Infectious Agents and Cancer

REVIEW

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Polyomaviruses and the risk of breast cancer: a systematic review and meta-analysis

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Abstract

Background Breast cancer is a major global health problem worldwide, affecting more than 2.25 million women annually. The disease is influenced by various factors, including some viruses, gender, age, and family history. This study aimed to conducting a comprehensive systematic review and meta-analysis of existing studies on the polyomaviruses in breast cancer.

Methods This systematic review and meta-analysis aimed to provide an evidence-based analysis of the relationship between polyomaviruses and breast cancer. The global online databases were used to identify relevant studies published from 2000 to July 2024. The quality of each article was assessed using the Newcastle-Ottawa Scale (NOS) checklist. Data analysis was performed using STATA software, and standard errors of prevalence were calculated using the binomial distribution formula. Heterogeneity of study results was evaluated using the I-square and Q index, while publication bias was examined using the Begg's test. A random effects model was used to determine prevalence rates, and a forest plot diagram was used to present results with 95% confidence intervals. The Trim and Fill test was applied to estimate publication bias, and sensitivity analysis was performed to assess the influence of individual studies on the overall estimate.

Results Nine studies met the inclusion and exclusion criteria for this analysis. In this study, the prevalence of BKV, JCV, HPyV7, KIV, WUV, SV40, and TSV in breast cancer patients was found to be 0%. By combining the results of these studies, the prevalence of PyV, MCV, and HPyV6 in breast cancer patients was 11%, 4%, and 1%, respectively.

Conclusion The meta-analysis presented here provides an exhaustive overview of the current literature on the prevalence of polyomaviruses in breast cancer patients. Findings indicate a potentially stronger association between PyV and breast cancer than other human polyomaviruses.

Keywords Human polyomaviruses, Breast cancer, Meta-analysis

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Introduction

Breast cancer (BC) is a major global public health problem worldwide, affecting more than 2.25 million women and causing more than 680,000 deaths each year [1]. Extensive research worldwide has revealed that breast cancer is a complex disease influenced by various factors, with gender, age, environmental, family history and specific viral infections being the most important risk factors [2]. Among these, viral infections are associated with approximately 15–20% of cancers [3].

The family Polyomaviridae contains eight genera (Alphapolyomavirus, Betapolyomavirus, Deltapolyomavirus, Gammapolyomavirus, Epsilonpolyomavirus, Etapolyomavirus, Thetapolyomavirus, and Zetapolyomavirus) [4]. Polyomaviruses, including Merkel cell polyomavirus (MCV), BK virus (BKV), and John Cunningham virus (JCV), have been reported to be associated with human cancers [5]. Polyomaviruses are non-enveloped viruses characterized by their double-stranded DNA genome, which encodes regulatory proteins known as large T-antigen and small t-antigen, as well as structural proteins that constitute the capsid. Both large T-antigens and small t-antigens have the capacity to disrupt various signaling pathways within the host [6, 7].

JC virus and the BKV, the first two species discovered in 1971, infect immunocompromised individuals and lead to unusual clinical conditions. BKV, also known as Human Polyomavirus1, is transmitted primarily by the respiratory or the fecal-oral route during childhood and after initial infection of mononuclear blood cells and urinary tract [8]. Due to the limited genome size of polyomaviruses, which comprises the entire genome, it is capable of encoding only a few proteins and is highly dependent on the host cells for the majority of its early development. This virus is capable of replicating and destroying cells, or transforming certain cells into malignant forms that develop into fatal tumors [9]. BKV products alter the cell cycle, leading to immortalization and neoplastic transformation. BKV TAg interacts with p53 and pRb, disrupting cell cycle control and leading to unscheduled entry into S-phase and genetic alterations. BKV small T antigen (tAg) inhibits protein phosphatase 2 A (PP2A) and promotes cell proliferation. Transformation in human cells is less efficient, often resulting in abortifacient infections and integration of viral sequences into the host genome may enhance transformation activity [10].

SV40 T-antigen disrupts various cellular processes, including DNA repair, apoptosis, transcription, protein degradation, telomerase activity, and immune and inflammatory responses. Additionally, it promotes cell proliferation, angiogenesis, and cell migration. SV40 sT-ag has the capability to transform various cell types, including human cells, and can induce tumor formation in transgenic animals, either independently or in conjunction with LT-ag. Furthermore, SV40 sT-ag can affect the expression of cellular genes, encompassing proto-oncogenes and tumor suppressor genes [11, 12].

Polyomavirus JC, also known as Human Polyomavirus 2, has been identified as the causative agent of a rare, fatal disease called progressive multifocal leukoencephalopathy (PML) that occurs when the immune system is suppressed [13]. Study of the life cycle of JCPyV has been difficult due to its very limited range of activity within human host cells, which remains poorly understood even more than 40 years after the virus was first isolated in cell culture. It has been proposed that there are at least two levels of restriction: the first occurs extracellularly at the cell surface, influenced by the presence or absence of viral receptors and potential coreceptors, while the second occurs intracellularly at various later stages [14–21]. In the distal region of the LTag gene, a gene encoding microRNAs, namely miR-J1B1-3p, has been identified, which is conserved among JCPyV, BKPyV, and several other polyomaviruses. These microRNAs can be produced from the extended LVGR transcript or initiated by their own promoter. Its host range is particularly limited to humans, and the oncogenic potential of JCPyV in humans remains uncertain, and it is classified as possibly oncogenic by the international committee on carcinogenic viruses [22]. JCV enters eukaryotic cells and integrates into the genomic DNA. It promotes tumorigenesis with tissue-specific targeting by affecting the p53, β-catenin, IRS, Rb, TGF-β1, PI3K/Akt, and AMPK signaling pathways, and JCV T antigen may trigger tumorigenesis in neural, gastrointestinal, and breast tissues. Therefore, JCV may be an etiological risk factor for cancer development and should be prioritized in tertiary cancer prevention and treatment strategies [23].

Both JCV and BKV have also been detected in certain cases of breast carcinomas; however, further research is needed to determine the significance of these findings in relation to the potential causal relationship between the polyomaviruses and breast cancer [24]. Recently, the association between polyomaviruses and breast cancer has received more attention, but the research results are still inconclusive. Similarly, an association between JCV infection and breast cancer has also been observed [25]. However, due to variations in detection methods, study populations, and selection of control groups in these studies, the results are inconsistent, limiting the comparability of their results. According to the disparities and inconsistencies in the results of previous studies and the need for a comprehensive assessment to determine a possible association, this study aimed to conduct a comprehensive systematic review and meta-analysis of existing studies on the polyomaviruses in breast cancer, providing an evidence-based literature review of the association between these viruses and breast cancer.

Materials and methods

The study was conducted and executed by the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol for this study was registered on PROSPERO (CRD42024548079). The primary objective of the study was to evaluate the prevalence of human polyomaviruses in individuals diagnosed with breast cancer.

Search strategy

In the current investigation, two researchers (F.SH and T.M) independently performed the literature search. We included studies assessed by double-reading during routine screening. We did not limit the evaluations to a certain number of selection stage, i.e. Evaluations that focused on only one selection stage (title/abstract selection) were eligible for inclusion. Only evaluations published in English were included.

Published articles were collected through a systematic exploration of literature databases such as Scopus, Science Direct, PubMed, Web of Science, ProQuest, and the Google Scholar search engine from July 2000 to 2024 (Appendix 1). The search terms used were "BK", "JC", "Polyomaviruses", "Breast Cancer", "Simian Virus 40", "MCPyV", and "Merkel cell Polyomavirus" using a combination of Boolean Operators "OR" and "AND" in the Title/Abstract/Keywords field (Table 1). Furthermore, the references in the articles were reviewed to identify additional relevant studies and improve search sensitivity. All collected references were then imported into reference management software (EndNote, RRID: SCR_014001). The reference lists of all relevant studies were also reviewed for other pertinent publications. One of the team's researchers randomly assessed the search outcomes and confirmed that no relevant studies were missed. The search was limited to original articles/abstracts published in English that reported the prevalence of BK and JC polyomaviruses in patients with breast cancer. All these procedures were conducted by two authors (F.SH and T.M), and any discrepancies in article selection were resolved through discussion and any ongoing disagreements were resolved by a third reviewer with the third author (M.M).

Inclusion criteria

1. The PICO (Population, Intervention, Comparison, and Outcome) method was used to establish study selection criteria, focusing on patients with breast cancer (P), Polyomaviruses (I), and the prevalence of these viruses in breast cancer patients (O). Various types of studies, including cross-sectional studies, and case-control studies, were included in the meta-analysis to determine the prevalence of human polyomaviruses in patients with breast cancer.

Exclusion criteria

- Low study quality.
- Duplicate publications, reviews, animal studies, case reports, and animal studies were eliminated from the meta-analysis.
- Studies that did not report on the presence of human polyomaviruses in patients with breast cancer were excluded from the analysis.

Study selection

Initially, full texts or abstracts, documents, and reports were collected from various databases. After removing duplicate articles, irrelevant articles were excluded from the study. Then, full-text articles of eligibility were

Table 1 Search strategy

(" Breast Cancer " [MeSH Terms]) AND (" BKV" [MeSH Terms])
("Breast Cancer" [MeSH Terms]) AND (" JCV" [MeSH Terms])
(" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms])
("Breast Cancer" [MeSH Terms]) AND (" Simian Virus 40 " [MeSH Terms])
(" Breast Cancer " [MeSH Terms]) AND ("PyV" [MeSH Terms])
(" Breast Cancer " [MeSH Terms]) AND ("MCV" [MeSH Terms])
(" Breast Cancer " [MeSH Terms]) AND ("HPyV6" [MeSH Terms])
(" Breast Cancer " [MeSH Terms]) AND ("HPyV7" [MeSH Terms])
(" Breast Cancer " [MeSH Terms]) AND ("KIV" [MeSH Terms])
(" Breast Cancer " [MeSH Terms]) AND ("WUV" [MeSH Terms])
(" Breast Cancer " [MeSH Terms]) AND ("TSV" [MeSH Terms])
("Breast Cancer" [MeSH Terms]) AND "Merkel cell polyomavirus"[MeSH Terms]
(" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR (" BKV" [MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR (" JCV" [MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR (" Simian Virus 40 "[MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR ("MCV" [MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR ("PyV" [MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR ("HPyV6" [MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR ("HPyV7" [MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR ("KIV" [MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR ("WUV" [MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR ("TSV" [MeSH Terms]), (" Breast Cancer " [MeSH Terms]) AND ("Polyomaviruses " [MeSH Terms]) OR ("Merkel cell polyomavirus " [MeSH Terms])

evaluated for eligibility, and review studies, case reports, and unavailable articles were excluded from the meta-analysis. Finally, data was extracted from full-text articles according to the inclusion and exclusion criteria. (Fig. 1).

Data extraction

Two researchers independently assessed the studies, focusing on the name of the first author, publication year, country of study, viral detection assay, and total number of positive cases for each virus.

Quality evaluation

All prospective cohort studies included in our meta-analysis were assessed using the NOS checklist to determine their quality. The checklist consists of nine questions that are scored based on various criteria such as study type, sample size, study objective, study population, sampling method, data analysis method, appropriate presentation of results, and linking results to the study objectives. The checklist is divided into three parts: selection, comparability, and exposure, with a scoring range of 0 to 9.

Good quality: 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain.

Fair quality: 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain.

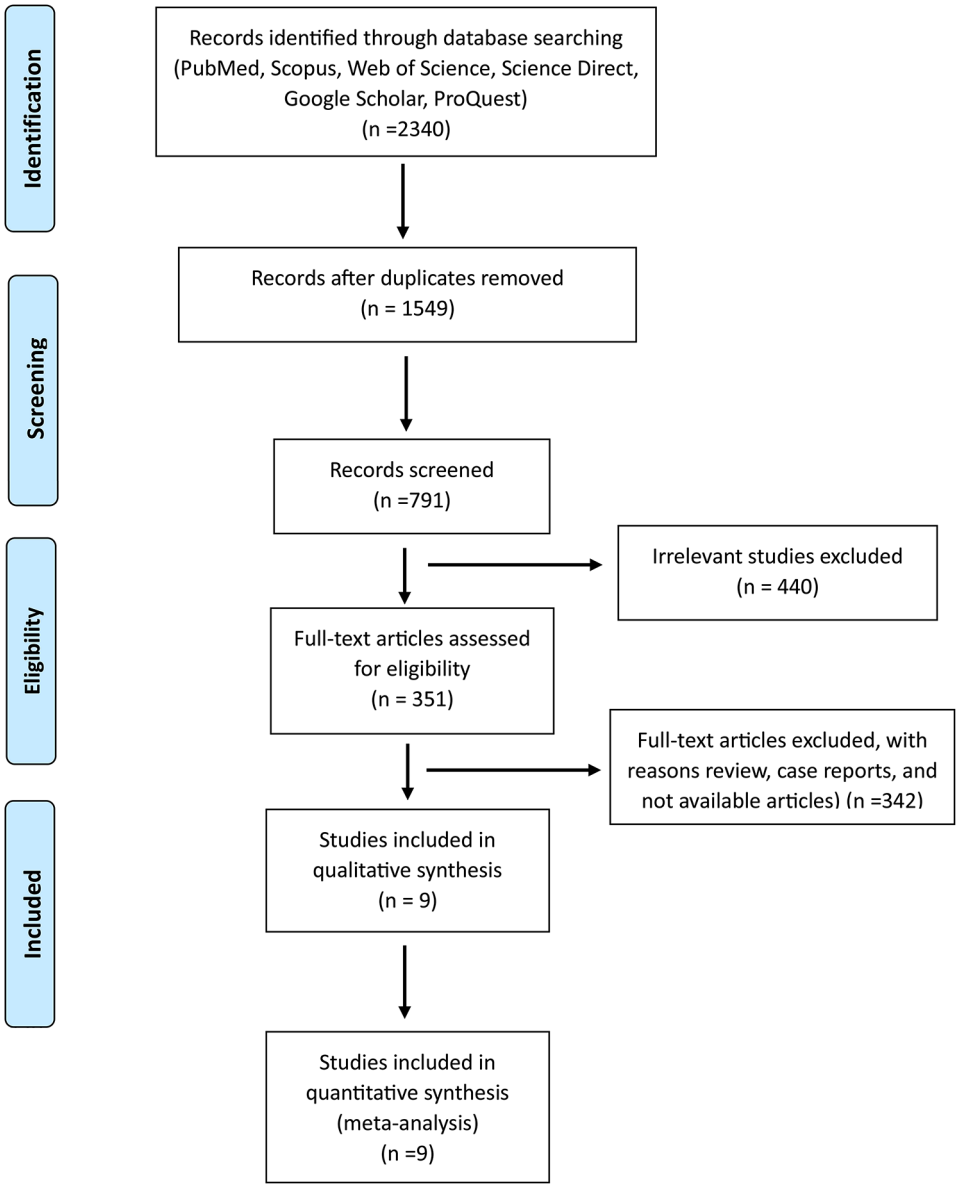

Fig. 1 Flowchart of included studies

Poor quality: 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain.

The maximum score for selection and comparability was 2, while the maximum score for exposure was 3 [26, 27] (Tables 2 and 3).

Analysis

The current investigation used STATA (RRID: SCR_012763) Ver. 11 for data analysis. The standard error in the prevalence was calculated using the binomial distribution formula. Heterogeneity among the primary study results was assessed using the I-square and the Q index. Due to the limited number of primary studies, publication bias was evaluated using the Begg's test. A random effects model was employed to determine prevalence rates. A forest plot diagram presents the prevalence estimates for each primary study, along with 95% confidence intervals. The Trim and Fill test was used to estimate publication bias, and sensitivity analysis was performed to assess the impact of each primary study on the overall estimate.

Results

A total of 2340 full-text or summary articles, documents, and reports were extracted from various databases. After removing duplicate articles, 440 irrelevant articles were excluded from this study. Next, 351 full-text articles were assessed for eligibility and 342 review studies were excluded from this meta-analysis. Finally, 9 studies were included in this analysis based on the inclusion and exclusion criteria.

Six studies reported the prevalence of BKV in breast cancer patients (Table 4). These studies included a total of 652 patients, with sample sizes ranging from 54 to 150. The countries in which these studies were conducted included: Morocco (One study), Australia (One study), Algeria (One study), Tunisia (One study), and Iran (Two studies). The prevalence of BK among cancer patients was zero in all primary studies except the study by Alipour et al. 2% (95% CI: 0.01–0.07) [8]. (Fig. 2). Based on heterogeneity tests, the heterogeneity between primary studies was low (I-square: 0%, Q; 2.03, $P = 0.85$). By combining the results of these six studies with the random effect model, the overall estimate of the prevalence of BK among breast cancer patients is 0%. Considering that the number of primary studies was low (less than 10 cases), Begg's test was used to evaluate publication bias, and the results of this test indicate no publication bias ($P = 0.005$). Due to publication bias, trim and fill analysis was performed to estimate the number of possible missed studies. Based on this test, the number of two new studies has been estimated. With the addition of these two primary studies, the overall estimate of the prevalence of BK

Table 2 NOS Checklist for selected studies (case-control study)

Study (First author (year)) Cross-sectional (Total ten scores)	Selection				Total scores	Comparability	Total scores	Exposure			Total scores	Total scores for all	Level
	Is the case definition adequate? (1)	Representativeness of the cases (1)	Selection of Controls (1)	Definition of Controls (1)		Comparability of cases and controls on the basis of the design or analysis (2)		Ascertainment of exposure (1)	Same method of ascertainment for cases and controls (1)	Non-Response rate (1)			
Razieh Dowran	1	0	0	0	1	1	1	1	1	1	3	5	Satisfactory
Hua-chuan Zheng	1	0	0	1	2	2	1	1	1	1	3	6	Satisfactory
Amina Gihbid	1	0	0	0	1	1	1	1	1	1	3	5	Satisfactory
Harithabdual sahibsharrif	1	0	0	1	2	1	1	1	1	1	3	6	Satisfactory

Table 3 NOS Checklist for selected studies (cross-sectional study)

Study (First author (year)) Cross-sectional (Total ten scores)	Selection													Comparability			Outcome							Total scores for all	Level
	Representativeness				Sample size		Non-respondents			Ascertainment (risk factor)			Total scores	Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors controlled.		Total scores	Assessment				statistical test		Total scores		
	Truly representative (1)	Somewhat representative (1)	Selected group (0)	No description (0)	Justified (including sample size calculation) (1)	Not justified (0)	Satisfactory (1)	Unsatisfactory (0)	No description (0)	Validated (2)	Non-validated (1)	No description (0)		Data/ results adjusted (2)	not Data/ results not adjusted (0)		Independent blind assessment (2)	Unblinded assessment (2)	Used non-standard (1)	No description (0)	clearly described & appropriate (1)	not appropriate or described (0)			
Zohreh Alipour	1	0	0	0	0	0	0	0	0	2	0	0	3	0	0	0	0	2	0	0	1	0	3	6	Good quality
Mohamed Hachana	1	0	0	0	0	0	0	0	0	2	0	0	3	2	0	2	0	2	0	0	1	0	3	8	Good quality
Annika Antonsson	1	0	0	0	0	0	0	0	0	2	0	0	3	2	0	2	0	2	0	0	1	0	3	8	Good quality
M. Hachana	1	0	0	0	0	0	0	0	0	2	0	0	3	2	0	2	0	2	0	0	1	0	3	8	Good quality
Marilys Corbex	1	0	0	0	0	0	0	0	0	2	0	0	3	2	0	2	0	2	0	0	1	0	3	8	Good quality

Table 4 Characteristics of studies included

references	Author/ Year	Study Area	Detection Test	JCV	BKV	pyv	kiv	mcv	sv40	tsv	hpyv6	hpyv7
[28]	Gihbid/ 2023	Morocco	PCR, TS-MPG	0	0	14	0	11	0	0	2	1
[31]	Antonsson/ 2021	Australia	PCR	0	0		0	1	0	0	1	1
[25]	Zheng/ 2021	China	PCR	66								
[32]	Hachana/ 2009	Tunisia	PCR						24			
[29]	Corbex/ 2014	Algeria	TS-MPG	0	0	1	0	1	0	0	0	0
[24]	Hachana/ 2012	Tunisia	PCR	28	0							
[30]	Sahibsharrif/ 2022	Iraq	PCR			13						
[5]	Dowran/ 2019	Iran	PCR	0	0							
[8]	Alipour/ 2024	Iran	PCR	0	2							

among breast cancer patients has not changed. Based on the results of the sensitivity analysis, the effect of each of the primary studies on the overall estimate was not different.

Seven studies reported the prevalence of JC virus (JCV) in breast cancer patients (Table 4). These studies included a total of 782 patients, with sample sizes ranging from 54 to 150. The countries in which these studies were conducted included: China (One study), Morocco (One study), Australia (One study), Algeria (One study), Tunisia (One study), and Iran (Two studies). The prevalence of JCV in breast cancer patients in the study by Zheng et al. [25] and Hachana et al. [24] was reported as 51% (95% CI: 42–59) and 23% (95% CI: 16–31) respectively. (Fig. 3). It should be noted that the prevalence of JC among breast cancer patients in five other primary studies was zero. Also, based on heterogeneity tests, the heterogeneity between primary studies was high (I-square: 96.48%, Q; 170.31, $P<0.001$). By combining the results of these seven studies, the overall estimate of the prevalence of JC among breast cancer patients is 0%. Because of this point the number of primary studies was low (less than 10 cases), Begg's test was used to evaluate publication bias, and the results of this test indicate no publication bias ($P=0.099$). Based on the results of the sensitivity analysis, the effect of each of the primary studies on the overall estimate was not different.

Three studies reported the prevalence of polyomavirus (PyV) in breast cancer patients (Table 4). The studies included a total of 305 patients, with sample sizes ranging from 76 to 149. The countries in which these studies were conducted included: Iraq (One study), Algeria (One study), and Morocco (One study). The prevalence of PyV in breast cancer patients has been reported as follows: Gihbid et al. [28] reported a prevalence of 18% (95% CI: 11–29); Corbex et al. [29] reported a prevalence of 1% (95% CI: 0–4); and Sahibsharrif et al. [30] reported a prevalence of 16% (95% CI: 10–26). Based on heterogeneity tests, the heterogeneity between primary studies was high (I-square: 93.05%, Q; 28.80, $P<0.001$). By combining the results of these three studies, the overall estimate of pyv prevalence among breast cancer patients is 11%.

Three studies reported the prevalence of Merkel cell virus (MCV) in breast cancer patients (Table 4). These studies included a total of 279 patients, with sample sizes ranging from 54 to 149. The countries where these studies were conducted included: Australia (One study), Algeria (One study), and Morocco (One study). The prevalence of MCV in breast cancer patients has been reported as follows: Gihbid et al. [28] reported a prevalence of 14% (95% CI: 8–24); Antonsson et al. [31] reported a prevalence of 2% (95% CI: 0–10); and Corbex et al. [29] reported a prevalence of 1% (95% CI: 0–4). Based on heterogeneity tests, the heterogeneity between primary studies was

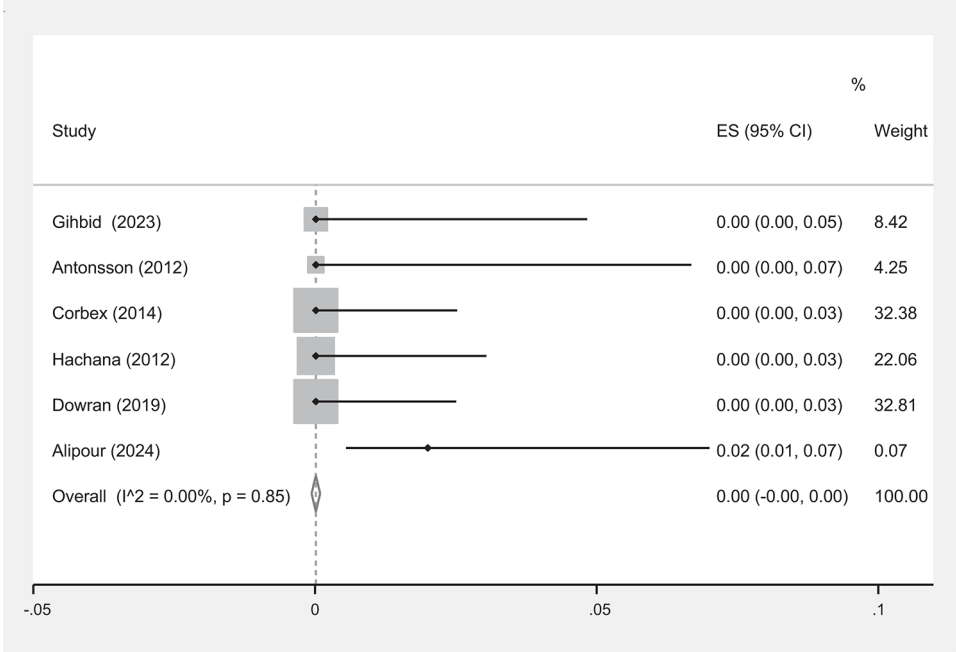

Fig. 2 Prevalence of BK virus with a 95% confidence interval in patients with breast cancer according to initial studies and overall report

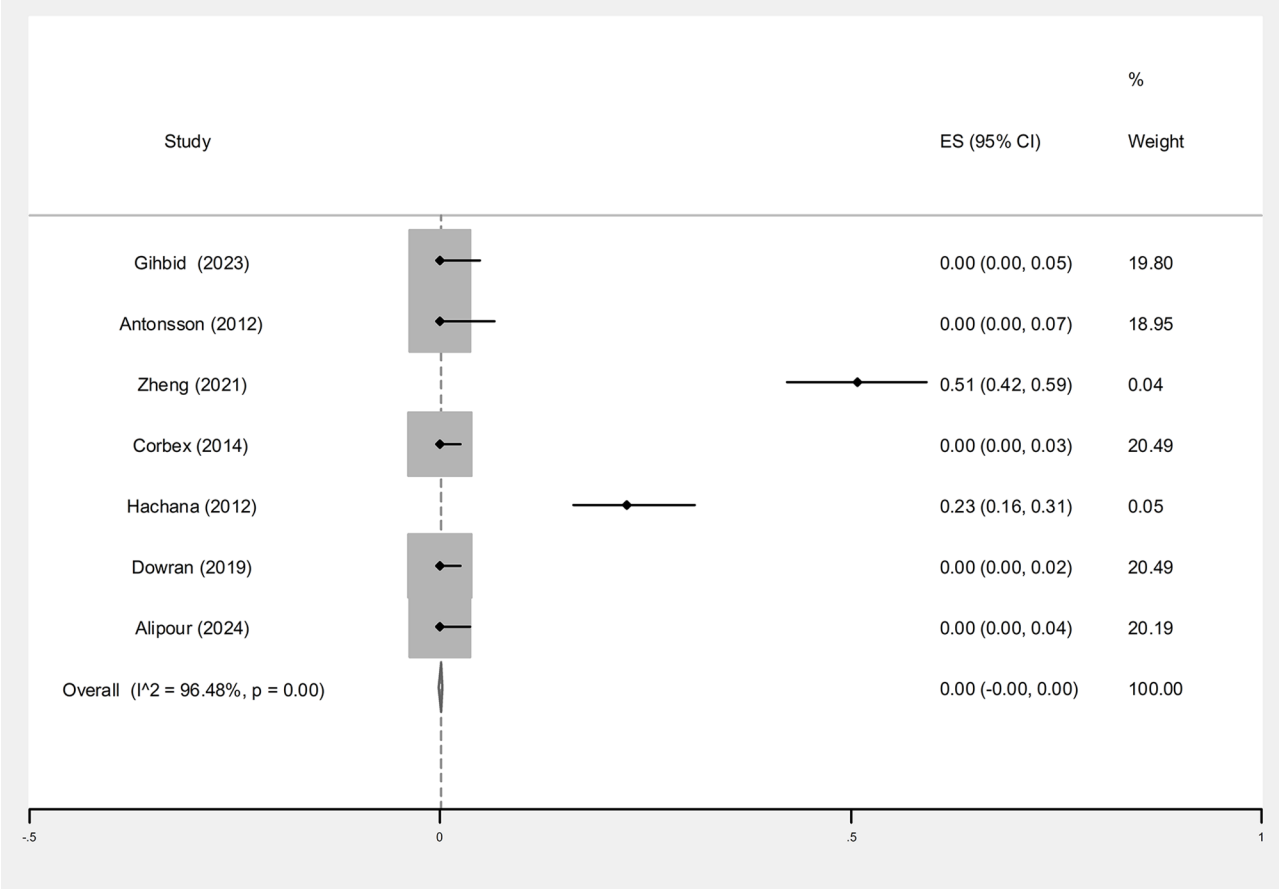

Fig. 3 Prevalence of JC virus with a 95% confidence interval in patients with breast cancer according to initial studies and overall report

high (I-square: 82.69%, Q; 11.56, $P < 0.001$). By combining the results of these three studies, the overall estimate of MCV prevalence among breast cancer patients is 4%.

Four studies reported the prevalence of simian virus 40 (SV40) in breast cancer patients (Table 4). These studies included a total of 388 patients, with sample sizes ranging from 54 to 149. The countries in which these studies were conducted included: Australia (One study), Algeria (One study), Tunisia (One study), and Morocco (One study). The prevalence of SV40 in breast cancer patients has been reported as follows: Hachana et al. [24, 32] reported a prevalence of 0.22% (95% CI: 15–31) and in three other studies it was zero. Based on heterogeneity tests, the heterogeneity between primary studies was not high (I-square: 90.25%, Q; 30.77, $P < 0.001$). By combining the results of these four studies, the overall estimate of the prevalence of sv40 among breast cancer patients is zero.

Three studies reported the prevalence of human polyomavirus type 6 (HPyV6) in breast cancer patients (Table 4). These studies included a total of 279 patients, with sample sizes ranging from 54 to 149. The countries in which these studies were conducted included: Australia (One study), Algeria (One study), and Morocco (One study) (Table 4). The prevalence of HPyV6 in breast cancer patients has been reported as follows: Gihbid et al. [28] in Morocco reported a prevalence of 3% (95% CI: 1–9); Antonsson et al. [31] in Australia reported a prevalence of 2% (95% CI: 0–10); and Corbex et al. [29] in Algeria reported a prevalence of 0%. Based on heterogeneity tests, the heterogeneity between primary studies was not high (I-square: 34.37%, Q; 3.05, $P = 0.22$). By combining the results of these three studies, the overall prevalence of hpyv6 among breast cancer patients is 1%.

Three studies reported the prevalence of human polyomavirus type 7 (HPyV7) in breast cancer patients (Table 4). These studies included a total of 279 patients, with sample sizes ranging from 54 to 149. The countries in which these studies were conducted were Australia (One study), Algeria (One study), and Morocco (One study) (Table 4). The prevalence of HPyV7 in breast cancer patients has been reported as follows: Antonsson et al. [31] in Australia reported a prevalence of 2% (95% CI: 0–10); Gihbid et al. [28] in Morocco reported a prevalence of 1% (95% CI: 0–7); and Corbex et al. [29] in Algeria reported a prevalence of 0%. Heterogeneity testing showed no significant heterogeneity between primary studies (I-square: 1.46%, $Q = 2.03$, $P = 0.36$). By combining the results of these three studies, the overall estimate of hpyv7 prevalence among breast cancer patients is zero.

Three studies reported the prevalence of KIV in breast cancer patients (Table 4). These studies included a total of 279 patients, with sample sizes ranging from 54 to 149. The countries in which these studies were conducted included: Australia (One study), Algeria (One study), and Morocco (One study) (Table 4). The prevalence of KIV among breast cancer patients was zero in all three primary studies.

Three studies reported the prevalence of WUV in breast cancer patients (Table 4). These studies included a total of 279 patients, with sample sizes ranging from 54 to 149. The countries where these studies were conducted included: Australia (One study), Algeria (One study), and Morocco (One study) (Table 4). The prevalence of WUV among breast cancer patients was zero in all three primary studies.

Three studies reported the prevalence of TSV in breast cancer patients (Table 4). These studies included a total of 279 patients, with sample sizes ranging from 54 to 149. The countries where these studies were conducted were Australia (One study), Algeria (One study), and Morocco (One study) (Table 4). The prevalence of TSV among breast cancer patients was zero in all three primary studies.

Discussion

Polyomaviruses have the potential to replicate and destroy cells or transform some cells into malignant forms and can develop into fatal tumors. Therefore, it is not unexpected to observe nonmalignant lesions in the tissues infected with polyomavirus. Therefore, the present meta-analysis aimed to systematically review and summarize the existing literature on the prevalence of polyomaviruses in breast cancer patients. A total of nine studies were included in this study, reporting the prevalence of various polyomaviruses, including BKV, JCV, PyV, MCV, SV40, HPyV6, HPyV7, KIV, WUV, and TSV.

In this study, the prevalence of BKV, JCV, HPyV7, KIV, WUV, SV40, and TSV in breast cancer patients was found to be 0%. By combining the results of these studies, the prevalence of PyV, MCV, and HPyV6 in breast cancer patients was 11%, 4%, and 1%, respectively, making the association between PyV and breast cancer significant. This makes the virus potentially significant in early diagnosis, treatment and prevention and may require further studies to investigate it, especially in immunocompromised patients who are at higher risk. There was also heterogeneity between the included studies and the prevalence of JC and BK viruses with 95% CI in patients with breast cancer according to the initial studies and overall reports were concluded in our study.

A study conducted by Gihbid et al. sought to investigate the detection of various viral DNA in specimens obtained from 76 Moroccan individuals with breast cancer and 12 control subjects through the utilization of Luminex technology (RRID: SCR_018025). The findings indicated the identification of PyVs DNA in control tissues (16.7%) as well as in breast cancer tissues (18.4%) [28]. On the other hand, Dowran et al. analyzed 300 breast biopsy samples,

of which 150 were malignant and 150 were benign. However, no genomic DNA fragments of BKV and JCV were detected in any malignant or benign breast tissue [5]. In addition, Alipour et al. analyzed 100 breast cancer tissue samples and found that only 2 of 100 (2%) ductal carcinoma in situ with grade 2 lesions were positive for BK virus genotype IV. In contrast, JC virus DNA was not detected in any of the samples [8]. Additionally, Zheng and colleagues investigated breast cancer, dysplasia, and normal breast tissue. They used immunohistochemistry and in situ PCR to morphologically detect the presence of JCV. The findings indicate that JCV T antigen may have a significant impact on breast carcinogenesis. This suggests that it may serve as a valuable molecular marker for distinguishing between different types of breast cancer and predicting aggressive behavior ($p < 0.05$) [25]. Hachana et al. demonstrated the existence of the SV40 [32], in their subsequent research, they found that JCV T-antigen DNA was present in 23% of breast carcinomas, with all cases being negative for BKV [24].

Antonsson et al. conducted a study on the presence of polyomaviruses in fresh frozen breast tumor samples. MCV, HPyV6, and HPyV7 were present in each patient sample (2%), while WUV, KIV, JCV, BKV, LPV, SV40, TSV, and CMV were not detected [31]. In addition, Corbex and colleagues conducted a study in which they randomly selected 155 paraffin-embedded malignant breast tumors from the pathology laboratory of the Annaba University Hospital (Algeria). The selection included one-third inflammatory breast cancer (IBC) tumors and two-thirds non-IBC tumors. Their results showed that MCV was detected in all tumors, while BKV, JCV, KIV, TSV, HPyV7, SV40, and HPyV9 were not found in any samples [29]. Overall, in our study, the prevalence of MCV, HPyV6 and HPyV7 was 4%, 1%, and 0%, respectively, and the prevalence of KIV, WUV, and TSV was 0%, suggesting that these viruses were undetectable in breast cancer patients. It is likely that the discrepancy in results may be due to the limited number of included studies and different methods, including virus detection and study population.

Conclusion

In conclusion, this meta-analysis provides a comprehensive summary of the existing literature on the prevalence of polyomaviruses in breast cancer patients. The results suggest that PyV may be more commonly associated with breast cancer than other human polyomaviruses. Further studies are needed to confirm these findings and explore the potential role of polyomaviruses in the development and progression of breast cancer. We recommend more studies using the PCR detection method with larger sample sizes or exploring other populations or clinical contexts and evaluating other viruses in the polyomavirus family (MCV, SV40, HPyV6, HPyV7, KIV, WUV, and TSV, etc.).

Limitation

This meta-analysis has several limitations. First, the number of included studies was limited, which may affect the precision of the estimates. Second, the studies included in this analysis were conducted in different countries and used different methods to detect polyomavirus. Also, various types of studies were included, which may affect the comparability of the results and cause heterogeneity.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
T.M, and F.SH carried out the studies, participated in collecting data, and drafted the manuscript. M.M performed the statistical analysis and participated in its design. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing interests
The authors declare no competing interests.

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