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Human papillomavirus infection and sporadic breast carcinoma risk: a meta-analysis

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Abstract

Despite an increase in the number of molecular epidemiological studies conducted in recent years to evaluate the association between HPV infection and risk of breast carcinoma, the studies remain inconclusive. Here, a meta-analysis was conducted to estimate the prevalence of HPV in breast carcinoma and test the association. Studies on HPV DNA detection in sporadic breast carcinoma in female using polymerase chain reaction were included. Information on overall and type-specific (HPV 6, 11, 16, 18, 31, 33, 35, 45 and 51) HPV prevalence were required, plus detailed descriptions of study populations, HPV DNA source, publication calendar period and PCR primers used for HPV DNA detection and typing. We revealed that 24.49% of the breast carcinoma cases were associated with HPV, 32.42% occurred in Asia and 12.91% in Europe. The four most commonly identified HPV types, in the order of decreased prevalence, were HPV33, 18, 16, and 35. The detection of HPV was mostly influenced by publication calendar period and PCR primers used. In addition, the analysis of ten case-control studies containing 447 breast carcinoma

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Conflict of interest None.

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cases and 275 controls showed a significant increase in breast carcinoma risk with HPV positivity (OR = 3.63, 95% CI = 1.42–9.27). These results suggest that it's difficult to rule out the possibility of the association of HPV and breast carcinoma at present according to available publication proofs.

Keywords

Human papillomavirus; Breast carcinoma; Meta-analysis; Epidemiology

Introduction

Certain types of Human papillomavirus (HPV), such as HPV 16 and 18, are necessary in the development of cervical cancer [1]. It has been also considered that HPV may cause cancer of other sites such as head and neck, anus and vulva [2]. In 1990, Band et al. [3] reported that HPV could immortalize normal human mammary epithelial cells, and reduce their requirement on growth factors. Since 1992, a growing number of studies have detected HPV DNA in breast carcinoma tissues by polymerase chain reaction (PCR)-based techniques with the prevalence rate ranging from 0 to 86.21% [4–15]. With these descriptive reports of HPV in breast carcinoma tissues and the advance of molecular mechanisms of HPV carcinogenesis on breast tissue [5, 14, 16], a series of case-control studies emerged, particularly since 2004, to evaluate the correlation between HPV infection and breast carcinoma risk [11, 13, 17–24]. However, the study designs, involved populations, and HPV detection techniques utilized were heterogeneous and the results were inconsistent.

The aim of this study was to collect published information on HPV prevalence in breast carcinoma cases, explore parameters related to the prevalence, and to test the association between HPV infection and risk of breast carcinoma.

Materials and methods

Study selection

Medline was employed to search for citations published from January 1989 to May 2010 using the MeSH terms “papillomavirus,” “human,” “female”, and “breast carcinoma”. Additional relevant references cited in retrieved articles were also evaluated. Included studies had to meet the following criteria: (i) Use of PCR-based techniques to detect HPV DNA in tissues. (ii) Only studies on sporadic breast carcinoma in females. Research on special malignant tumors of the breast, for example, papillary carcinoma [13], lymphoepithelioma-like carcinoma of the breast [25] and Paget's disease [26], or in special population, such as, in younger girls [27], patients with high grade cervical lesions simultaneously [28] or history of cervical cancer [29] were excluded. (iii) If data or data subsets were published in more than one article, only the publication with the largest sample size was included [11, 30].

Data extraction

Two investigators (Ni Li and Min Dai) independently extracted data and reached consensus on all the items. For each included study, the following information was extracted: first author's name, journal and year of publication, country of origin, sample size, HPV DNA sources, PCR primers, HPV prevalence (overall and type-specific: HPV6, 11, 16, 18, 31, 33, 35, 45 and 51) in breast carcinoma tissues by disease status (case or control) and matching criteria if controls were present. Detailed information on all included studies is presented in Appendix A in Electronic supplementary material.

Statistical analyses

This meta-analysis had two parts. The first part was an epidemiological description on the overall and type-specific HPV prevalence (seven HPV types in the high-risk phylogenetic clade, namely HPV16, 18, 31, 33, 35, 45 and 51 [31], as well as two low-risk HPV types, HPV6 and 11) in breast carcinoma cases. The second part was a statistical pooling of HPV infection and breast carcinoma risk estimates.

Unconditional logistic regression model was used to compare the HPV prevalence by the influential parameters, and adjusted, where appropriate, for them as following: region (Asia, Europe, South America, North America and Oceania), HPV DNA source (paraffin-embedded tissue and fresh tissue), and publication calendar period (1992–1999, 2000–2005 and 2006–2009). The influence of used PCR primers on the prevalence of HPV in breast carcinoma tissues was also evaluated by grouping the primers as the broad spectrum [4, 9, 10, 19, 21, 32], the type-specific [8, 11, 13–15, 17, 18, 24, 33] and the combined usage of these two kinds of primers [5–7, 22, 23]. One study [20] was excluded from the first part because not all samples were detected by unique primers which made it difficult in primer estimation.

Fix-effect or random-effect models were used to pool the case-control data based on Mantel-Haenszel [34] and DerSimonian and Laird methods [35], respectively. These two models provide similar results when between-studies heterogeneity is absent; otherwise, a random-effect model is more appropriate. Between-group heterogeneity testing was performed by using the χ^2 -based Q test [36], and heterogeneity was considered significant when $P < 0.05$. Publication bias was evaluated with the linear regression asymmetry test by Egger et al [37] and Begg et al [38]. All analyses were performed using STATA statistical software (version 11.0; StataCorp, College Station, TX).

Results

In total, 21 publications were included in this study [4–15, 17–24, 32]. Seventeen countries and areas from four continents presented their data on HPV in breast carcinoma cases (Appendix A in Electronic supplementary material). Among these 21 publications, 20 [4–15, 17–19, 21–24, 32] were selected for describing the HPV prevalence in breast carcinoma and one [20] was excluded.

There were 1184 cases of breast carcinoma in total and most of them came from Asia (46.11%) and Europe (30.74%) (Table 1). The prevalence of HPV ranged from 0% to 86.21% (Appendix A in Electronic supplementary material) but yielded an overall HPV prevalence of 24.49% (95% CI = 22.07–27.05%), and 21.99% (95% CI = 19.08–25.20%) (data not shown) after adjusted for region, HPV DNA source, and publication calendar period. The HPV prevalence was lowest in Europe (12.91%, 95% CI = 9.64–16.80%) and highest in Oceania (42.11%, 95% CI = 30.86–53.98%) followed by Asia (32.42%, 95% CI = 28.50–36.52%). Compared with Asia (with the largest sample size), Europe and South America showed significant lower prevalence of HPV in breast carcinoma cases (OR = 0.41, 95% CI = 0.28–0.60 and OR = 0.19, 95% CI = 0.11–0.32, respectively) (Table 1). HPV prevalence was significantly higher (OR = 1.73, 95% CI = 1.21–2.74) when HPV DNA was extracted from paraffin-embedded tissues (26.65%, 95% CI = 23.50–29.98%) than from fresh tissues (20.86%, 95% CI = 17.16–24.96%). As for publication calendar period, the prevalence of HPV was highest (37.28%, 95% CI = 31.67–43.16%) for studies published between 2000 and 2005 (Table 1).

Nine HPV types (HPV6, 11, 16, 18, 31, 33, 35, 45 and 51) were analyzed in breast carcinoma tissues across studies. HPV 33 was the most common type with a prevalence of

14.36% (95% CI = 12.02–16.95%), followed by HPV18 (7.13%, 95% CI = 5.68–8.82%), HPV16 (7.04%, 95% CI = 5.59–8.82%) and HPV35 (7.01%, 95% CI = 5.12–9.33%) (Fig. 1). The prevalence of other HPV types was lower than 3%.

Before 2000, only type-specific PCR primers were used in the detection of HPV in breast tissues. Afterwards, broad spectrum PCR primers and the combined usage of type-specific and broad spectrum primers were used (Appendix A in Electronic supplementary material). Comparison of PCR primers showed that both type-specific PCR primers and the combination of type-specific and broad spectrum primers had a significantly higher detection rate of HPV DNA in breast tissues than broad spectrum primers (OR = 2.46, 95% CI = 1.66–3.65 and OR = 3.68, 95% CI = 2.52–5.37, respectively) (Table 2). For the four commonly detected HPV types, HPV16, 18, 33 and 35, type-specific PCR primers or the combined PCR primers also demonstrated to be more efficient than broad spectrum primers (Table 2).

Ten case-control studies [11, 13, 17–24] were included in the analysis of HPV infection and breast carcinoma risk, of which two were excluded automatically after data pooling because of the absence of HPV in both case and control groups [13, 24]. Furthermore, one study [11] reported on Chinese and Japanese population was divided into two studies (Fig. 2). Because the heterogeneity test showed $Q = 19.99$ ($P = 0.010$), random-effect model was chosen to evaluate the pooled OR (Fig. 2). Overall, there was a significant 3.63 fold (95% CI = 1.42–9.27) increased breast carcinoma risk by HPV infection. Khan et al. [22] uniquely showed an opposite association on HPV infection and breast carcinoma risk but it was not significant. When we excluded this study, a significant 6.31-fold (95% CI = 3.52–11.31) increased breast carcinoma risk was shown by HPV infection without between-studies heterogeneity ($P = 0.563$) (data not shown). Egger's and Begg's test, which was designed to indicate publication bias, proved to be insignificant ($P = 0.309$ and 0.348 , respectively).

Discussion

By pooling the data published between 1992 and 2009, this study represents an important gain in showing HPV prevalence rate in breast carcinoma tissues and possible association between HPV infection and breast carcinoma, and also demonstrated some parameters influencing the detected prevalence of HPV in breast carcinoma tissues.

Overall, approximately a quarter of the breast carcinoma cases were affected by HPV infection. Although 32.42% of breast carcinoma cases were HPV-associated in Asians, only 12.91% were in Europeans. Our finding suggested a moderate heterogeneity in HPV distribution in breast carcinoma cases across continents. HPV detection rates were slightly higher when HPV DNA was extracted from paraffin-embedded tissues than from fresh tissues, which hints that biopsy taken or slide preparation may affect the detection results. Twenty percent of all breast carcinoma cases in the present study were positive for HPV DNA in 1990s followed by an increasing positivity between 2000 and 2005, and a decreasing positivity after 2006 but still higher than 1990s. The increase was expected to be related to general improvements in HPV DNA testing. However, the decrease after 2006 may show more stable results with larger study sample sizes.

Although some probable parameters, such as HPV DNA source, had effect on HPV DNA detection in breast carcinoma cases, PCR primers used greatly influence the detection rate. Type-specific primers were widely used before broad spectrum primers which have been adapted since 2000 to detect HPV DNA. Although the broad spectrum PCR primers have been used more successfully in HPV detection in cervical cancer, this trend was reversed in breast carcinoma cases. It is hard to estimate to what extent other unknown sources of

variation such as sample storage conditions, specific PCR conditions and quality of histopathology may affect these comparisons, but our findings suggest that PCR primers for HPV detection in breast carcinoma should be more specific, which may be due to the low copy of HPV DNA in breast tissues.

It is worth noting that HPV33 was the most common HPV type in breast carcinoma. Moreover, all the subjects positive for HPV33 were Asians [5, 11, 22, 23]. Therefore, it was reasonable to speculate that HPV33 may be a predominant HPV type in breast carcinoma in Asians. HPV16 and 18 were less common in breast carcinoma but still important due to their role in other cancers, such as cervical cancer. A similar HPV16/18 prevalence ratio (PR) (PR = 0.98, 95% CI = 0.89–1.08%) in cervical adenocarcinoma [39], was seen (PR = 0.99, 95% CI = 0.70–1.39%) in breast carcinoma cases in this study. HPV16 was a little less common than HPV18 in breast carcinoma. Since the majority of histological type of breast carcinoma is adenocarcinoma [40], it is understandable that HPV18 was similar or even a little higher than HPV16 here. The prevalence of some of possibly carcinogenic HPV types in cervical cancer were less than 3% in breast carcinoma and even lower than HPV6 and HPV11. Hence, the high-risk types of HPV for breast carcinoma is probably different from cervical cancer.

This study is the first meta-analysis to explore the correlation between HPV infection and risk of breast carcinoma. In addition, information on HPV prevalence across continents, publication calendar year, and influence of DNA specimens and PCR primers on HPV prevalence in breast carcinoma was collected and analyzed in the study. Our study suggests that it's difficult to rule out the possibility of the association of HPV and breast carcinoma at present according to available publication proofs. Further multiple-centric large scale random trials are needed to get more consistent conclusions on HPV infection and breast carcinoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Prevalence of selected HPV types in breast carcinoma

Fig. 2.
ORs of breast carcinoma associated with HPV (cases vs. controls)

Crude and adjusted HPV prevalence in breast carcinoma cases across strata of region, HPV DNA specimen and publication calendar period

Table 1

	No. of studies	No. of cases	%	Prevalence (%) (95% CI)	OR	Adjusted ^a OR
Total	20	1184	100.00	24.49 (22.07–27.05)	–	–
Region						
Asia	8	546	46.11	32.42 (28.50–36.52)	Ref.	Ref.
Europe	6	364	30.74	12.91 (9.64–16.80)	0.31 (0.22–0.44)	0.41 (0.28–0.60)
South America	2	168	14.19	16.67 (11.37–23.18)	0.42 (0.27–0.65)	0.19 (0.11–0.32)
North America	2	30	2.53	20.00 (7.71–38.57)	0.52 (0.21–1.30)	0.43 (0.16–1.13)
Oceania	2	76	6.42	42.11 (30.86–53.98)	1.52 (0.93–2.47)	1.03 (0.60–1.75)
HPV DNA specimen						
Fresh tissue	8	743	62.75	20.86 (17.16–24.96)	Ref.	Ref.
Paraffin-embedded tissue	12	441	37.25	26.65 (23.50–29.98)	1.38 (1.04–1.83)	1.73 (1.21–2.47)
Publication calendar period						
1992–1999	5	187	15.79	12.30 (7.96–17.88)	Ref.	Ref.
2000–2005	6	287	24.24	37.28 (31.67–43.16)	4.24 (2.58–6.97)	5.33 (3.07–9.25)
2006–2009	9	710	59.97	22.54 (19.51–25.79)	2.07 (1.30–3.32)	1.70 (1.04–2.77)

95% CI: confidence interval, OR: odds ratio

^a Adjusted for region, HPV DNA specimen and publication calendar period

Table 2

HPV prevalence of overall and selected types in breast carcinoma, by PCR primer

HPV type	PCR primers						OR ^a (95%CI)		
	Broad spectrum			Type-specific			Type-specific vs. Broad spectrum		
	No. of studies	No. of cases	Prevalence (%) (95% CI)	No. of studies	No. of cases	Prevalence (%) (95% CI)	No. of studies	No. of cases	Prevalence(%) (95% CI)
Any	6	348	12.07 (8.84–15.96)	9	392	25.26 (21.03–29.86)	5	444	33.56 (29.18–38.16)
HPV16	5	286	2.45 (0.99–4.98)	8	364	6.04 (3.83–9.01)	5	444	10.81 (8.08–14.08)
HPV18	5	286	0.70 (0.08–2.50)	8	364	11.54 (8.44–15.28)	5	444	7.66 (5.36–10.54)
HPV33	4	269	0.00 (0.00–1.36)	2	102	17.65 (10.81–26.45)	5	444	22.30 (18.51–26.46)
HPV35	4	269	0.37 (0.01–2.05)	0	–	–	3	344	12.21 (8.94–16.14)
									37.27 (5.1–272.65)

^a Adjusted for region, HPV DNA specimen and publication calendar period