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Review

A Comprehensive Study of Prostate Cancer and Epstein-Barr Virus Infection: A Systematic Review and Meta-analysis

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Abstract

This systematic review and meta-analysis examine the potential link between Epstein-Barr virus infection and prostate cancer development, highlighting its role in the second most common malignancy in developed countries. A complete literature search was conducted using PubMed, EMBASE, Scopus, and Web of Science to identify relevant studies published between 2002 and 2024. The study incorporated publications from various countries, peer-reviewed studies, systematic reviews, and meta-analyses as supplementary sources to identify additional relevant studies. The study analyzed data from 16 articles, involving 1,340 PC cases, assessing EBV detection based on geographical distribution, publication year, and EBV-positive cases. The odds ratio for EBV-associated PC was 26.79%, with a global prevalence of 0.38. The study indicates regional variations in EBV positivity among PC cases, suggesting a possible link between EBV infection and PC, but further research is needed to clarify its role.

1. INTRODUCTION

Prostate cancer (PC) is one of the most prevalent malignancies among older men, originating in the prostate gland (PG), the largest gland in the male reproductive system [1]. According to the International Agency for Research on Cancer (IARC), PC was the fourth most common cancer worldwide and the second most common cancer in men after trachea, bronchus and lung malignancies in 2022, with 1,466,680 (%7.3) new cases and 396,792 (4.1%) deaths reported globally. Additionally, PC was the most frequently

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diagnosed cancer in men in 118 countries, with Europe and Asia exhibiting the highest incidence and mortality rates [2]. Several factors contribute to PC development, include age, ethnicity, family history, genetic predisposition, infection, chronic inflammation, androgen levels, and dietary influences [1, 3]. The risk increases significantly with age, particularly in men aged 60 and older [4]. Notably, PC accounted for 31.7% of malignancies in men aged 65–79 [5].

Lower urinary tract symptoms (LUTS), such as nocturia, hesitancy, urgency, frequency, and urinary retention, along with other genitourinary signs such as hematuria, are common presentations of PC [4]. LUTS prevalence exceeds 50% in men over 50 and increases with advancing age [4, 6]. Diagnostic methods for PC include the Prostate-Specific Antigen (PSA) test, transrectal ultrasound (TRUS), transrectal magnetic resonance imaging (MRI), and transrectal biopsy [7]. The PSA test measures PSA levels in the blood, where elevated levels may indicate malignancy or infection [8]. MRI, particularly transrectal MRI, provides detailed imaging for tumor staging and assessing potential extracapsular extension [9]. A transrectal biopsy involves extracting prostate tissue via a thin needle inserted through the rectum, followed by histopathological examination [10]. The multidisciplinary approach to PC depends on disease progression and patient health corporation active surveillance, surgery, radiation therapy, hormone therapy, chemotherapy, immunotherapy, and targeted therapy [11]. Localized tumors confined to the prostate can be surgically removed through prostatectomy, with surgical techniques evolving from open prostatectomy to nerve-sparing robotic surgery to minimize postoperative complications and accelerate recovery [12, 13]. Various radiation therapy modalities are available for PC treatment, including external beam radiation therapy (EBRT), three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), stereotactic ablative radiotherapy (SBRT), MRI-guided radiation therapy, and proton beam radiation therapy [14-17]. Hormone therapy, in the form of androgen deprivation therapy (ADT), can be achieved surgically through castration or pharmacologically including the use of luteinizing hormone-releasing hormone (LHRH) agonists and antagonists and androgen receptor antagonists [18, 19].

2. EBV AND PROSTATE CANCER

Epstein-Barr virus (EBV) is a herpesvirus responsible for infectious mononucleosis and has been implicated in various malignancies, including Hodgkin's and non-Hodgkin's lymphomas [20-22], as well as gastric [23-25], lung [26], and breast cancers [27]. Emerging evidence suggests a potential association between EBV and PC. For instance, a study in Sweden by Bergh et al. detected EBV in 31 of 351 PC samples [28], while research by Sfanos et al. in the United States identified EBV in 16 of 200 PC case [29].

This article aims to systematically evaluate recent studies investigating the relationship between EBV infection and PC, contributing to a deeper understanding of its potential role in prostate cancer development.

3. PROSTATE GLAND: ANATOMY AND HISTOLOGY

The PG is approximately 3 cm in length, conical in shape, and surrounds the prostatic urethra (PU). A normal prostate weighs between 15–20 g, with the seminal vesicles positioned bilaterally at the its base [30].

3.1. Anatomical structure

McNeal et al. identified three glandular zones in the human prostate, along with a non-glandular anterior fibromuscular stroma [31]. The prostate consists of a base, apex, anterior, posterior, and inferolateral surfaces. It is situated between the bladder neck and the genitourinary diaphragm, with the base adjacent to the bladder neck and the apex positioned superior to the urogenital diaphragm. These regions are tightly connected by a fibromuscular capsule [32].

The prostate and seminal vesicles are separated from the rectum by a thin connective tissue layer known as Denonvilliers' fascia [33]. Skeletal muscle fibers extend from the genitourinary diaphragm to the prostate at both the apex mid-region. The peripheral region includes all PG tissue at the apex and the posterior region near the capsule. Post-inflammatory atrophy, chronic prostatitis, and carcinoma are more frequently observed in this region compared to other prostate zones [33].

The posterior surface of the prostate is triangular and flat, positioned against the anterior rectal wall, while the anterior surface lies adjacent to the pubic symphysis, separated by extraperitoneal fat. The inferolateral surface connects to the anterior surface and rests on the levator ani fascia above the urogenital diaphragm.

3.2. Zonal classification

The prostate is divided into three primary zones: peripheral zone (PZ), central zone (CZ), and transition zone (TZ).

- *Peripheral Zone (PZ):* Constitutes 70% of the glandular tissue and is the primary site for prostate cancer in 70-80% of cases [34]. It wraps around the distal outer

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portion of the prostate, and its ducts extend posterolaterally from the urethral wall on both sides, curving toward the apex [35].

- *Central zone (CZ):* Comprises 30% of the prostate and surrounds the ejaculatory ducts, forming a cone-shaped region at the base. [35]. While CZ is not a primary site for disease, it may be secondarily involved in PC [30].
- *Transition zone (TZ):* A small oblique coronary region extending from the verumontanum to the bladder neck, containing two tiny lobes whose ducts originate from the posterolateral urethral wall [31]. TZ is associated with benign prostatic hyperplasia (BPH) and, in rare cases, PC [33]. TZ tends to enlarge significantly with age due to benign hyperplasia, a condition rarely seen in younger men.

The anterior fibromuscular stroma (AFMS) is the primary non-glandular component of the prostate, varying in volume and consistency along the gland. The apical region, rich in striated muscle, connects the prostate to the pelvic diaphragm, while the basal region, rich in smooth muscle, integrates with bladder neck fibers. The distal and proximal regions of the AFMS regulate the function of voluntary and involuntary urethral sphincters, respectively [33].

3.3. Vascular and Nerve Supply

The prostatic plexus provides the prostate's nerve supply, while branches of the internal iliac artery supply its arterial blood flow. The sphincter muscles encircle the entire length of the PU, contributing to urinary control [36].

3.4. Histology

Histologically, the prostate is a branched ductal gland lined by a secretory columnar epithelial layer with an underlying basal cell layer. In older men, corpora amylacea, multilayered eosinophilic concretions, frequently accumulate in the lumen of the prostate and its ducts [33].

4. RISK FACTORS FOR PROSTATE CANCER

PC is influenced by both non-modifiable and modifiable risk factors. Non-modifiable risk factors include age, race, and family history. PC incidence increases with age, being most prevalent in men over 60, with the highest rates observed in those above 80 years [37]. African American men have a 60% higher risk of developing PC compared to white men and face nearly twice the mortality rate [38]. Individuals with a first-degree relative (father or brother) diagnosed with PC have a 2–3-fold increased risk of developing the disease [38].

Diet has been recognized as a modifiable risk factor for PC. Consumption of unsaturated fats contributes to increased PC incidence and mortality, potentially due to influencing hormonal pathways, oxidative stress, and DNA-reactive metabolites [39]. Furthermore, excessive consumption of red, smoked, or processed meats, as well as dairy products, has been linked to an increased PC risk [40]. Smoking is associated with a higher PC mortality and heavy smokers exhibit a 24%–30% greater risk of PC-related mortality compared to nonsmokers [41].

5. Epstein-Barr virus (EBV)

EBV, also known as gamma human herpesvirus-4 (HHV-4), is a ubiquitous human virus that infects nearly all humans during their lifetime. Over 90% of adults worldwide demonstrate serological evidence of past infection. EBV primarily targets B lymphocytes, though it can infect epithelial cells, especially in immunocompromised individuals. EBV is transmitted through saliva, oral, and laryngeal secretions, leading to various clinical manifestations depending on the host's immune status and age [42]. Two major subtypes infect humans (EBV-1 and EBV-2), with differences is their latent genes and their expression profiles [43]. Since its discovery as the first human oncogenic virus, EBV has been implicated in a wide range of malignancies, including: Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma, gastric cancer, breast cancer, and leiomyosarcoma. Additionally, EBV is the leading cause of infectious mononucleosis [44]. While humoral and cellular immune responses develop against EBV, cell-mediated immunity plays a crucial role in controlling its infection [45].

6. EBV GENETICS AND CHARACTERISTICS

EBV shares structural similarity with other herpesviruses, including a core containing a linear dsDNA genome within a nucleocapsid surrounded by a protein layer called tegument, and finally covered by an outer lipid envelope embedded with glycoproteins [46]. The most abundant structural glycoprotein in the viral envelope is Gp350/220, which is expressed as a sort of glycoprotein spike on its surface. The viral genome is a 172-kilobase pairs (kbp) double-stranded linear DNA with 0.5 kbp terminal repeats (TR) and 3 kbp internal direct repeats [46]. The genome also contains unique long sequence domains. The BamHI restriction fragment, particularly BamHI-A and BamHI-B, is used for genome sequencing in the B95.8 laboratory strain [46].

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EBV exhibits significant sequence polymorphisms in Epstein-Barr Nuclear Antigen 2 (EBNA2) and EBNA3A–C sequences that define type A and B strains. Modest alterations in BNA1 (BKRF1), Latent Membrane Protein 1 (LMP1), and BZLF1 (Zebra protein) were also discovered during genome sequencing [47]. Type A strains are predominantly associated with EBV-related cancers and B-cell malignancies [46]. In primary B-cell infection, EBV establishes latent infection, where only eight proteins are expressed without active viral replication. The viral genome circularizes into an episome, where TR sequences at the ends joins together. The number of TRs tumor cells is used to determine whether the malignancy originates from a single EBV-infected progenitor cell, confirming its clonal nature [43]. Each TR is 538 base pairs (bp) long and plays a key role in viral genome cleavage and encapsidation. Mutant EBV strains lacking TRs generate empty or DNA-free virions, though these defective viruses are extremely rare [48].

Four internal direct replication classes divide the genome into five unique sequence domains. The general structure of the genome can be represented as TR–U–IR1–U2–IR2–U3–IR3–U4–IR4–U5–TR. Among these, IR1 is particularly important as it encodes cytoplasmic polyadenylated RNA and poly-ribosomal RNA in latently infected Burkitt tumor cells. IR1 also encodes part of a 3 kbp cytoplasmic polyadenylated RNA in latently infected, growth-transformed cells [49].

7. EBV AND PROSTATE CANCER

As previously stated, infection with EBV is attested in over 90% of adults worldwide[50]. In addition to its well-established role in lymphoid cancers, EBV has been linked to several epithelial malignancies, including breast, kidney, colon, lung, and stomach cancers [51]. Recent studies have associated prostate disorders, such as benign prostatic hyperplasia (BPH) and prostatic adenocarcinoma (PAC), the predominant histopathological type of PC, with EBV infection [52]. Specifically, EBV expresses Epstein-Barr Encoded RNAs (EBER-1 and EBER-2)—short untranslated RNAs that accumulate extensively during viral latency and modulate apoptotic pathways. EBER-1 suppresses interferon (IFN)-dependent apoptosis via interacting with protein kinase R (PKR), inhibiting its role in the IFN signaling pathway [52].

By producing short encoded RNAs, EBV has been found to boost the development and proliferation of lymphoblastoid cell lines, lowering the release of pro-inflammatory cytokines like IL-6 [53, 54]. In epithelial cells, EBER expression stimulates the expression of cellular growth factors, enhancing malignant cell survival [55].

Several EBV-encoded oncogenic proteins contribute to PC pathogenesis. Latent Membrane Proteins (LMP-1 and LMP-2) play an essential role in carcinogenesis in latent cancer cells by participating in carcinogenesis, inhibiting apoptosis, promoting angiogenesis, and enhancing tumor proliferation and survival. EBNA-1 facilitates viral genome persistence and malignant transformation in infected cells, while EBERs disrupt host immune responses and allow evasion of the immune system by the tumor cells, thereby enhancing tumor malignancy [52]. In this context, Iwatsuki et al. reported that EBER expression was significantly higher in PAC patients than in those with BPH, further supporting a role for EBV in PC pathogenesis [56].

In addition to viral genes, somatic point mutations in the retinoblastoma (Rb) gene contribute to PC progression. The EBV-encoded nuclear antigen EBNA-5 interacts with E2F transcription factors during the S phase, disrupting the cell cycle [52]. On the other hand, EBNA-5 can bind to Rb protein *in vitro*, interfering with its tumor suppressor functions. Indeed, the Rb protein suppresses the expression of the c-MYC oncogene—a function disrupted in EBV-infected cells [57]. According to a 2020 study by Abdullah Abbas et al., a direct relationship exists between EBV infection and interleukin (IL)-10 expression in PC. IL-10 functions as an immunosuppressive cytokine, inhibiting the synthesis of pro-inflammatory cytokines and reducing T-helper cell activity [58]. IL-10 also suppresses the function of monocytes and macrophages, downregulating nitric oxide production, MHC II expression, and monokine synthesis. Additionally, IL-10 inhibits the NF-κB pathway, reducing the expression of key inflammatory mediators such as TNF-α, IL-6, and IL-12, thereby disrupting anti-tumoral immune responses [58, 59].

Despite accumulating evidence, the exact oncogenic mechanisms of EBV in PC remain unclear. As demonstrated in Figure 1, considering the suitable prostate environment for viral and nonviral infections, EBV may act as cofactor in PC progression, altering immune responses and promoting malignant transformation [52].

8. METHODS AND MATERIALS

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [60].

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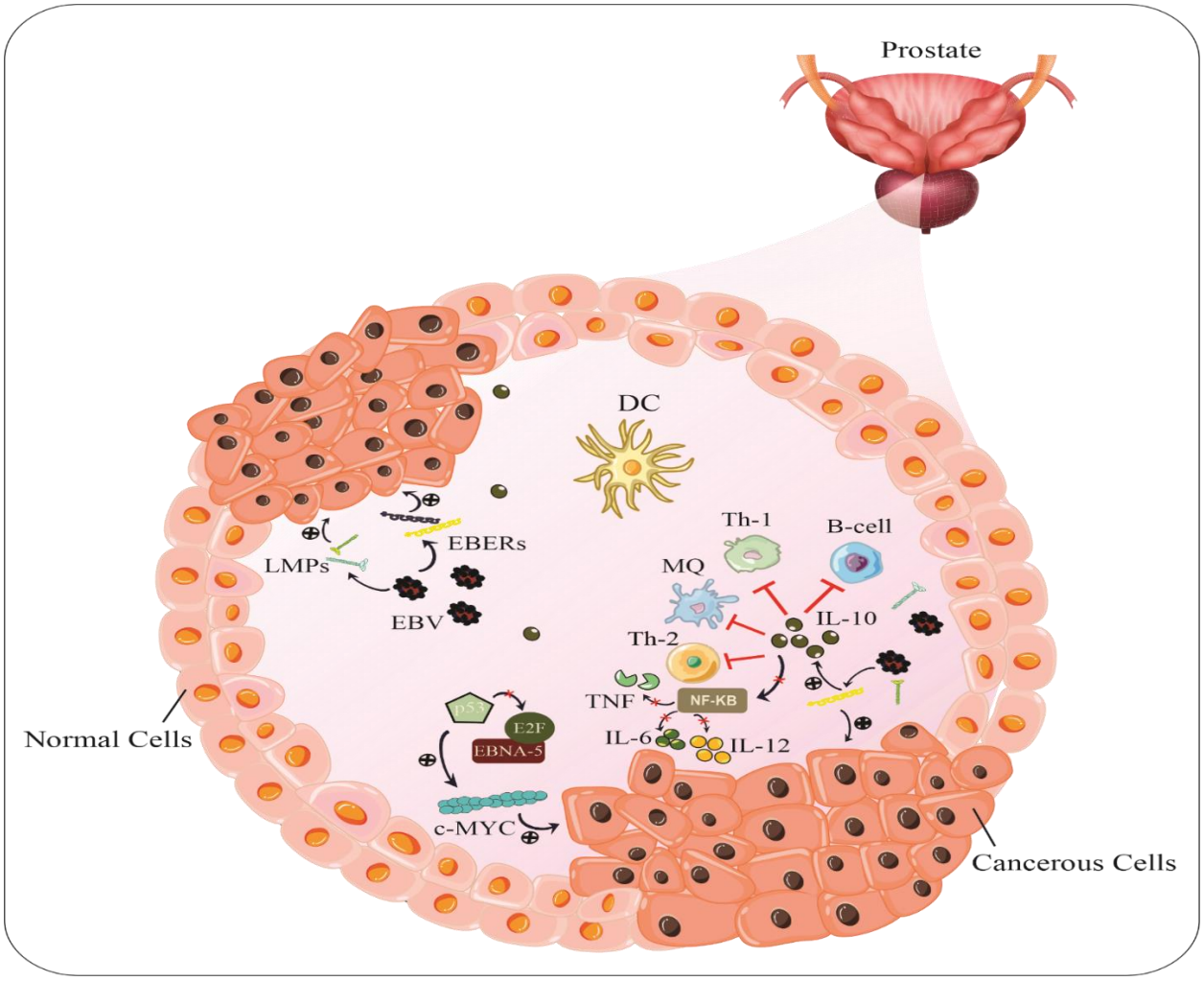

Figure 1. A schematic representation of EBV infection and prostate cancer progression. EBV as a cofactor in PC development. EBV enhances PC progression through the expression of oncogenic viral genes, including EBERs, LMPs, and EBNAs. These viral proteins disrupt key host cellular pathways, such as NF-κB signaling pathway, and promote the secretion of IL-10, which suppresses anti-tumoral immune responses, further facilitating tumor progression and increasing malignancy.

8.1. Search strategy

A systematic literature search was performed using PubMed, Science Direct, EMBASE, Scopus, and Web of Science. The following keywords were used: ("Burkitt Herpesvirus" OR "Burkitt Lymphoma Virus" OR "Burkitt's Lymphoma Virus" OR "E-B Virus" OR "EBV" OR "Epstein-Barr Virus" OR "HHV-4" OR "Herpesvirus 4 (gamma), Human" OR "Human Herpesvirus 4" OR "Infectious mononucleosis Virus") AND ("Cancer of Prostate" OR "Cancer of the prostate" OR "Neoplasms, Prostate" OR "Neoplasms, Prostatic" OR "Prostate Cancer" OR "Prostate Neoplasms" OR "Prostatic Cancer"). The search was limited to human studies, with no restrictions on cancer stage or treatment strategy. Studies published between 2002 and 2024 across various countries were included.

8.2. Inclusion criteria

Studies were included if they met the following criteria: 1. Human studies, 2. Published between 2002 and 2024, 3. No population restrictions, 4. Histopathological confirmation of prostate cancer (PC), 5. Sufficient published data to estimate the odds ratio (OR), and 6. Published in English.

8.3. Exclusion criteria

Studies were excluded based on the following criteria: 1. Animal studies, 2. Studies involving other viruses or malignancies, 3. Letters to the Editor, 4. Abstract-only

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publications, 5. Case reports, 6. Conference proceedings and theses, and 7. Manuscripts under peer review. The inclusion and exclusion criteria were independently reviewed by M.P. and H.B.B. to ensure methodological rigor.

8.4. Study Selection

Study selection was conducted in two phases:

- Phase I: Three researchers (P.S., Z.S.D., and A.J.S.) screened the abstracts and full texts. Any disagreements were resolved by an independent researcher (M.P.)
- Phase II: Data extraction was performed by three researchers (N.A., F.J., and S.M.H.). Differences in extracted data were resolved through researcher consensus, with final verification by H.B.B.

8.5. Data Extraction

Two researchers (A.J.S. and M.P.) independently extracted the following data from eligible studies to minimize bias: 1. First author, 2. Year of publication, 3. Study location (country), 4. Sample size, 5. Number of EBV-positive cases, and 6. Viral genome detection method. Disagreements were resolved by consulting H.B.B.

7.6. Quality Assessment

Potential biases in the included studies were assessed using the Risk of Bias in Non-Randomized Studies (ROBINS) tool [61, 62].

Specific sources of bias included:

- Selection bias due to reliance on a single reviewer for inclusion/exclusion criteria.
- Interpretation bias in data extraction, despite independent reviewers.
- Methodological heterogeneity, as studies used varying detection methods.
- Selection bias due to exclusion of studies with insufficient methodological details.

To mitigate these biases, all data were reviewed by H.B.B. and M.P. before final analysis.

7.7. Statistical Analysis

Global data on the prevalence of EBV were compiled, and for each study, a point estimate of the effect size along with a 95% confidence interval (95% CI) was calculated. To evaluate the heterogeneity of studies, Cochran's Q test and the I^2 index were used. Due to heterogeneity among studies, random effects models were applied to combine the studies. Publication bias was examined using Egger's regression model. Meta-analysis was conducted using Stata software (version 17, STATA Corp, College Station, TX, USA). Statistical significance was set at $P < 0.05$.

9. RESULTS

9.1. Selected Studies

The systematic search identified 290 records across PubMed, EMBASE, Scopus, and Web of Science. After removing 52 duplicate records, 238 studies remained.

- Phase I: Title and abstract screening excluded 213 studies.
- Phase II: The full texts of the remaining 25 studies were reviewed.
- After full-text assessment, 13 studies were included in the final qualitative synthesis.

A PRISMA flowchart (Figure 2) illustrates the study selection process, including inclusion and exclusion criteria.

9.2. Characteristics of the included studies

A total of 16 studies met the inclusion criteria. These studies were conducted across eight countries and assessed 1,340 prostate cancer (PC) cases for EBV prevalence. Among these cases, 359 were found to be EBV-positive. The polymerase chain reaction (PCR) test was the most commonly used method for detecting the EBV genome in the studies.

8.3. Statistical analysis

All statistical analyses were performed using Microsoft Excel. The EBV prevalence in PC cases varied from 0% to 100%. After adjusting for positive cases and total PC cases, the average prevalence of EBV was 26.79%. Country-specific prevalence was calculated by classifying the studies by location. Switzerland (87.5%) and the United Kingdom (84.21%) exhibited the highest EBV prevalence in PC cases, while Iran had the lowest prevalence at 1.6%. A summary of EBV prevalence across countries in presented in Table 1, while continent-wise EBV prevalence is detailed in Table 2. The odds ratios (ORs) for EBV prevalence in PC cases were compared across continents, with the following rankings: Africa (72%), Australia (40%), Asia (28.76%), Europe (22.46%), and the Americas (10.55%). A forest plot (Figure 3) illustrates the global prevalence of EBV infection in PC cases, as estimated using a random effects model.

In the heterogeneity analysis, the I^2 statistic was calculated as 98.93%, indicated a high level of heterogeneity among the studies. The Chi-squared test statistic was 986.32 ($p < 0.001$), rejecting the null hypothesis of homogeneity. Given this substantial heterogeneity, a random effects model was employed to estimate the prevalence of EBV infection. Egger's test revealed no significant publication Bias ($z = 1.24$, $P = 0.215$), and a funnel plot was used to visually assess publication bias. The total estimated

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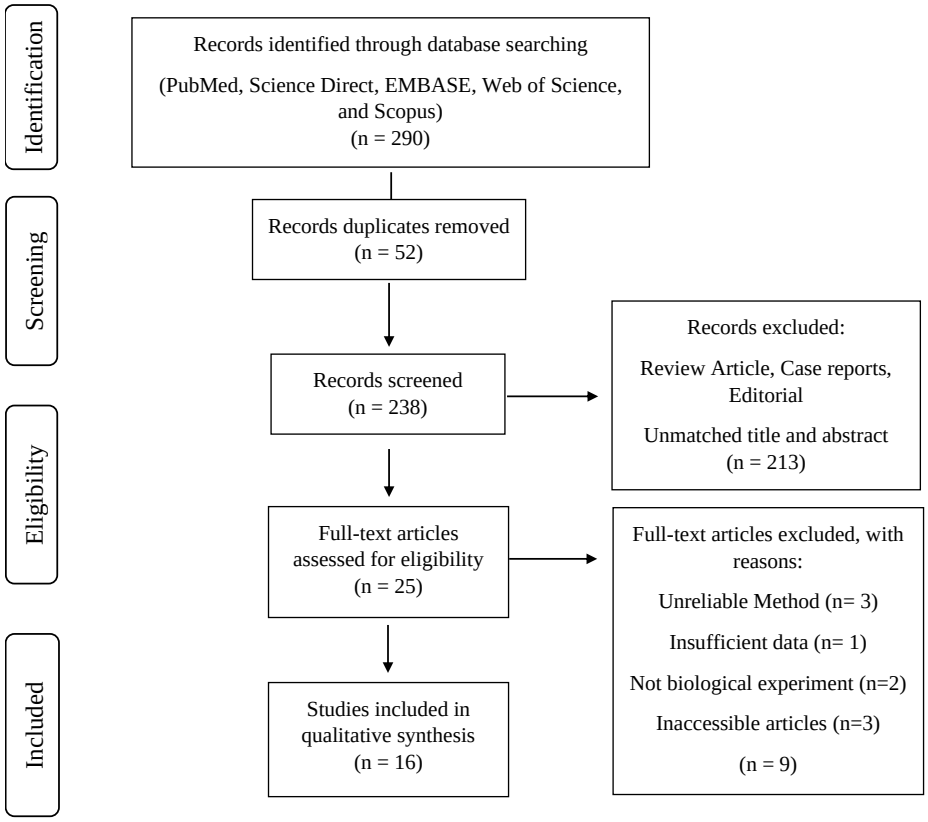

Figure 2. The PRISMA flowchart of the present study, illustrating the various steps in the study selection process.

prevalence of EBV infection in PC cases worldwide was 0.38 (95%CI 0.25–0.52).

10. DISCUSSION

As discussed in previous sections, multiple factors contribute to prostate cancer (PC) development, including age, family history, diet, and infections. Due to its anatomical location, the prostate is particularly susceptible to various infectious agents transmitted through urination and sexual activity. Chronic inflammation, a well-established risk factor for PC, may also play a significant role in virus-induced carcinogenesis [77]. Notably, 10–15% of human cancers are attributed to viral infections [78]. The association between oncogenic DNA viruses and tumor development has been well-documented in various cancers, including those caused by human papillomavirus (HPV), polyomaviruses (BKV, JC, and SV40), and members of the family *Herpesviridae* (EBV, HCMV) [28].

This meta-analysis investigates the association between EBV and PC by systematically reviewing existing literature. The findings suggest that EBV may play a role in the initiation or progression of PC, potentially through interactions with other cofactors [52].

One proposed mechanism linking EBV to PC involves the dysregulation of tumor suppressor proteins, such as p53 and pRb [79]. Research by Ali and Al-Alwany (2014) demonstrated that mutations in the Rb gene could promote PC progression. Specifically, the EBV nuclear antigen 5 (EBNA-5) binds to the Rb protein and the E2F transcription factor, disrupting cell cycle regulation. Additionally, Rb directly suppresses c-MYC promoter activity in keratinocytes by binding its promoter, an activity suppressed by EBV oncogenes [57]. A high percentage of EBV association has been demonstrated in both PAC and BPH, supporting the oncogenic potential of EBV in these diseases [65].

Several studies have highlighted a potential synergistic effect of EBV and HPV in PC progression. For instance, the combination of EBV LMP-1 and HPV16 E6 downregulates key tumor suppressors (p27, pRb, and p53) while activating oncogenic pathways (checkpoint kinase 1 (Chk1), Akt,

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Table 1. Presence of EBV infection in PC (classified by release year, region, and odds ratio).

Country	Year	Author	Method	Number of cases	Positive cases	P/N %	Ref
Argentina	2002	Grinstein et al.	Immunohistochemistry	18	7	37	[63]
Northern Sweden	2007	Bergh et al.	PCR	352	31	8.8	[28]
United States of America	2008	Sfanos et al.	PCR	200	16	8	[29]
Australia	2013	Whitaker et al.	*In situ* polymerase chain reaction (IS-PCR) and standard PCR	10	4	40	[64]
Iraq	2014	Ali and Al-Alwany	*In situ* hybridization	40	19	47.5	[65]
Switzerland	2015	Wetterauer et al.	Immunohistochemistry	8	7	87.5	[66]
United Kingdom	2017	Taurozzi et al.	PCR	19	16	84	[67]
Iraq	2017	Mezher and Auda	Immunohistochemistry and PCR	20	5	25	[68]
Iran	2020	Malekshahi et al.	Nested PCR	64	1	1.6	[69]
Iraq	2020	AbdullahAbbas, and Saadoon	Real-time PCR	95	16	16.84	[70]
Iraq	2020	Taha et al.	ELISA	73	41	56.16	[71]
Iraq	2021	Al-Ramahy	PCR	60	5	8.33	[72]
Iran	2021	Nahand et al.	ELISA and qRT-PCR	67	23	34.32	[73]
Pakistan	2022	Ahmed et al.	PCR	99	39	39.39	[74]
Morocco	2023	Ennaji et al.	PCR	100	72	72	[75]
Poland	2024	Kiś et al.	PCR	115	57	49.56	[76]
Total				1340	359	26.79	

MAPK, and NF-κB signaling) [80]. In this context, Nahand et al. (2021) reported that EBV-HPV coinfection leads to increased expression of pro-inflammatory cytokines (IL-1, IL-6, IL-11) and enhanced NF-κB signaling, potentially promoting tumorigenesis [81]. Whitaker et al., identified EBV in normal, benign, and malignant prostate tissue, suggesting a potential beneficial effect. However, they also studied HPV alongside EBV, noting the possible interactions between HPV and EBV in PC, with EBV potentially enhancing HPV-induced carcinogenesis [64].

A key factor contributing to EBV-induced malignant progression is the effect of the LMP-1 viral protein on tumor suppressor protein p53. Guo et al. demonstrated that LMP-1 enhances the induction of survivin via p53, promoting cellular growth in the G1/S phase of the cell cycle [82]. Additionally, in B cells, LMP-1 induces BCL-2 expression, further supporting cell survival [83]. Wetterauer et al. reported that in the context of immune system weakening, EBV-infected B lymphocytes play a crucial role in immune regulation [66].

A study conducted in Al-Najaf Governorate reported that 25% of PC samples tested positive for EBV, with the highest percentage observed in grade 5 malignancies (3/7, 43.8%) [68]. Another study in 2020 found EBV in 16.84% of men with PC but didn't identify a statistically significant association between EBV infection and age. Interestingly, EBV-positive PC cases were more prevalent in urban areas [70]. Similarly, a separate study confirmed a higher incidence of EBV infection in urban compared to rural regions [68]. Additionally, research in Iraq revealed that 56.16% of the prostate samples were EBV-positive, suggesting that EBV may play a significant role in the development of both BPH and PC [71]

A potential link between EBV infection and PC development may be attributed to the expression of CD21 on certain epithelial cells. Nahand et al. reported that EBV can upregulate CD44 expression on the surface of the epithelial cells, with LMP1 and LMP2 expression being directly correlated with CD44 levels. Mechanistically, LMP1 has been shown to induce resistance to anoikis by promoting the expression of anti-apoptotic proteins such as survivin, CD44, inhibitor of DNA binding 1 (ID1), BIM, and reactive oxygen species (ROS) [84, 85].

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Table 2- Presence of EBV infection in PC cases across continents.

Continent	Total Number of Cases	Positive Cases	P/N %
America	218	23	10.55
Europe	494	111	22.46
Australia	10	4	40
Africa	100	72	72
Asia	518	149	28.76

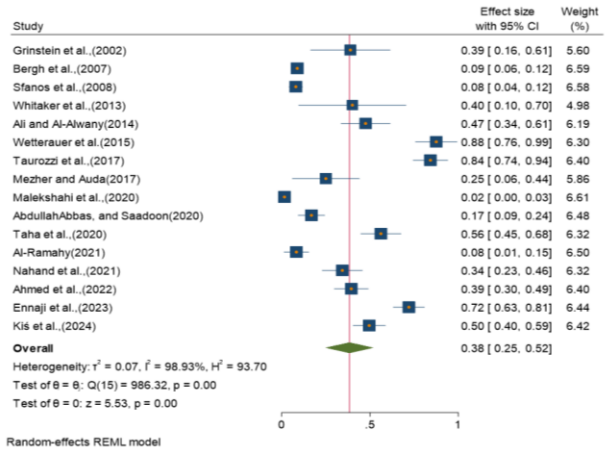

Figure 3. A forest plot of the prevalence of EBV infection in the world based on the random effects model.

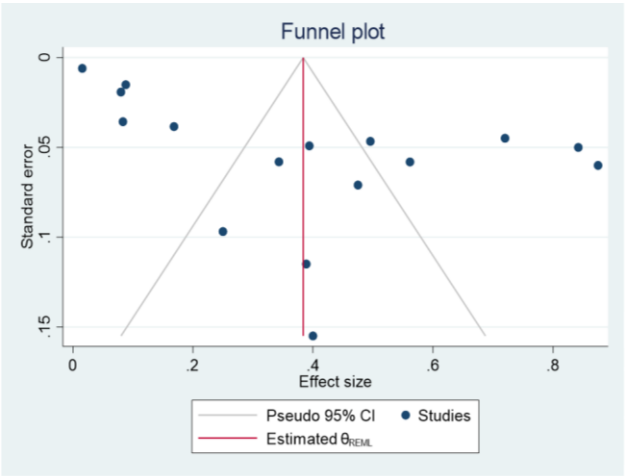

Figure 4. Funnel plot related to the results of the meta-analysis of the prevalence of EBV infection in PC cases worldwide.

However, a 2007 study found no apparent role of EBV in chronic prostatitis or PC [30]. Similarly, a study conducted in Iran identified EBV in only one case of PC [69]. Various factors may influence the evaluation of the relationship between the EBV and PC, including geographical variations, sample sizes, detection methods, and potential cofactors contributing to carcinogenesis. Further research with standardized methodologies is necessary to clarify this association.

This review placed no restrictions on age, sample types, or detection methods, allowing for a comprehensive analysis across various studies, publication years, and geographical regions. While EBV is recognized as an oncogenic virus, its precise role in PC development and progression remains unclear. Although some studies suggest a potential association, definitive evidence linking EBV infection to an increased risk of PC is still unavailable. Affirmative findings have been reported in certain countries but these have not been consistently replicated or confirmed in others. Additionally, variations in case numbers and differences in sample sizes across regions significantly influence the final statistical outcomes. Therefore, well-controlled, multi-regional studies are needed to establish a definitive correlation between EBV and PC.

11. CONCLUSION

While some evidence suggests a potential link between Epstein-Barr virus (EBV) and prostate cancer (PC), inconsistencies across studies underscore the need for further research. The oncogenic potential of EBV, particularly in relation to benign prostatic hyperplasia (BPH) and PC, remains uncertain. Variability in risk assessments and prevalence rates among different studies highlights the necessity for more comprehensive investigations to establish a definitive association. A clearer understanding of this relationship could have significant implications for prevention, screening, and treatment strategies for PC, including the development of targeted and immune-based therapies. Therefore, extensive, well-controlled investigations are crucial to fully elucidate the role of EBV in PC pathogenesis.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethical statement

This research did not involve ethical considerations.

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