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Original Article

Molecular detection of Epstein–Barr virus in invasive ductal carcinoma of the breast: a case–control study

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Abstract

The uncertain contribution of Epstein–Barr virus (EBV) to the etiological processes underlying invasive ductal carcinoma (IDC) of the mammary gland, especially in relation to its molecular interactions within inflamed histological contexts, remains to be elucidated. This case–control research assessed the link between EBV infection and mammary IDC in a population of Iraqi females from Kirkuk. A total of 300 breast tissue specimens preserved in paraffin blocks were evaluated, including 150 samples diagnosed with IDC and 150 samples classified as fibroadenoma serving as controls. EBV latent membrane protein-1 expression was identified through the application of immunohistochemical staining and polymerase chain reaction methodologies. EBV positivity, defined as detection by both IHC and PCR, was observed in 7.3% of IDC cases and 4% of controls, with no statistically significant difference between groups (P=0.996). No significant association was found between EBV presence and estrogen or progesterone receptor status, while Her-2 expression differed significantly between EBV-positive and EBV-negative patients (P<0.001). EBV was more frequently detected in grade I tumors and stage II breast cancers, and older patients showed a higher prevalence of EBV infection. The results indicate that although Epstein–Barr virus (EBV) is identifiable in a fraction of invasive ductal carcinoma (IDC) breast specimens, a definitive causative relationship between EBV presence and IDC occurrence within this demographic is not established. Nonetheless, EBV detection appears to exhibit higher frequency in specific histopathological grades, clinical stages, and patient age categories.

Keywords: Breast cancer, Ductal carcinoma, EBV, IHC, PCR.

1. Introduction

Worldwide, mammary carcinoma represents the most commonly diagnosed neoplastic disorder among women (excluding cutaneous malignancies of the non-melanoma type) and accounts for the highest proportion of cancer-related deaths in the female population [1]. Its incidence varies across multicultural communities, indicating that the biological expression and the influence of etiological factors may vary [2,3]. In Iraq, the age-standardized incidence rate (ASR) was 39.7 per 100,000 person-years during 2011-2019, and its incidence varies across multicultural communities, indicating that the biological expression and influence of etiological factors on the course of the disease [4,5]. With an overall incidence of 11.7% of cases diagnosed, breast cancer ranked first among the 36 most common cancer types in 159 countries in 2020, accounting for 2,261,419 cases. High-income regions like Australia and New Zealand had the highest age-standardized incidence rate (95.5/100,000), whereas South Central Asia had the lowest rate (26.2/100,000) [6]. In Iraq, the breast was the most prevalent cancer location in terms of incidence among females (35.95/100,000 persons per year) and death (6.22/100,000 persons annually) [7].

It is yet unknown what molecular processes EBV may use to cause breast cancer. Nonetheless, some insight into possible processes has been provided by the molecular characterization of breast cancers. Consequently, analogous to other EBV-associated epithelial malignancies, expression of EBV-derived transcripts including EBNA1, LMP1, BZLF1, and BARF1 has been identified within mammary cancer samples [8]. Furthermore, latency type II tumors associated with EBV were identified by the expression of EBNA1 and LMP1-2B together with lytic gene expression of BXLF2 and BFRF3, indicating a potential role for latent/lytic switch activation [9]. Mofrad *et al*. found in 2020 that all breast cancer control samples tested negative for EBNA-1, but 4/59 (6.7%) of Iranian samples tested positive. Furthermore, tumors that tested positive for EBV were categorized as high grade (II and III) [10].

Detection of viral nucleic acid within tissue specimens can be achieved through multiple analytical techniques, including polymerase chain reaction and in situ hybridization. Given that PCR alone may exhibit limited specificity in differentiating malignant cells from infiltrating lym-

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phoid populations, it is recommended that both ISH and PCR be employed concurrently to enhance the precision of viral genome identification in neoplastic breast tissue [11-13]. The finding of EBV nucleic acid DNA in breast tissue may potentially be impacted by tissue preparation. Although there was no documented link between EBV and the mammary cancers in a study done on dogs, for the first time, the authors discovered EBV DNA in canine mammary cancers. This implies that the amount and quality of DNA recovered from paraffin-embedded tissues may have an impact on virus detection [14]. Even with these advancements in EBV detection, it is difficult to assess oncogenic viruses in all types of breast cancer because viral loads are so low.

Immunohistochemistry (IHC) is an essential auxiliary technique in the clinical practice of breast pathology that helps with the detection and classification of a wide variety of breast abnormalities. Despite the fact that many benign and malignant breast lesions have well-defined morphologic characteristics, numerous tumors may exhibit overlapping traits. IHC may be particularly useful in the differential diagnosis of some diagnostically challenging breast lesions [15]. Here, we used both IHC and PCR to investigate the potential link between EBV infection and invasive ductal breast cancer.

2. Materials and Methods

2.1. The study design and setting

The study cases were retrieved from the archive of Histopathology Laboratory in Azadi Teaching Hospital, Kirkuk, Iraq for the period between January 1st 2022 and January 20th 2024 and including 150 formalin fixed and paraffin embedded tissue specimens of mastectomies with a diagnosis of invasive ductal carcinoma (not otherwise specified) IDC (NOS) as a case group and 150 formalin fixed and paraffin embedded tissue specimens with a diagnosis of fibroadenoma as a control group.

Clinical information was gathered from these patients' medical records. Age, tumor grade, tumor stage, hormone receptor status, and Her-2/neu status were some of these variables. The study was authorized by Kirkuk Medical College's ethics committee and adhered to the World Medical Association's (Declaration of Helsinki) guidelines for human research.

2.2. EBV detection

2.2.1. Immunohistochemistry

Immunohistochemical staining for LMP1 was performed using antibodies, buffers, and linking systems obtained from in vitro Master Diagnostic™ (Spain). The primary antibody used was a clonal mouse monoclonal antibody against LMP1 (clone CS1-4, reference MAD-001619QD). All products, including the primary antibodies, ultra-sensitive micro polymer-based universal detection systems, and auxiliary reagents, were sourced from the same manufacturer. The staining procedure was carried out following the manufacturer's instructions.

2.2.2. Molecular tests

2.2.2.1. DNA extraction

Genomic DNA was isolated from formalin-fixed, paraffin-embedded tissue sections utilizing the RIBO-prep nucleic acid isolation system, catalog number K2-9-Et-100-CE. All procedures were executed in strict accordance with the protocol provided by the manufacturer.

2.2.2.2. Detection of the virus by PCR

Using specialized EBV primers, a section of the pathogen's genome was amplified to identify EBV via the polymerase chain reaction (PCR). Fluorescent dyes were used in real-time PCR to detect the amplified product. Conventionally, these chromogenic signals were linked to specific oligonucleotide probes that hybridized exclusively with the amplified target during thermal cycling. This enabled real-time detection of the accumulating amplicon without the need to reopen the reaction vessels post-amplification. The AmpliSens® EBV-screen/monitor-FRT PCR assay, designed for both qualitative and quantitative analysis, was employed incorporating internal controls of both endogenous and exogenous origin.

The Internal Control STI-87 (IC), known as the exogenous internal reference, was applied throughout the plasma isolation process from peripheral blood to oversee the analytical stages of individual specimens and identify any potential interference affecting the reaction. The DNA fragment of the β-globin gene was amplified when a clinical sample, including cells, including white blood cells, and complete human blood. A human genome piece called the β-globin gene's DNA fragment served as an internal endogenous regulator. Therefore, monitoring test steps (DNA extraction and amplification) and evaluating the suitability of clinical material sampling and storage were made possible by the use of an endogenous internal control.

The "hot-start" mechanism integrated into the AmpliSens® EBV-screen/monitor-FRT PCR system significantly minimized the occurrence of unintended primer annealing events. This feature was enabled through the use of TaqF, a polymerase enzyme modified via chemical means, ensuring controlled initiation. Activation of the altered TaqF enzyme was achieved by subjecting it to thermal exposure at 95 °C for a duration of 15 minutes.

The uracil-DNA-glycosylase (UDG) and dUTP enzymes were used in the PCR kit to prevent amplicon contamination. DNA containing deoxyuridine was recognized and destroyed by the enzyme UDG, although DNA containing deoxythymidine was unaffected. Since dUTP was a component of the dNTP mixture in the amplification reagents, deoxyuridine was always present in amplicons but lacking in real DNA. Because contaminating amplicons included deoxyuridine, they were susceptible to UDG's destruction before DNA-target amplification. Thus, it was not possible to amplify the amplicons. UDG was a thermolabile enzyme. Heating it to a temperature higher than 50 °C deactivated it. Consequently, the target amplicons that were collected during PCR were not destroyed by UDG (Reference number: R-V9-100-S (RG,iQ, Mx)-CE).

2.2.2.3. Analysis of data

The real-time PCR device software analyzed fluorescence signal accumulation across three channels to interpret the results. Amplification of the β-globin gene DNA (internal control, IC Glob) was detected via the FAM fluorophore channel. The Epstein-Barr virus (EBV) DNA signal, representing positive control DNA alongside human DNA, was detected through the JOE fluorophore channel. Amplification of the internal control STI-87 (IC) DNA was monitored using the ROX fluorophore channel. The

instrument's algorithms evaluated the data based on whether the fluorescence amplification curve crossed the predefined threshold line at cycle 33.

2.3. Identification of positive cases

It is important to emphasize that the outcomes obtained via polymerase chain reaction were consistent with those derived from immunohistochemical analysis, with the exception of the cohort of patients exhibiting minor discrepancies. Each specimen underwent independent and isolated evaluation through both PCR and IHC methodologies; classification as EBV-positive was assigned exclusively to cases demonstrating positivity in both analytical approaches.

2.4. Ethical consideration:

The research framework received authorization from the ethics board affiliated with the College of Medicine at the University of Kirkuk.

2.5. Exclusion criteria

Instances in which polymerase chain reaction yielded positive results while immunohistochemistry was negative were not classified as positive and were omitted from consideration.

2.6. Statistical analysis

Digital statistical evaluation was performed utilizing SPSS software version 26. The Chi-square test was employed to assess data distributions (P-value) and examine nominal variables and associated probabilities (P). Findings were interpreted as statistically significant (S) when the P-value was below 0.05, as highly significant (HS) when the P-value fell below 0.01, and as significant when the P-value was under 0.05. Values of P exceeding 0.05 were regarded as lacking statistical significance.

3. Results

Regarding the age distribution of the patients and control group, the largest proportion of patients, 49 (32.6%), were aged 66–75 years, whereas the highest percentage in the control group, 66 (44%), was observed in the 25–35 years age range. It was also noted that the 25–35 years age group had the lowest representation among patients, with 8 (5.3%), while the control group's lowest percentage, 21 (14%), was in the 46–55 years age range, as shown in Table 1.

Table 1. Age distribution of the patients and the control group.

Age groups	Patient No. (%)	Control No. (%)
25-35	8 (5.3)	66 (44)
36-45	32 (21.3)	63 (42)
46-55	43 (28.6)	21 (14)
56-65	18 (12)	-
66-75	49 (32.6)	-
Total	150 (100)	150 (100)

Figure 1 shows the fluorescence curve crossing the threshold line at 33, and a detected positive case of EBV through the use of the real-time PCR technique.

In respect to the comparison between the patients and control group in regards to detection of the virus by either PCR technique or IHC, the present study revealed that the number of the positive cases of EBV in comparison to negative cases among patients' group was trivial and the differences were statistically non-significant (P= 0.832), indicating non-significant correlation between EBV presence and breast cancer. In addition, the present study revealed only 4% of positive cases in the control group, and the variances between the positive and negative cases of EBV were non-significant (P=0.996) (Table 2, Figure 2).

Furthermore, the present study showed the highest rate 2 (25%) of the positive cases of EBV detected through using of PCR technique was among patient's group aged less than 30 years old, while minor differences noticed among the positive cases between age groups (30-50) and > 50 years old where they recorded (7.6 VS 7.9%) respectively. The differences between the positive and negative cases were highly significant (P <0.01) as shown in Table 3.

Regarding the association between the tumor grade and detection of EBV by PCR technique, the current study

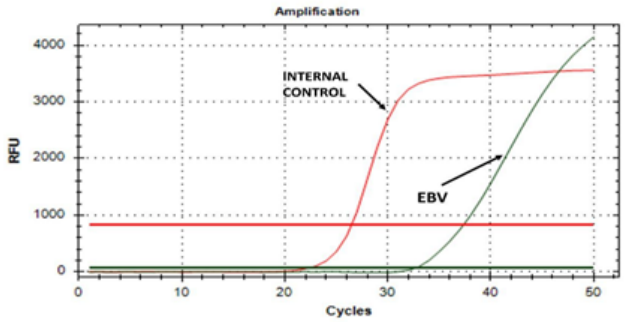

Fig. 1. A standard curve showing positive EBV of a patient with breast cancer

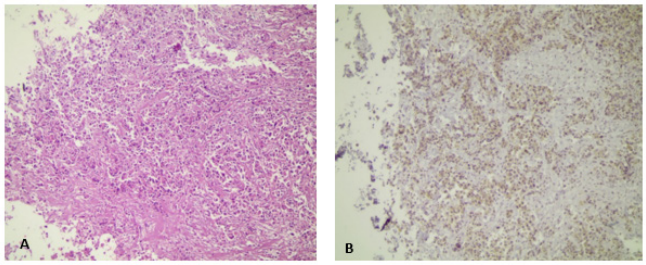

Fig. 2. Histopathological sections from invasive ductal carcinoma (NST); A-Hematoxylin and Eosin B-Immunohistochemical stained slide for EBV LMP1.

Table 2. Comparison between patients and controls in regards to detection of EBV by Immunohistochemistry and PCR.

Groups	Detection by PCR		Detection by IHC		P-Value
	+	-	+	-	
	No. (%)	No. (%)	No. (%)	No. (%)	
Patients	13/150 (8.66)	137/150 (91.33)	11/150 (7.33)	139/150 (92.66)	0.832
Control	6/150 (4)	144/150 (96)	6/150 (4)	144/150 (96)	0.996

Table 3. Clinical and pathological features of breast cancer patients and their association with PCR-based detection of EBV.

Character		Detection of EBV by PCR		P. Value
		+ No. (%)	- No. (%)	
Age	<30	2 (25)	6 (75)	<0.001
	30-50	6 (7.6)	73 (92.4)	
	>50	5 (7.9)	58 (92.1)	
Tumor grade	I	4 (14.3)	24 (85.7)	<0.001
	II	4 (7.5)	49 (92.5)	
	III	5 (7.2)	64 (92.8)	
Tumor stage	I	1 (5.6)	17 (94.4)	<0.001
	II	9 (12)	66 (88)	
	III	3 (5.3)	54 (94.7)	
ER	+	8 (10.3)	70 (89.7)	0.568
	-	5 (6.9)	67 (94.1)	
PR	+	9 (12.3)	64 (87.7)	0.152
	-	4 (5.2)	73 (94.8)	
Her-2	+	10 (22.2)	35 (78.8)	<0.001
	-	3 (2.9)	102 (97.1)	

documented the greatest rate of positive cases 4 (14.3%) among patients with tumor grade I in comparison to slight variances (7.5 VS 7.2) for both tumor grade II and III respectively and the variation between the positive and negative cases were highly significant P <0.0001.

Considering the tumor stage, the highest percentage, 9 (12%) of EBV positive cases detected among patients with tumor stage II, while the highest proportion of negative samples, 94.4% of EBV, was observed among patients' group with tumor stage III. The results were highly significant (P <0.0001). Table 3.

With respect to estrogen receptor (ER), only 10.3 % were positive and had positive EBV, in comparison to 89.7% were negative. The differences were non-significant (P=0.568), as shown in Table 3.

With respect to the Progesterone Receptor (PR), the current investigation demonstrated no statistically meaningful differences (P>0.05) between EBV-positive and EBV-negative cases in relation to PR expression status. In contrast, Her-2 exhibited markedly significant variation (P<0.001). Refer to Table 3.

4. Discussion

Epstein-Barr virus (EBV), a member of the human herpesvirus family, is detected in approximately 90% to 95% of the population, predominantly among pediatric and adolescent groups, and may manifest through diverse clinical presentations. Furthermore, EBV is implicated in oncogenic disorders including gastric adenocarcinoma, Hodgkin's disease, nasopharyngeal malignancy, and Burkitt's lymphoma. The International Agency for Research on Cancer (IARC) has designated EBV as a Group 1 carcinogenic agent. Consequently, its potential role in breast tumorigenesis has been the subject of investigation [16].

The current study showed that the greatest proportion, 49 (32.6%) of the patients were aged 66-75, which was in line with Mofrad MG *et al*., who detected that the highest proportion of breast cancer was found among patients in the age group older than 50 years old [10]. The current study was likewise close to a study conducted on Jordanian women, who revealed that the greatest percentage of the patients was older than 55 years old [17].

Moreover, the present study revealed that the number of EBV-positive cases compared to negative cases in the patient group was minimal, with no statistically significant difference (P = 0.832) based on PCR and IHC analyses. This indicates a non-significant correlation between EBV presence and breast cancer, consistent with the findings of El-Naby et al. [18] who also reported only slight differences between positive and negative cases detected by PCR or IHC. The current study was also in line with a study done in Iran, where they detected that there was no causal link between female breast invasive ductal carcinoma and EBV infection [19]. Our results disagreed with an Iranian study, where they found that 6.7% (4/59) of patients had EBV, whilst all breast control samples came back negative, which disagreed with our findings, where the control group showed 4% of the positive cases. These differences might be attributed to the differences in the technical issues or the differences in access to the virus in these communities [10]. From these points, it is clear that there might be no association between EBV presence and breast cancer.

Furthermore our study exhibited that the highest proportion 25% of the positive cases of the virus distinguished through using of PCR technique was in patient's group who aged less than 30 years old, this was near to a study done in India, where it revealed the greatest percentage of EBV was found among breast cancer women aged (25-45) [20]. The current study was likewise in line with a Sudanese study that revealed a high frequency of the disease among young women [21].

The present research documented the greatest ratio of positive cases, 4 (14.3%), among patients with tumor grade I, in comparison to slight variances (7.5 VS 7.2) for both tumor grade II and III, respectively. This disagrees with the study conducted by Mazouni et al [22], where they detected significant differences across tumor grades I (16.2%), II (32.0%), and III (46.4%), with the highest EBV positivity in grade III. These differences may be due

to the sample size differences between our study and this study, in addition to that the method of selection of the patients is different.

Taking into account the stage of the tumor, patients with stage II tumors had the highest percentage of EBV-positive cases (12%), whereas patients with stage III tumors had the highest percentage of EBV-negative samples (94.4%). Richardson *et al*. found that 70 breast cancer patients from New Zealand had 34.3% EBNA-1 positivity and 9 out of 70 had 13% in paired normal tissue; nevertheless, EBV positivity was unrelated to grade, receptor status, or disease stage, which was disagreed with our findings, the variances might be due to differences in response to the virus in these areas [23], whereas our study was in line with a Jordanian study in regards to the correlation of tumor stage and EBV positivity [24].

With respect to estrogen receptor (ER), only 10.3 % were positive and had positive EBV, in comparison to 89.7% were negative. The differences were non-significant (P=0.568). Regarding Progesterone receptor (PR), the present study revealed non-significant variations (P>0.05); these findings were in agreement with Richardson *et al*. [23].

The detection of Her-2 exhibited markedly significant variation (P<0.0001) between EBV-positive and EBV-negative patient subsets, closely resembling the observations made by Cyprian FS et al. [25], who noted that HER-2 and EBV-derived oncoproteins utilize overlapping downstream molecular pathways, including PI3k/Akt/mTOR, SRC/β-catenin, and RAS/MEK/ERK. This convergence may lead to disruptions in cellular differentiation processes (EMT), uncontrolled proliferation, evasion of programmed cell death, and enhanced vascular formation, thereby contributing to tumor initiation and/or promoting neoplastic advancement.

In conclusion, our findings indicate that Epstein–Barr virus can be detected in a subset of breast invasive ductal carcinoma cases, but there is no significant etiological association between EBV infection and the development of this malignancy in Iraqi women from Kirkuk. While EBV positivity was more frequently observed in certain tumor grades, stages, and among older patients, these associations do not support a direct causal role for the virus in breast carcinogenesis. Further studies with larger cohorts and advanced molecular techniques are warranted to clarify the potential contribution of EBV to breast cancer pathogenesis and its possible prognostic or therapeutic implications.

Abbreviations

EBV (Epstein-Barr Virus), PCR (Polymerase Chain Reaction), ICH (Immunohistochemistry), ISH (In-Situ Hybridization), ASR (Age-Standardized Rate), ER (Estrogen Receptor), PR (Progesterone Receptor), Her-2 (Human Epidermal Growth Factor Receptor 2), NOS (Not Otherwise Specified), IDC (Invasive Ductal Carcinoma), DNA (Deoxyribonucleic Acid), RNA (Ribonucleic Acid), EBNA1 (Epstein-Barr Nuclear Antigen 1), LMP1 (Latent Membrane Protein 1), BZLF1 (BamHI Z Leftward Reading Frame 1), BARF1 (BamHI-A Rightward Frame 1), BXLF2 (BamHI X Leftward Frame 2), BFRF3 (BamHI F Rightward Frame 3), UDG (Uracil-DNA Glycosylase), dUTP (Deoxyuridine Triphosphate), dNTP (Deoxynucleotide Triphosphate), FRT (Fluorescent Resonance Transfer), TaqF (Fruorescent Taq Polymerase), FAM (Fluorescein Amidite), JOE (6-Carboxy-4',5'-Dichloro-2',7'-Dimethoxyfluorescein), ROX (Carboxy-X-Rhodamine), IC (Internal Control), SPSS (Statistical Package for the Social Sciences), IARC (International Agency for Research on Cancer), PI3k/Akt/mTOR (Phosphoinositide 3-Kinase/Protein Kinase B/Mammalian Target of Rapamycin), RAS/MEK/ERK (Rat Sarcoma/Mitogen-Activated Protein Kinase Kinase/Extracellular Signal-Regulated Kinase), EMT (Epithelial-Mesenchymal Transition)

Conflict of interest

The authors declare that they have no conflict of interest.

Consent for publications

All contributors attest to having reviewed and sanctioned the finalized manuscript for publication..

Ethics approval and consent to participate

This investigation was carried out subsequent to receiving clearance from the Ethics Committee of the College of Medicine, University of Kirkuk. All methodologies involving human subjects adhered to the ethical principles established by both institutional and national research regulatory bodies, in accordance with the guidelines outlined in the Declaration of Helsinki.

Informed consent

Signed informed consent was secured from every subject before enrollment in the research. Participants were comprehensively briefed regarding the study's aims, methodologies, and potential risks.

Availability of data and materials

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Authors' contributions

M.M.M., A.K.A., and D.O.M. each played an equivalent role in the methodological structuring and theoretical formulation of the investigation. M.M.M. carried out the procurement of biological specimens and performed the associated benchwork procedures. A.K.A. undertook the interpretation and processing of the acquired data. D.O.M. authored the preliminary document and implemented analytical modifications to refine its scientific rigor. The conclusive manuscript was collectively examined and ratified by all listed contributors.

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