimated the incidence of any HPV type following treatment, while 7 (28%) focused specifically on high-risk (HR) HPV. HPV incidence after treatment varied widely, ranging from 0 to 47% (interquartile range: 0%-15%) in up to 3 years of follow-up after treatment. Lower HPV incidence was observed among studies that included relatively younger women, used laser conization, focused on HR-HPV rather than overall HPV infection, and had a lower proportion of recurrent cervical disease.

Conclusions. These modest summary incidence estimates from the published literature can guide clinicians, epidemiologists and health economists in developing best practices for post-treatment cervical cancer prevention.

Contents

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Introduction

Cervical cancer remains a leading cause of morbidity and mortality in women worldwide [1,2]. It is caused by the acquisition and persistence of high-risk (oncogenic) types of human papillomavirus (HR-HPV) infection and the subsequent malignant transformation of cervical epithelial cells [3]. To prevent progression of these cervical precancerous lesions to invasive cancer, women with cervical intraepithelial neoplasia (CIN) grade 2/3 are commonly treated using ablative and excisional treatment modalities such as laser ablation, loop electrical excision procedure (LEEP), cryotherapy, and cold-knife conization [4]. Women previously treated for CIN 2/3 and those with HR-HPV infections post-treatment have an increased risk of subsequent high-grade neoplasia and invasive cervical cancer as compared with women in the general population [5–8].

Recurrent CIN may result from the inadequate treatment of precancerous cervical lesions or treatment failure, re-infection with an HR-HPV type, incomplete removal of latent HPV infections or long-term persistence of HR-HPV infections not associated with the previously treated cervical lesion [9–11]. Therefore, continued monitoring of women following cervical treatment is currently recommended. American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines recommend follow-up HPV testing at 6 to 12 months for women treated for CIN 2/3 [4], since women at highest risk for recurrent cervical disease are those with positive post-treatment HPV test results [12]. Post-treatment screening with cytology alone, or in combination with colposcopy, at 6-month intervals are alternative recommended approaches [4].

Despite the growing use of HPV testing for post-treatment follow-up, there are currently no summary data on the burden of newly detected HPV infections following treatment for CIN. Therefore, we conducted a systematic literature review to describe study- and population-specific factors that may contribute to the magnitude and variability of estimates of HPV incidence following cervical treatment. The focus of this review is on newly detected HPV genotypes that were not detected prior to or at cervical treatment, which most likely represent newly acquired or newly reactivated latent infections, as opposed to type-specific re-infection or infections associated with incomplete excision of precancerous lesions.

Methods

Literature search strategy

We searched PubMed, EMBASE, ISI Web of Science, Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) through January 31, 2012 without date or language restrictions to identify peer-reviewed articles reporting incident HPV data from women treated for HPV-associated cervical neoplasia. Our keyword search was designed in consultation with a reference librarian at the University of North Carolina Health Sciences Library. The search contained a combination of terms including HPV (i.e., HPV, papillomaviridae, human papillomavirus, papillomavirus infection), cervical neoplasia (i.e., cervical neoplasms, cervical cancer, cervical neoplasia, cervical intraepithelial neoplasia), occurrence (i.e., incidence, newly detected, persistence, clearance, duration, epidemiology, cohort study), and treatment- or screening-related terms (i.e., post-treatment, follow-up, over time, long-term, therapeutics, cryotherapy, LEEP, laser, and colposcopy).

Citations were imported into a reference managing software program (EndNote X5, Thomson Reuters) and duplicate citations were removed. Backward citation tracking was used to ensure appropriate keywords were selected for the literature search and resulted in modification of these terms followed by an updated search of databases. Titles and abstracts of search results were selected for full-text evaluation with respect to two inclusion criteria: (i) women receiving treatment for cervical neoplasia; and (ii) post-treatment HPV acquisition data.

Eligibility criteria

Eligible articles provided data on HPV infection within 6 months prior to or at time of treatment (i.e., pre-treatment time point) and incident HPV detection occurring during follow-up, with the first follow-up visit with HPV test results occurring within the first 36 months post-treatment. Thus, it must have been clear in the article that an HPV infection was newly detected in the post- compared to pre-treatment period. The majority of results were type-specific, based on HPV genotyping assays, although four studies used non-type-specific Hybrid Capture II among pre-treatment HPV-negative women, where a positive result would indicate a new HPV type.

Studies of women with human immunodeficiency virus (HIV) infection were only included if HPV data were available on the HIV-negative subpopulation. Articles that did not state HIV serostatus were assumed to be HIV-negative and thus included. Studies that included women treated for invasive cervical carcinoma (ICC) in their study population were included only if HPV data were also available on the subset of women treated for earlier stages of CIN. Studies that tested for cervical HPV infections using polymerase chain reaction (PCR) and hybrid capture DNA were included. HPV serology-only studies and studies that included only anal, vulvar or labial specimens were excluded. Studies that reported exclusively on men, oral HPV infection or oral cancer, animal studies, or simulation studies were ineligible.

Data abstraction

From articles meeting our inclusion criteria, we abstracted data on study characteristics, participants, cervical treatment type, and pre- and post-treatment HPV infection and testing. Study characteristics included journal of publication, publication date, study dates, study design, geographic region, and sample size. Participant characteristics included age and population description (e.g., clinical patients,