The etiologic role of Epstein-Barr virus and cytomegalovirus infections in breast cancer development: a meta-analysis of case-control studies

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Abstract

Introduction: The role of viral infection in alterations of vital cellular pathways and genomic integration – and thus, human carcinogenesis – is well documented in molecular epidemiology studies. Epstein-Barr virus (EBV) and cytomegaloviruses (CMV) are two of the most studied human viruses for their potential association with cancer risk, progression, and outcome. The aim of this study was to assess the association of EBV and CMV infections with the risk of breast cancer, to more accurately evaluate the effect of these potential risk factors.

Material and methods: A thorough comprehensive electronic search was performed using the PubMed, EMBASE and Web of Science databases for relevant publications until February 28, 2021, based on predefined eligibility criteria. Data extracted from eligible studies were used to calculate pooled effect size, heterogeneity, publication bias, sensitivity, and subgroup analyses for both viruses independently. Meta-analyses were performed using Prometa 3 software.

Results: For EBV, a total of 19 studies were included, while 8 studies were included for CMV. A significantly high risk of breast cancer with EBV infection (OR = 5.04, 95% CI: 3.44–7.39, $p < 0.05$), and a similar, though smaller, risk with CMV (OR = 4.53, 95% CI: 2.04–10.03, $p < 0.05$), were found. EBV studies in which viral genetic material was detected in fresh breast cancer tissue showed higher risk compared to studies that relied on formalin-fixed paraffin-embedded specimens (FFPE) specimen. Conversely, for CMV, the FFPE studies showed a higher risk compared to studies relying on fresh breast cancer tissues.

Conclusions: It can be inferred that infection with either of the two viruses increases the risk of breast cancer, suggesting an etiologic role of these viruses in breast carcinogenesis.

Key words: risk, breast cancer, Epstein-Barr virus, cytomegalovirus, meta-analyses.

Introduction

Cancer is a leading cause of death globally and accounted for nearly 10 million deaths in 2020 [1]. Breast cancer (BC), the most common cancer among women, is recognized as a heterogeneous disease characterized by unique pathological characteristics, including morphology, grade, and hormone receptor profile. In addition, hormone receptors are used to divide tumors into clinically and biologically differentiated groups based on their characteristics [2]. There were an estimated 2.26 million newly diagnosed cases of breast cancers in 2020 [3]. Furthermore, breast cancer is diagnosed in the United States at an annual rate of more than 200,000 cases [4]. As defined in epidemiological studies, age, heredity, diet, tobacco use, and inflammation have all been identified as risk factors for cancer [5]. Interestingly, an evolving body of research has estimated that approximately 20% of human cancers could be related to virus infections encompassing Epstein-Barr virus (EBV) in addition to cytomegaloviruses (CMV) [6-10]. The CMV genome and antigens have been detected in several types of human cancer, including breast cancer, brain cancer, prostate cancer, and colon cancer [11-14]. Furthermore, millions of people are being infected with viruses around the world. Many of them are still at increased risk for cancer due to viral infection [15]. On the other hand, the idea that virus infections cause cancer has been neglected for many years.

In recent years, there has been increasing evidence that has helped us understand the association between viral infections and cancer, including breast cancer [15-17]. In the present meta-analysis, we attempted to explore EBV and CMV's role in breast cancer, potentially leading to new insight into how this disease incites, advances and can be detected, diagnosed and treated early.

Material and methods

Literature search strategy

The present meta-analysis was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We searched for relevant literature published until February 28, 2021 in the PubMed, EMBASE, and Web of Science databases, using a combination of the following search terms: "Epstein-Barr/EBV" or "Cytomegalovirus/CMV", with "Breast/Mammary", "Cancer/Carcinoma/Tumor", "Risk/Association". Open Grey, MedRxiv, BioRxiv, and Open Science Framework (OSF) preprints were searched for grey literature. Additionally, reference lists of all potentially eligible articles were manually searched.

Eligibility criteria and quality assessment

Eligible studies included in this meta-analysis met the following inclusion criteria: (1) case control design carried out on patients with breast cancer alone, (2) viral DNA examined in breast tissues in both study arms, (3) detection of viral genetic material is performed by real-time PCR or PCR, (4) clear pathological diagnosis, (5) studies reported odds ratio and the corresponding 95% confidence interval or enough data to calculate these values, the corresponding authors were contacted in case of missing data, (6) published in English language.

Studies were excluded if conducted on specimens from non-human sources; if they were reviews, editorials, or case studies; or viral DNA was not detected in both study arms.

We assessed the quality of each study using the modified Newcastle-Ottawa Scale (NOS) for case control studies [18]. To calculate a total quality score, we assessed criteria that cover selection, comparability, and exposure. A study can be awarded a maximum of one point for each item within the selection and exposure categories and a maximum of two points for comparability, with a total of 9 attainable points. Studies with a score ≥ 7 are considered of high quality, 5–7 moderate quality and < 5 poor quality.

The quality rating for each item was carried out independently by two reviewers and disagreements were resolved by consensus.

Data extraction

Data from eligible studies were extracted by one reviewer (BK) and verified by the second reviewer (KM) using a data extraction table; the data included the name of the author, year of publication, the population studied, type of specimen, viral gene or primers used, type of breast cancer, method for detection of viral DNA, total number of cases and controls, number of positive cases and controls, odds ratio, and 95% confidence interval.

Statistical analysis

The present meta-analysis was performed using Prometa3 software. We computed the pooled estimate (OR) and 95% confidence interval by means of a random effects model (DerSimonian Laird method). The heterogeneity among studies was estimated using the Cochran Q statistic and I^2. Heterogeneity was considered insignificant with $I^2 < 40\%$, moderate heterogeneity with I^2 between 40% and 60%, and substantial heterogeneity with $I^2 > 60\%$.

Publication bias was evaluated with the funnel plot, Egger's linear regression test, and the Begg and Mazumdar rank correlation test, with a p value < 0.1 indicating potential bias. Sensitivity anal-

ysis was also performed to assess the influence of each individual study.

Results

Identification and retrieval of studies

A total of 14,260 articles were retrieved through a systematic search of the three databases for EBV and breast cancer. Additionally, 67 articles were identified through grey literature and manual search (Figure 1). Following the removal of duplicates and irrelevant articles, 482 articles were subjected to title and abstract screening, resulting in the exclusion of 246 articles. For the remaining 236 articles, a full text evaluation was carried out, which led to further exclusion of 217 articles, out of which 139 articles lacked extractable data, 52 articles had a different study design, and 26 studies relied on techniques other than PCR or qPCR for viral DNA identification. Ultimately, 19 articles were included in this meta-analysis.

On the other hand, the search for records on CMV resulted in 13,522 articles from the database search, in addition to 37 articles identified through grey literature and manual search. The removal of duplicates and irrelevant articles led to 235 articles, which were then screened based on title and abstract, a process that led to further exclusion of 181 articles; the full text of the remaining 54 articles was thoroughly assessed for eligibility, which led to 8 studies being included in the final meta-analysis (Figure 2).

Study characteristics

The 19 EBV studies included in the present meta-analysis covered relatively large geodemographic variations, with a sample size of 2815 participants, encompassing 3 studies each from Australia and Iran, 2 studies each from France, England, and Egypt, and one study each from New Zealand, Argentina, Tunisia, Jordan, Sudan, Eretria and Pakistan. The viral genes investigated in these studies included EBER genes, EBNA-1, BamH1W, BALF5, BamHIC, BamHiG, EBER-2, and LMP-1.

On the other hand, the eight CMV studies consisted of two studies each from Egypt and Iran and one study each from the United States, Mexico, New Zealand and Taiwan. The viral genes investigated by these studies included the IE1, IE2, the GB region, and PP65 from either paraffin-embedded or fresh breast tissues (Table I). Upon quality assessment, all studies obtained a quality score of ≥ 7 on the NOS tool, indicating high quality (Figure 3).

Meta-analysis and heterogeneity

The pooled effect size for the association of EBV and CMV infections and the risk of breast cancer was estimated using the DerSimonian Laird method of the random effects model (OR = 5.04, 95% CI: 3.44–7.39) for EBV and (OR = 4.53, 95% CI: 2.04–10.03) for CMV. The random effects model was used in meta-analyses for both viruses despite the relatively low heterogeneity between the EBV studies (Q = 20.44, p = 0.308, I^2 = 11.95%) and

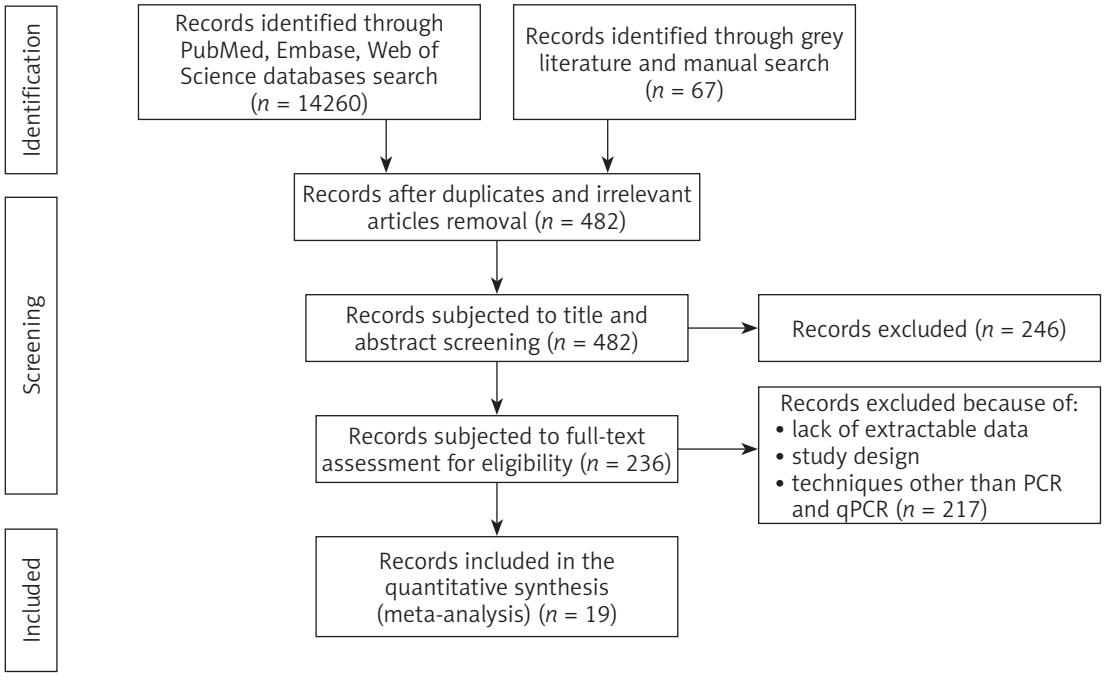


Figure 1. PRISMA flowchart of studies included in Epstein-Barr virus (EBV) meta-analysis

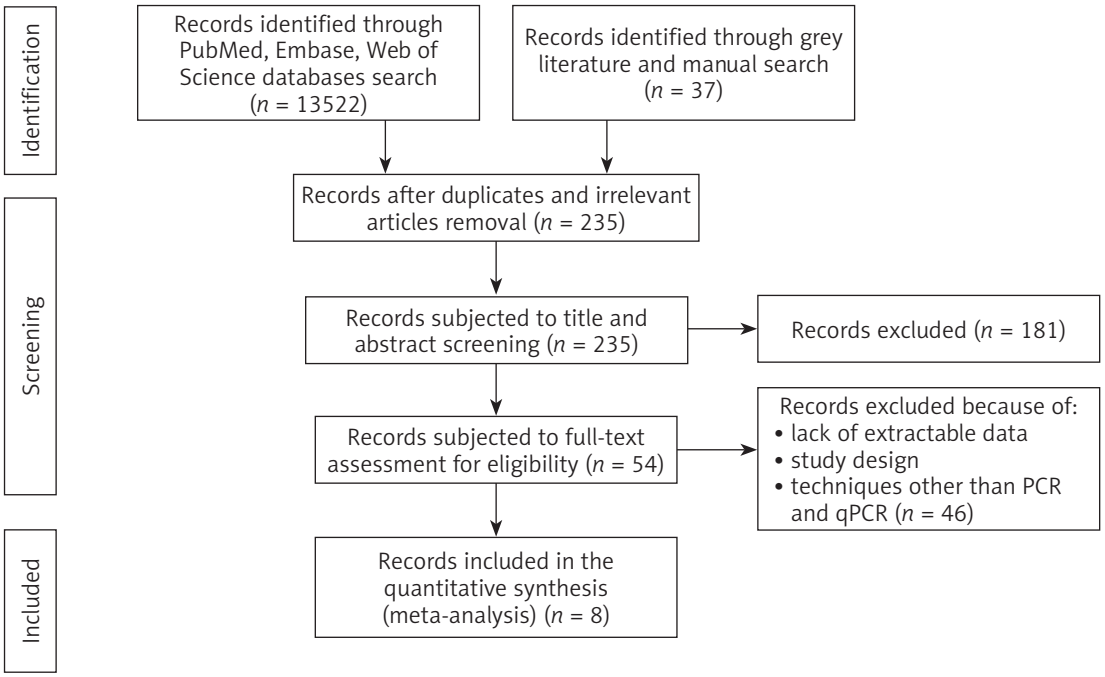


Figure 2. PRISMA flowchart of studies included in cytomegalovirus (CMV) meta-analysis

moderate heterogeneity between the CMV studies (Q = 14.85, $p = 0.038$, $I^2 = 52.85\%$) (Figures 4, 5).

Sensitivity analysis and publication bias

Sensitivity analysis was carried out by repeating the primary meta-analysis accompanied by removal of one study at a time during the analysis and detecting any effect size alteration due to presence of any arbitrary values in these studies. The lack of significant change in the pooled effect size for studies of both viruses indicated the stability of the present meta-analyses. Furthermore, publication bias was assessed using the Begg and Mazumdar rank correlation test, Egger's linear regression test, and funnel plot. Neither Begg's test (EBV: $Z = 0.31$, $p = 0.753$) (CMV: Z = 0.25, $p = 0.805$), Egger's test (EBV: $t = 2.12$, $p = 0.05$) (CMV: $t = -0.34$, $p = 0.746$), nor the funnel plots (Figures 6, 7) showed any evidence of publication bias.

Subgroup analysis

Subgroup analysis was carried out to determine the difference in the risk of breast cancer with viral infection according to the type of sample used for viral detection and to highlight the source of heterogeneity among the included studies. For EBV, a slight difference was noted in the risk of breast cancer when fresh or frozen breast tissues were used (OR = 5.51, 95%CI: 3.42–8.89, $p < 0.001$), with extremely low heterogeneity (Q = 8.05, $p = 0.429$, $I^2 = 0.57\%$) compared to formalin-fixed paraffin-embedded specimens (FFPE) (OR = 4.51, 95% CI: 2.48–8.20, $p < 0.001$) with slightly raised heterogeneity (Q = 11.88, $p = 0.220$, $I^2 = 24.22\%$) (Figure 8). Meanwhile, for CMV, the fresh/frozen breast tissues showed slightly lower risk of association, although not statistically significant (OR = 3.65, 95% CI: 0.94–14.14, $p = 0.061$) and significant heterogeneity (Q = 12.35, $p = 0.006$, $I^2 = 75.71\%$) as compared to higher risk in the FFPE subgroup (OR = 4.12, 95% CI: 1.81–9.38, $p = 0.001$) with no heterogeneity (Q = 2.35, $p = 0.504$, $I^2 = 0.00\%$) (Figure 9).

Discussion

Cancer is the second leading cause of death worldwide, surpassed only by cardiovascular diseases, and breast cancer ranks second among the most commonly occurring cancers overall [19].

Beside its ability to easily infect B lymphocytes, EBV can also infect epithelial cells, but not with the same ease. The virus uses different sets of envelop proteins to bind and enter these cells, namely, gp350 protein for the former and gp40 protein for the later [20]. The virus is known to promote oncogenesis with the help of several intriguing products that interfere with apoptosis, cause genomic instabilities, cellular transformation and metastasis [21].

Similarly, CMV is characterized by its life-long latency following the evasion of the immune system responses. Upon its reactivation, it expresses several proteins such as US27, US28, and UL78, that increase the host cell metabolism, enable the cell to avoid the G1 phase, and ultimately transforming the host cell [12, 22].

Table I. Characteristics of studies included in the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) meta-analyses

Author	Year	Country	Specimen type	Primer/ gene	Type of BC	Detection method	Quality score
EBV							
Abdel-Rahman	2012	Egypt	FFPE	EBNA-1	IDC	qPCR	8
Ann	2015	New Zealand	Fresh BC tissues	EBNA-1	IDC	qPCR	9
Annika	2012	Australia	Frozen tissues	BALF5	IDC	qPCR	8
Chia	2018	Iran	FFPE	EBNA 3C	DC	qPCR	8
Fina	2001	France	Fresh BC tissues	BamHIC	IDC	qPCR	8
Ghimja	2017	Eretria	FFPE	EBER	DC/LC	qPCR	7
James	2017	Australia	FFPE	EBNA-1	IDC/ILC	qPCR	9
Louise	1995	England	Fresh BC tissues	BamH1W	IDC/ILC	PCR	9
Mario	2010	Argentina	Fresh BC tissues	EBNA-1	IDC/ILC	qPCR	8
Maryam	2017	Iran	FFPE	BamH1W	MC/TC	qPCR	7
Mathilde	1999	France	Fresh BC tissues	EBER-2	DC/LC	PCR	7
Mohamed	2011	Tunisia	Frozen tissues	BamHIG	DC /LC	PCR	9
Mohamed	2012	Jordan	FFPE	EBER-2	IDC/LC	qPCR	8
Morvarid	2020	Iran	FFPE	EBNA-1	IDC/ILC	qPCR	9
SA	2003	England	Fresh BC tissues	EBNA-1	DC/LC	PCR	8
Shereen	2008	Egypt	FFPE	EBNA-1	IDC/ILC	PCR	7
Wasifa	2017	Pakistan	FFPE	EBNA-2	DC/IDC	qPCR	9
Wendy	2012	Australia	FFPE	EBNA-1	DC in situ	qPCR	9
Zeinab	2014	Sudan	Fresh BC tissues	LMP-1	IL/IDC	qPCR	7
CMV							
Eghbali	2012	Iran	FFPE	GB	DC	PCR	9
El-shazly	2017	Egypt	Fresh BC tissues	IE2	IDC/ILC	qPCR	9
El-shinawi	2013	Egypt	Fresh BC tissues	IE2	IBC	PCR	8
Harkins	2010	USA	FFPE	IE1	BC	qPCR	8
Richardson	2015	New Zealand	Fresh BC tissue	PP65	IBC	qPCR	8
Sepahvand	2019	Iran	FFPE	GB	DC	PCR	7
Tasi	2005	Taiwan	Frozen tissues	IE2	IDC	PCR	9
Utrera-Barillas	2013	Mexico	FFPE	IE2	BC	qPCR	8

FFPE – formalin-fixed paraffin-embedded, BC – breast cancer, IDC – invasive ductal carcinoma, ILC – invasive lobular carcinoma, MC – modular carcinoma, DC – ductal carcinoma, IBC – invasive breast cancer, LC – lobular carcinoma.

In the present meta-analysis, we attempted to unravel the etiological role of EBV and CMV in breast carcinogenesis, raising the prospect of an exploitable relation for better understanding disease induction, progression, and early detection, diagnosis, treatment, and possible prophylaxis. We examined the association of EBV infection on one hand and CMV infection on the other hand with the risk of breast cancer. Ten of the 19 studies included in the meta-analysis of EBV showed a significantly higher risk of breast cancer with EBV infection, while 4 out of 8 studies in CMV showed a significantly higher risk of breast cancer with viral infection. Our findings showed that EBV infection increases the risk of developing breast cancer five times, and four and a half times with CMV infection.

The etiological roles of EBV and CMV in the risk of breast cancer were previously explored under different contexts; however, contradictory results were reported, with several studies [18, 19, 23–25] reporting a lack of possible association between EBV and breast cancer, while other studies [26–28] suggest a strong association. Similar contradictory results were also reported for CMV [29–31].

Our results are consistent with the findings reported in previous studies [28, 32, 33]. Although EBV infection in these studies was detected differently using *in situ* hybridization (ISH) and immunohistochemistry (IHC) techniques, the level of risk of breast cancer remained consistent with our pooled effect size. Similar consistency was also observed with previous studies [32] in the results of CMV infection.

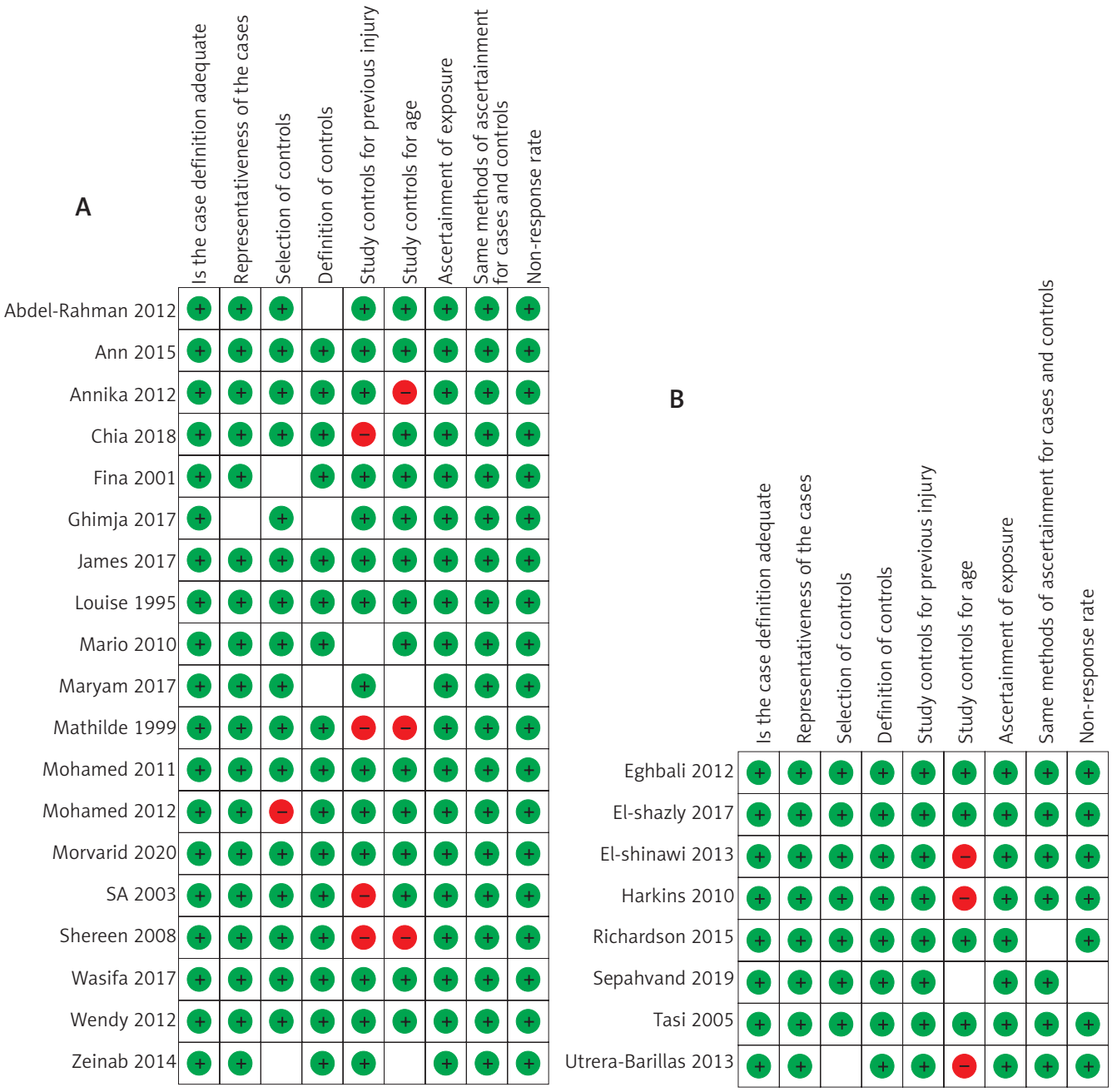


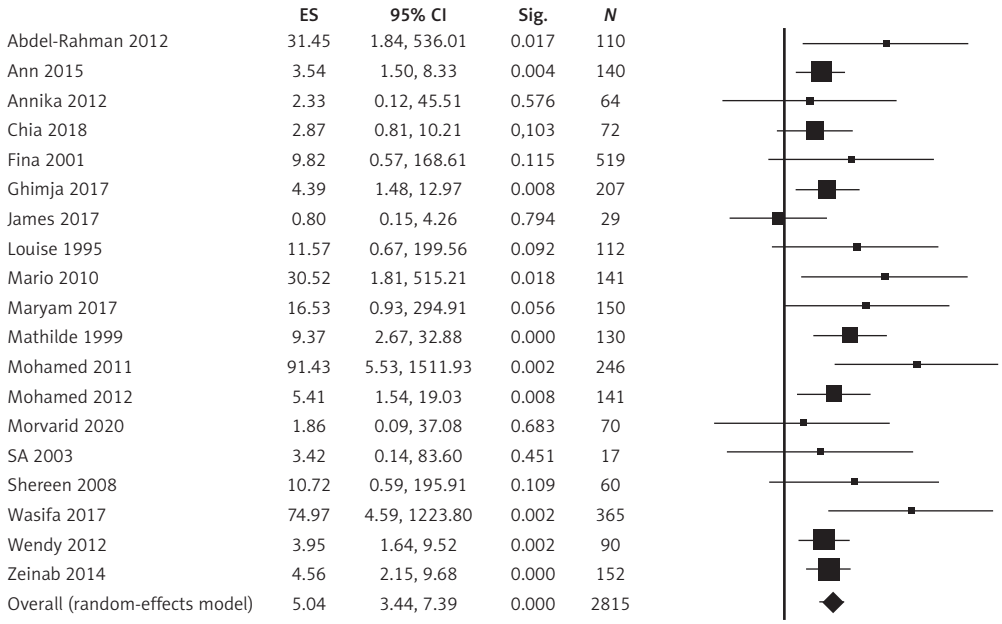
Figure 3. Quality assessment of included studies using NOS tool (**A**) Epstein-Barr virus, (**B**) cytomegalovirus

Epstein-Barr virus infection has been reported to be involved in several epithelial and lymphatic neoplasms, including gastric cancer [34], hepatobiliary system cancer [35], nasopharyngeal carcinoma [36] Hodgkin's lymphoma [37], and non-Hodgkin lymphomas [38]. The virus is believed to promote tumorigenesis through different pathways, such as the expression of the viral protein LMP1, which activates the Her2/Her3 signaling cascades in mammary cells [39].

The oncogenic properties of CMV, such as the expression of four genes that encode G-protein-coupled receptor (GPCR)-like proteins, namely US27, US28, UL33, and UL78, which play a key role in the signaling pathways of cAMP and PI3K, are important for anchorage-independent cell growth and epithelial cell transformation [40, 41]. These genes qualified the virus to play an important role in many cancers and other diseases [12, 42–44].

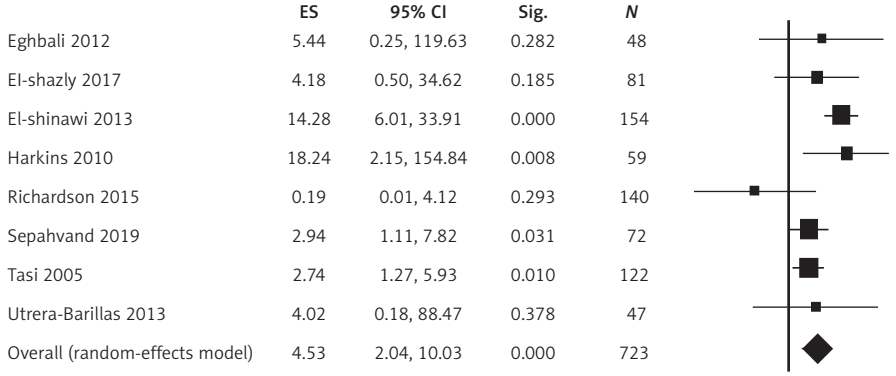
We carried out a subgroup analysis based on the type of sample used for the detection of viral DNA, FFPE, or fresh/frozen tissues, to determine the source of heterogeneity and detect variations in the risk of breast cancer according to the sample used.

Relatively low heterogeneity was detected between the studies used for the quantitative syn-



	ES	95% CI	Sig.	N
Abdel-Rahman 2012	31.45	1.84, 536.01	0.017	110
Ann 2015	3.54	1.50, 8.33	0.004	140
Annika 2012	2.33	0.12, 45.51	0.576	64
Chia 2018	2.87	0.81, 10.21	0,103	72
Fina 2001	9.82	0.57, 168.61	0.115	519
Ghimja 2017	4.39	1.48, 12.97	0.008	207
James 2017	0.80	0.15, 4.26	0.794	29
Louise 1995	11.57	0.67, 199.56	0.092	112
Mario 2010	30.52	1.81, 515.21	0.018	141
Maryam 2017	16.53	0.93, 294.91	0.056	150
Mathilde 1999	9.37	2.67, 32.88	0.000	130
Mohamed 2011	91.43	5.53, 1511.93	0.002	246
Mohamed 2012	5.41	1.54, 19.03	0.008	141
Morvarid 2020	1.86	0.09, 37.08	0.683	70
SA 2003	3.42	0.14, 83.60	0.451	17
Shereen 2008	10.72	0.59, 195.91	0.109	60
Wasifa 2017	74.97	4.59, 1223.80	0.002	365
Wendy 2012	3.95	1.64, 9.52	0.002	90
Zeinab 2014	4.56	2.15, 9.68	0.000	152
Overall (random-effects model)	5.04	3.44, 7.39	0.000	2815

Figure 4. Forest plot of the association of Epstein-Barr virus with the risk of breast cancer



	ES	95% CI	Sig.	N
Eghbali 2012	5.44	0.25, 119.63	0.282	48
El-shazly 2017	4.18	0.50, 34.62	0.185	81
El-shinawi 2013	14.28	6.01, 33.91	0.000	154
Harkins 2010	18.24	2.15, 154.84	0.008	59
Richardson 2015	0.19	0.01, 4.12	0.293	140
Sepahvand 2019	2.94	1.11, 7.82	0.031	72
Tasi 2005	2.74	1.27, 5.93	0.010	122
Utrera-Barillas 2013	4.02	0.18, 88.47	0.378	47
Overall (random-effects model)	4.53	2.04, 10.03	0.000	723

Figure 5. Forest plot of the association of cytomegalovirus the risk of breast cancer

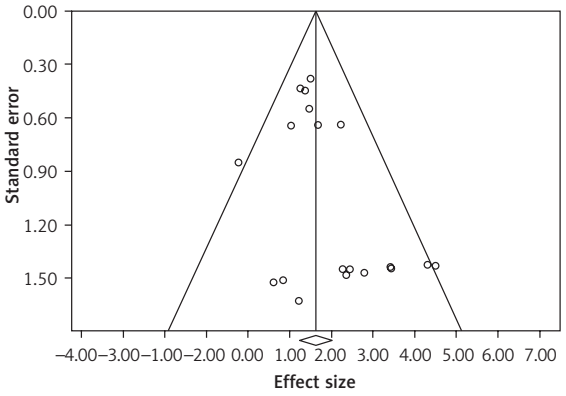


Figure 6. Funnel plot for estimation of publication bias of studies including Epstein-Barr virus

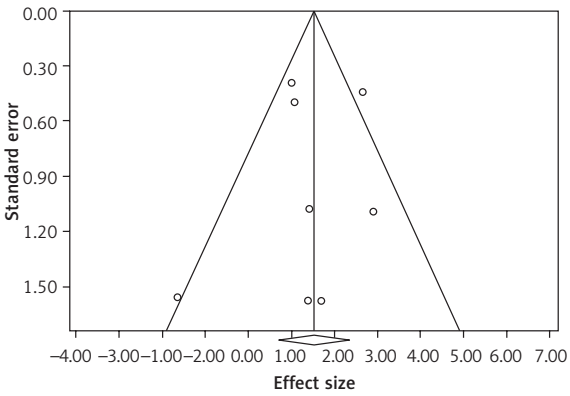


Figure 7. Funnel plot for estimation of publication bias of studies including cytomegalovirus

thesis of the relationship between EBV and breast cancer risk. The subgroup analysis revealed that the major contributors to this heterogeneity were studies involving the use of FFPE specimens. This study also found a higher risk of breast cancer when fresh breast tissues are used (OR = 5.5, 95% CI: 3.42–8.89, p = 0.000) compared to studies based on FFPE cancer specimens (OR = 4.51, 95% CI:

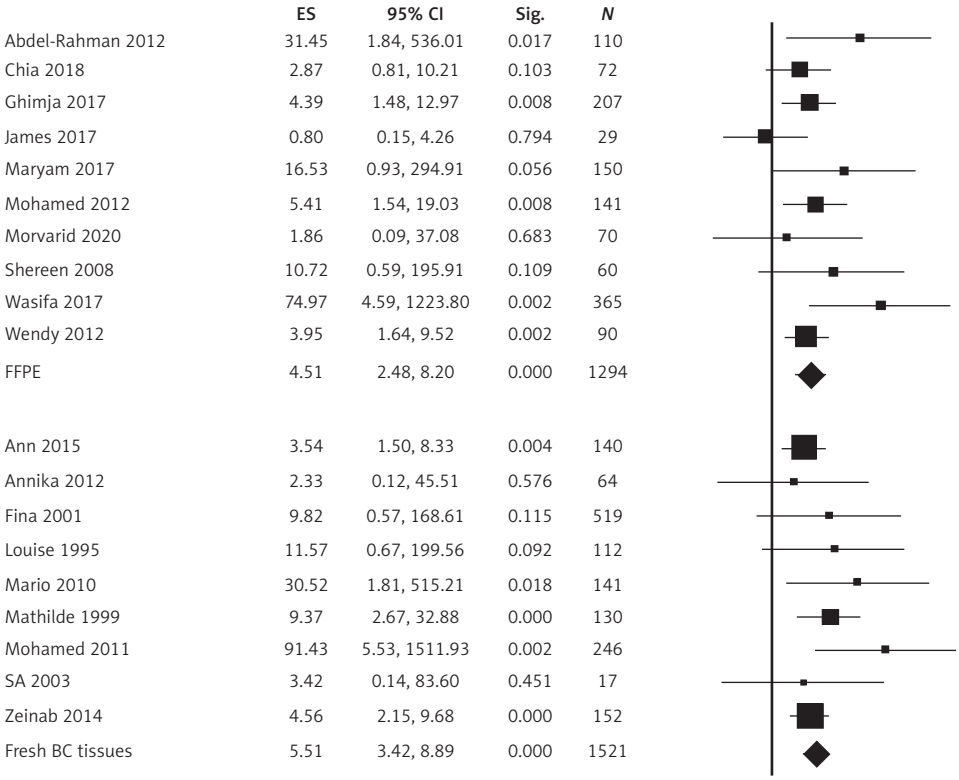


Figure 8. Subgroup analysis for Epstein-Barr virus and breast cancer according to the type of specimen

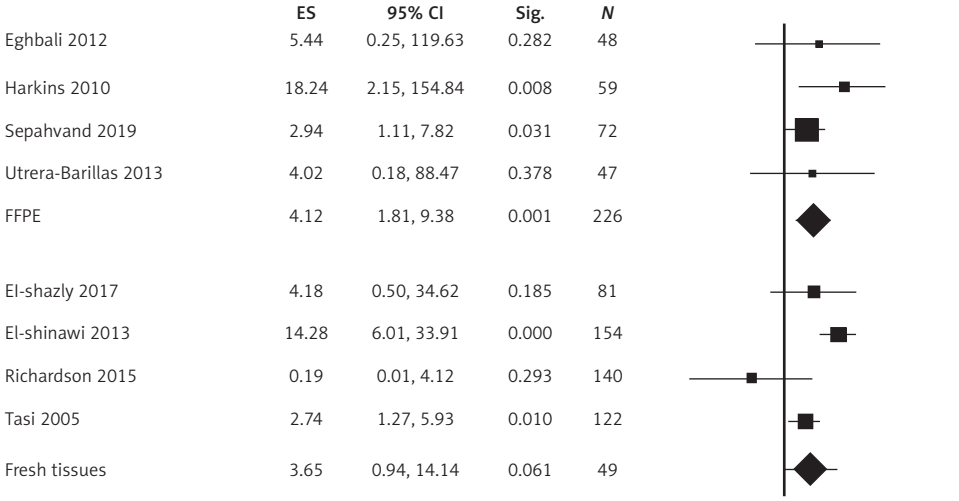


Figure 9. Subgroup analysis of cytomegalovirus and breast cancer according to the type of specimen

2.48–8.20, $p = 0.000$), which agrees with the findings reported by Farahmand *et al*. [45]; this indicates that fresh breast tissues are the best specimens to detect EBV. Conversely, studies included in the CMV meta-analysis showed a much higher heterogeneity, most of which was contributed by studies involving the use of fresh breast tissue specimens, while there was no heterogeneity between studies involving the use of FFPE specimens. This variation in heterogeneity apparently impacted the level of breast cancer risk in the two subgroups, with the subgroup involving the use of fresh breast tissue showing a lower risk of breast cancer, although statistically not significant (OR = 3.65, 95% CI: 0.94–14.14, $p = 0.061$) as compared to the higher risk in the FFPE subgroup (OR = 4.12, 95% CI: 1.81–9.38, $p = 0.001$).

In conclusion, infection with either of the two viruses significantly increases the risk of breast cancer. This risk is slightly higher with EBV infection compared to CMV infection, suggesting an etiological role of these two viruses in breast car-

cinogenesis and potential value in early detection, treatment, and prevention of the disease. The current meta-analysis explored the association of each of the two viruses with the risk of breast cancer independently; further comprehensive studies are recommended exploring the combined risk of the two viruses.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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