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Prevalence and distribution of human papillomavirus genotypes in Chinese women between 1991 and 2016: A systematic review

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ABSTRACT

Background: Human papillomavirus (HPV) associated cervical cancer is one of the most common cancers and ranked as the eighth most common killer for Chinese women. A dozen of HPV vaccines are being developed in China without a solid China-specific distribution of carcinogenic HPV types, thus, we performed this systematic review to explore the China-specific spectrum of high-risk types causing cancer. Methods: Studies on HPV infection among Chinese women were searched. All retrieved articles were screened and reviewed by a standardized algorithm. Distribution of carcinogenic HPV types and age-specific prevalence were analyzed using random-effects model.

Results: A total of 303 articles were included in the final analysis. The top 10 common HPV types detected in ICC patients, in descending order of frequency, were HPV 16 (62.5%), 18 (12.4%), 58 (8.6%), 52 (5.7%), 33 (4.6%), 31 (3.5%), 55 (2.4%), 68 (2.4%), 53 (2.2%) and 45 (2.0%) respectively. Similar spectrum was found in women with precancer. The prevalence of HPV infection peaked between 20 and 24 years with a rate of 24.3%, thereafter declined substantially and stabilized at middle-ages. Compared to women living in the developed provinces, the second peak was observed among women aged 45–55 years in less developed regions.

Conclusion: In general, the spectrum of HPV types in women with precancer/cancer and the pattern of age-specific prevalence were consistent with that of elsewhere worldwide. However, some distinguished characteristics could also be concluded, and these imprinting should be considered and integrated when developing vaccines and strategy for disease control in China.

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Introduction

Worldwide, cervical cancer is recognized as the fourth most common cancer in women and the seventh most common cancer overall. In terms of the latest National Cancer Statistics, cervical cancer became the No. 8 killer for Chinese women. 1 It is very clear

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that the human papillomavirus (HPV) is the primary cause of cervical cancer and cervical intraepithelial neoplasia. To date, more than 150 types of HPV have been identified. Of these, 12 HPV types are defined as high-risk types which are associated with cancers in humans, namely types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.2 Except for the occurrence of types 16 and 18, the distribution of other 10 types among those patients with abnormal cytological finding, including invasive carcinoma of cervix (ICC), high-grade squamous intraepithelial lesion (HSIL), and low-grade squamous intraepithelial lesion (LSIL) varied widely by regions.³⁻⁶ Referring to these international licensed HPV vaccines, a dozen of VLPs (which self-assemble spontaneously from pentamers of the L1 major capsid protein)-based HPV vaccine candidates utilized uneven types are being developed in China. However, a comprehensive Chinaspecific distribution of HPV types, as well as each constituent ratio among patients with abnormal cytological finding is absent. Hence,

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we performed this systematic review, aimed to define the Chinaspecific spectrum of high-risk types causing ICC and HSIL.

Methods

Search strategy

Studies on HPV infection in mainland Chinese women with and without cervical abnormalities, published before January 1, 2017 were identified using standardized search algorithms for systematic reviews. 7 Scientific articles published in English or Chinese were searched from PubMed, OVID-Embase, Cochrane Library, as well as Chinese databases, namely SinoMed, CNKI and WanFang. Different retrieval formulas were established according to individual databases. Standardized medical subject heading (MeSH) terms "Uterine Cervical Neoplasms", "Cervical Intraepithelial Neoplasia", "Papillomaviridae" and free word "China" were used for PubMed database; MeSH terms "uterine cervix tumor", "uterine cervix carcinoma in situ", "papovavirus" and free word "China" were used for Embase; MeSH terms "Uterine Cervical Neoplasms", "Cervical Intraepithelial Neoplasia", "Papillomaviridae" and free word "China" were used for Cochrane Library; "Cervical Cancer", "Cervical lesion", "Cervical Intraepithelial Neoplasia" and "Papillomaviridae" were set as subject heading (including title, abstract and keyword) to search Chinese database.

Review strategy

Endnote® (version X7, Thomson Reuters, Inc., Philadelphia, PA) bibliographic software was used to create an electronic library of citations identified in the database searches. All citations were imported into Endnote®, and duplicate records were deleted. Each study was assigned a unique identification code to enable tracking of reviews and analysis after title/abstract screening. Two independent reviewers were trained to perform the title/abstract screening and thereafter full text screening. When it comes to disagreements, discussion among the two reviewers and the corresponding author would be conducted to reach consensus. For each article that met the inclusion criteria, a structured questionnaire was used to appraise its quality based on journal of publication, sources of specimens, time sequence of data collection, sampling method, study region, study scope and method of typing HPV. To identify the homogeneity across these articles, each question was assigned a score, with zero being the lowest and five being the highest. Mean points per question were calculated for each article. Articles with ≥3.0 points/question were ranked as moderate/high quality. A structured questionnaire was implemented for data extraction, and the EpiData program (version 3.1) was used for data entry and management.

Study inclusion and exclusion criteria

All studies published before January 1, 2017, both in English or in Chinese languages from mainland China were retrieved from the sources defined above. To study the distribution of cancer and precancer associated HPV types, the following inclusion criteria were employed: 1) more than 50 cervical specimens from mainland Chinese women for genotyping; 2) with clear pathology or cytology diagnosis, including ICC, high-grade squamous intraepithelial lesion, low-grade squamous intraepithelial lesion or normal cytology/histology; and 3) with at least one HPV type detected. To study on age-specific HPV prevalence, the following inclusion criteria were used: 1) more than 1000 cervical specimens from mainland Chinese women were collected and tested; 2) with clear age aggregation for pooling HPV prevalence; and 3) prevalence derived from

population-based study. Studies were excluded from final analysis if their content was limited to a description of diagnostic methods, traditional medical therapies, case reports, health education, policy analysis or review articles.

Where available, ICC was further stratified by histological diagnosis into squamous cell (SCC), adenocarcinoma (ADC), adenosquamous carcinoma (ASC) and not able classified ICC. According to the Bethesda classification system, HSIL was defined as CIN2 and CIN3, while LSIL was equivalent to CIN1. If the same study was published in different journals, only the one with the largest sample size was included. A pilot study was conducted to refine the search algorithms, the questionnaire for quality assessment, and inclusion/exclusion criteria. This study was reviewed and approved by the Institutional Review Board in Institutes of Biomedical Sciences, Fudan University.

Analytical strategy and statistical analysis

The temporal and spatial distributions of HPV genotype in different cervical grades were analyzed to describe changes over time and across regions in mainland China. In view of HPV multiple infection, each of the co-infected type was calculated respectively. The Qinling Mountain-Huaihe River line, commonly recognized as the north–south dividing line of mainland China, was used to define the geographic regions, namely South (subtropical zone) and North (warm temperate zone).8 To study temporal variation of HPV types, the extracted data were categorized into two time periods, namely before year 2010 and since year 2010. Eventually, the potential protections offered by current licensed vaccines and being developed vaccine candidates with different HPV genotype combinations were calculated with regard to the distribution concluded from above analysis.

To plot the age-specific HPV prevalence in China, women were aggregated into 9 age groups with an interval of 5 years. In order to explore the potential influence of social economic status, age-specific prevalence between developed and less developed regions was further compared. Developed region was defined as province with a per capita GDP in 2015 that exceeded the average of entire country, else classified as less developed region whose GDP was less than average level. To better understand the correlation between the occurrence of HPV infection and cervical cancer, the age-specific incidence of cervical cancer derived from Chinese Cancer Registry System⁹ was plotted together with HPV prevalence.

Before the original data were synthesized, homogeneity across studies was tested by use of the Q statistic (P < 0.10). If substantial heterogeneity existed, the random-effects model was used; otherwise, the fixed-effects model was preferred to summarize the pooled percentage, as well as 95% confidence intervals. The random-effects model was solely used to obtain a point estimate, and listed original values as confidence interval when the number of analyzed studies was less than four. In order to detect potential bias introduced by the heterogeneous quality of publications, the pooled percentages from all studies and high-quality articles (mean score per question \geq 3.0) were calculated and compared. If there was significant difference, outputs derived from high-quality articles would be presented. All analyses were performed using STATA version 13.0 (Stata Corp, College Station, Texas, USA). Statistical significance was assessed using P < 0.05.

Results

Overview of studies

The initial search identified 26,897 related citations from PubMed, OVID-Embase, Cochrane Library, CNKI, SinoMed and WanFang.

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