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CASE STUDY

# CORRELATION OF EPSTEIN-BARR VIRUS WITH BREAST CANCER: A CASE CONTROL STUDY

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## Abstract

**Background and aims**: Epstein-Barr virus (EBV) is a gamma herpes virus and one of the most common infections globally. It has been linked to several health problems, including breast cancer, which is a leading cause of death among females worldwide. In Yemen, breast cancer is one of the top reported cancers in women. This study aimed to investigate the correlation between EBV and breast cancer among Yemeni women in Sana'a city.

**Methods:** The study is a case-control study that included newly diagnosed, untreated breast cancer patients as cases and healthy women attending the National Cancer Control Foundation as controls. A total of 150 participants were tested for EBV (VCA) IgG using ELISA.

**Results**: The association between EBV and BC in the case and control groups was found by the investigation. 48 women (64.0%) who tested positive for EBV IgG were included in the control group, whereas 71 women (94.7%) among the patients had the antibody identified. A substantial correlation between EBV and BC was found by statistical analysis; a chi-square value of 21.510 and a *p*-value of less than 0.001 supported this conclusion. With a 95% confidence interval, the odds ratio was 10.0 (3.3-30.4). Moreover, women above the age of thirty showed a higher risk than women under that age ($p$=0.006). In addition, compared to the control group, divorced and bereaved women had a significantly higher chance of contracting EBV ($p$=0.002).

**Conclusions:** According to the study's findings, there may be a link between EBV infection and a higher risk of breast cancer. To further understand the underlying mechanisms and potential strategies to reduce this risk, more research is required.

**Keywords**: Breast cancer, Epstein-Barr virus, Sana'a city, Viral capsid antigen, Yemen.

## INTRODUCTION

Epstein-Barr virus (EBV) infection is a common occurrence, but due to its oncogenic effects on certain individuals[1] and its association with cancers such as stomach, nose, and blood cell cancers, EBV is often referred to as a cancer virus[2]. Breast cancer, affecting 2.1 million women annually and accounting for a significant number of cancer-related deaths among women, is the most prevalent cancer[3]. Consequently, this study aimed to investigate the correlation between EBV infection and BC in Yemeni women. Recently, there has been growing interest in researching the potential role of viral infections, particularly EBV, in the development of breast cancer. The Epstein-Barr virus, a gamma herpes virus, was first identified using direct electron microscopy in the early 1960s[4]. More than 90% of the world's population is infected, and it usually manifests itself early in childhood and may remain throughout one's lifetime with little to no major health implications[5,6]. African Burkitt lymphoma, Hodgkin, nasal NK/T-cell lymphomas, nasopharyngeal carcinoma (NPC), gastric adenocarcinoma, breast cancer, and leiomyosarcoma[7] are among the cancers whose origin has been associated with EBV. The main process by which the virus converts healthy cells into cancerous ones is still unclear and being researched, however recent research has indicated that cell cycle proteins might be the intended target of these transformation processes[8]. One of the most common forms of cancer and the primary cause of death for women worldwide is breast cancer (BC)[9]. In Yemen,

the first of the top five reported cancers among Yemeni women is breast cancer[10]. This cancer develops as a result of numerous internal and external factors. Age, hormonal impacts, lifestyle, obesity, smoking, gender, anxiety, stress, genetic predisposition, and family history of breast cancer are internal variables. Oncogenic virus infection, such as the Epstein-Barr virus, is one example of an exogenous factor[11]. Labrecque *et al*.,[12] reported the first positive connection between EBV infection and breast cancer in 1995. Several investigations into the relationship between EBV infection and breast cancer have been conducted since then[13]. Most studies have been reported from African countries, such as a study in Sudan that found a highly significant positive correlation between breast cancer and the presence of EBV[14] and a study in Egypt that found EBV positivity in breast cancer cases[15]. Also, few studies have been reported from Asian countries; for example, in Iraq, the correlation between EBV infection and breast cancer was presented[16]. On the other hand, some studies have reported a lack of correlation between EBV and breast cancer, such as studies in Iran and Eritrea, which indicated that there is no significant relationship between breast cancer and EBV[11,17].

The following observations suggest that there may be a correlation between EBV and BC: Some EBV-associated lymphomas are known to occur in the breast, and there are morphological similarities between medullary carcinoma of the breast and nasopharyngeal carcinoma, an EBV-associated malignancy[18]. A high incidence of breast cancer has been reported in Mediterranean countries that are endemic to EBV. Additionally, EBV has been discovered in breast tissue and milk. Epstein-Barr virus-positive lymphoblastoid cell lines have been shown to be capable of infecting mammary epithelial cells in an *in vitro* setting[19]. In Yemen, breast cancer is one of the top reported cancers in women. This study aimed to investigate the correlation between EBV and breast cancer among Yemeni women in Sana'a city.

## SUBJECTS AND METHODS

**Study design:** This research was a case-control study.

**Subjects and study area:** This study included patients with breast cancer in early diagnosis and normal individuals as controls recruited by the National Cancer Control Foundation in Sana'a city, Yemen.

**Inclusion criteria:** Case: newly diagnosed patients with breast cancer before receiving any treatment. Control: Healthy women attended the National Cancer Control Foundation.

**Exclusion criteria:** patients with breast cancer under treatment.

**Sample size:** A total of 150 studied subjects were included in this study (75 cases and 75 controls).

**Data collection:** A full history was taken from the cases and controls, and then recorded in a predesigned questionnaire that included demographic data, personal information, and clinical information.

**Specimen collection:** Five ml of whole blood was collected aseptically by venous puncture from each patient, and the serum was separated by centrifugation after coagulation. Samples were placed in an Eppendorf tube, and the sera were stored at −20°C until tested.

**Laboratory tests:** specimens were measured by an open-system indirect enzyme-linked immune sorbent assay (ELISA) for the detection of Epstein-Barr virus (VCA) IgG using a commercially available ELISA kit provided by Vircell Microbiologists, Spain.

**Ethical approval:** The present study was approved by the Institutional Ethical Committee, Faculty of Medicine and Health Sciences, Sana'a University. Before enrollment and the start of the study procedures, written informed consent was obtained from all participants.

**Statistical analysis:** The statistical analyses were performed in the software for the statistical program and presented as percentages, tabulations, or graphical representations. Odd ratio for risks and its significance by calculated chi-square test, geometric means, 95% confidence interval, and logistic regression. Significant differences were indicated if the *p*-value was $< 0.05$. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 25.

## RESULTS

One hundred and fifty women participated in this study: 75 healthy women who visited the National Cancer Foundation as a control group, and 75 women who were newly diagnosed with breast cancer and had not yet received treatment. The distribution of sociodemographic information between the cases and controls is displayed in Table 1. The mean age of the controls was 43.9±10.1 years, whereas the mean age of the cases was 39.8±12.2 years. Women with no formal education made up the largest percentage of cases (45.3%) and controls (29.3%) in terms of education. The proportion of cases with a primary education was 17.3%, while the proportion of controls was 18.7%. Women with a secondary education made up 17.3% of the control group and 21.2% of the cases. Higher education levels were represented by 20% of cases and 34% of controls, respectively. The majority of participants, 64.0% of the cases and 81.3% of the controls, lived in metropolitan areas. With regard to marital status, the bulk of participants—65.3% of cases and 76.0% of controls—were married. Regarding divorce and widowhood, there was a discernible difference between the case and control groups, with a greater percentage in the case group (28.0% vs. 8.0%) than in the control group. Total 10.7% of the cases and 30.7% of the controls, when family history of breast cancer was taken into account, had a positive history of the disease. When it came to smoking, 28.0% of the controls and 37.3% of the cases said they were smokers. The connection between EBV-VCA-IgG and BC in the case and control groups is shown in Table 2. In the case group, 71 individuals (94.7%) had detectable EBV IgG, whereas just 4 individuals (5.3%) had negative results.

**Table 1: Socio-demographic data distribution among cases and controls.**

| | | Cases n=75 | Control n=75 | Total n=150 |
|---|---|---|---|---|
| | | N (%) | N (%) | N (%) |
| Age | Mean ± S D | 39.8±12.2 | 43.9±10.1 | |
| | >30 Years | 3 (4.0) | 16 (21.3) | 19 (12.7) |
| | 30-39 | 27 (36.0) | 24 (32.0) | 51 (34.0) |
| | ≤40 years | 45 (60.0) | 35 (46.7) | 80 (53.3) |
| Education level | Illiterate | 34 (45.3) | 22 (29.3) | 56 (37.3) |
| | Primary | 13 (17.3) | 14 (18.7) | 27 (18.0) |
| | Secondary | 13 (17.3) | 13 (17.3) | 26 (17.3) |
| | University | 15 (20.0) | 26 (34.7) | 41 (27.3) |
| Residence | Urban | 48 (64.0) | 61 (81.3) | 109 (72.7) |
| | Rural | 27 (36.0) | 14 (18.7) | 41 (27.3) |
| Marital status | Single | 5 (6.7) | 12 (16.0) | 17 (11.3) |
| | Married | 49 (65.3) | 57 (76.0) | 106 (70.7) |
| | Divorce\Widow | 21 (28.0) | 6 (8.0) | 27 (18) |
| Family history of breast cancer | No | 67 (89.3) | 52 (69.3) | 119 (79.3) |
| | Yes | 8 (10.7) | 23 (30.7) | 31 (20.7) |
| Smoking | No | 47 (62.7) | 54 (72.0) | 101 (67.3) |
| | Yes | 28 (37.3) | 21 (28.0) | 49 (32.7) |

In contrast, 27 individuals (36.0%) in the control group had negative EBV test results, while 48 participants (64.0%) tested positive. A substantial correlation between EBV and BC was found by statistical analysis; this was indicated by a chi-square value of 21.510 and a *p*-value of less than 0.001. The odds ratio was 10.0 with a 95% confidence range equal to 3.3-30.4.

The clinical presentation of the patients is shown in Table 3, which also compares the cases and controls with respect to a range of symptoms and diseases. In terms of stress, the case group reported feeling stressed less frequently than the control group (38.7% vs. 48.0%), but slightly more frequently than the control group (37.3% vs. 34.7%) when it came to feeling stressed. The case group had a marginally greater rate of fever (57.3% vs. 44.0%) than the control group. In addition, the case group reported feeling less hungry than the control group (29.3% vs. 34.7%).

**Table 2: Correlation between Epstein barr virus and breast cancer.**

| | | Cases | | Controls | | Total | $\chi^2$ | OR (95% C.I.) | *p* value |
|---|---|---|---|---|---|---|---|---|---|
| | | n=75 | (%) | n=75 | (%) | n=150 | | | |
| EBV-VCA IgG | Positive | 71 | 94.7 | 48 | 64.0 | 119 | 21.510 | 10.0 (3.3-30.4) | <0.001 |
| | Negative | 04 | 5.3 | 27 | 36.0 | 31 | | | |
| | Total | 75 | (50.0%) | 75 | (50.0%) | 150 | | | |

***p*** (Probability value) ≤ 0.05 (significant); **CI** Confidence Interval; **OR** Odd ratio > 1 (at risk); $\chi^2$ Chi-square ≥ 3.9 (significant )

In addition, the case group's rate of malnutrition was somewhat lower than the control group's (13.3% vs. 17.3%). In terms of rash incidence, the case group was less likely than the control group to experience it (9.3% vs. 14.7%). In comparison to the control group, the case group reported a greater percentage of fatigue (78.7% vs. 61.3%). The case group experienced fewer swollen glands in the neck (9.3% vs. 14.7%) than the control group. That being said, the case group's rate of sore throats was about the same as that of the control group (33.3% vs. 29.3%). Lastly, the frequencies of muscle pain (26.7%) in the case group and control group were comparable.

The findings of logistic regression studies that looked at the relationship between different risk variables and the presence of positive EBV in patients and controls were shown in Table 4. The findings showed a statistically significant correlation between positive EBV and an older age group. When compared to people under 30, those in the 30-39 and ≥ 40 age groups had a considerably higher chance of having positive EBV: for those in the 30-39 age group, the COR was 6. ($p$=0.012) and the AOR was 6.9 ($p$=0.013). AOR was 11.1 ($p$=0.003) and COR was 10.9 ($p$=0.001) for age of 40 years or more. In the univariate analysis, there was a noteworthy correlation between a lower level of education (illiterate) and positive EBV. Nevertheless, the association lost significance in the multivariable analysis once additional risk variables were taken into account. Rural-dwelling women were more likely than control to have positive EBV in case, as shown by the univariate analysis's OR 2.55 and corresponding *p*-value 0.042. After correcting for other risk variables, the connection in the multivariable analysis was not statistically significant (OR=2.051, $p$=0.199). In the univariate analysis, there was a suggestive correlation between divorce/widow (marital status) and positive EBV (OR=5.6, $p$=0.025). However, in the multivariable analysis, the link was not significant after controlling for other risk factors (OR=2.2, $p$=0.385). The findings showed a strong inverse relationship between having positive EBV and a family history of breast cancer. According to the (COR 0.279, AOR 0.258) and their significant p values ($p$=0.009, $p$=0.014) in both the univariate and multivariable analyses, women with a family history of breast cancer were less likely to have positive EBV than women without a history.

**Table 3: Participants' clinical presentations.**

| Clinical presentations | | Cases | | Controls | | Total | |
|---|---|---|---|---|---|---|---|
| | | (n=75) | (%) | (n=75) | (%) | (n=150) | (%) |
| Feel stress | Always | 29 | (38.7) | 36 | (48.0) | 65 | (43.3) |
| | Often | 9 | (12.0) | 12 | (16.0) | 21 | (14.0) |
| | Sometimes | 28 | (37.3) | 26 | (34.7) | 54 | (36.0) |
| | Rare | 9 | (12.0) | 1 | (1.3) | 10 | (6.7) |
| Suffered from malnutrition | Yes | 10 | (13.3) | 13 | (17.3) | 23 | (15.3) |
| | No | 65 | (86.7) | 62 | (82.7) | 127 | (84.7) |
| Fatigue | Yes | 59 | (78.7) | 46 | (61.3) | 105 | (70.0) |
| | No | 16 | (21.3) | 29 | (38.7) | 45 | (30.0) |
| Fever | Yes | 43 | (57.3) | 33 | (44.0) | 76 | (50.7) |
| | No | 32 | (42.7) | 42 | (56.0) | 74 | (49.3) |
| Lack of appetite | Yes | 22 | (29.3) | 26 | (34.7) | 48 | (32.0) |
| | No | 53 | (70.7) | 49 | (65.3) | 102 | (68.0) |
| Rash | Yes | 07 | (9.3) | 11 | (14.7) | 18 | (12.0) |
| | No | 68 | (90.7) | 64 | (85.3) | 132 | (88.0) |
| Sore throat | Yes | 25 | (33.3) | 22 | (29.3) | 47 | (31.3) |
| | No | 50 | (66.7) | 53 | (70.7) | 103 | (68.7) |
| Swollen glands in the neck | Yes | 07 | (9.3) | 11 | (14.7) | 18 | (12.0) |
| | No | 68 | (90.7) | 64 | (85.3) | 132 | (88.0) |
| Pain muscles | Yes | 20 | 26.7 | 20 | 26.7 | 40 | 26.7 |
| | No | 55 | (73.3) | 55 | (73.3) | 110 | (73.3) |

Smoking and positive EBV did not significantly correlate, according to the results of the univariate and multivariable analyses, with *p*-values of 0.657.

## DISCUSSION

The results of the present study identified a significant association between EBV and BC, where the rate of positive EBV infection among cases was 94.7%, while in the control group it was 64.0%, with the associated odds ratio equal to 10.0 times that of controls ($X^2$=21.51, $p$<0.001). Similar associations were reported in Iraq[15,20], Syria[21], Lebanon[22], Sudan[14], Tunisia[23], India[18,24], China[25], New Zealand[26], and Pakistan[27]. However, a few studies did not find a significant association between EBV and BC, including a study conducted by Fina *et al.*[28], who analyzed 200 breast cancer specimens for the presence of EBV and found no significant association between EBV infection and breast cancer.

**Table 4: Association between risk factors and positive Epstein Barr virus among cases and controls using logistic regression.**

| Risk factors | | Positive EBV(n=119) | | | |
|---|---|---|---|---|---|
| | | Univariate logistic regression | | Multivariable logistic regression | |
| | | COR (95% C.I.) | *p* value | AOR (95% C.I.) | *p* value |
| Age | >30 years | Reference | | Reference | |
| | 30-39 years | 6.019(1.493, 24.259) | 0.012 | 6.914(1.514, 31.561) | 0.013 |
| | ≤40 years | 10.961(2.771, 43.361) | 0.001 | 11.082(2.304, 53.313) | 0.003 |
| Education level | Illiterate | Reference | | Reference | |
| | Primary/secondary | 0.375(0.149, 0.946) | 0.038 | 1.257(0.396, 3.983) | 0.698 |
| | University | 0.26(0.097, 0.699) | 0.008 | 0.751(0.218, 2.595) | 0.651 |
| Residence | Urban | Reference | | Reference | |
| | Rural | 2.553(1.033, 6.308) | 0.042 | 2.051(0.685, 6.142) | 0.199 |
| Marital status | Single | Reference | | Reference | |
| | Married | 1.789(0.524, 6.106) | 0.353 | 0.986(0.225, 4.325) | 0.985 |
| | Divorce/widow | 5.60(1.238, 25.327) | 0.025 | 2.241(0.363, 13.840) | 0.385 |
| Family history of breast cancer | No | Reference | | Reference | |
| | Yes | 0.279(0.107, 0.727) | 0.009 | 0.258(0.087, 0.763) | 0.014 |
| Smoking | No | Reference | | | |
| | Yes | 1.187 (0.556, 2.537) | 0.657 | | |

***p*** (Probability value) ≤ 0.05 (significant); **CI** Confidence Interval; **OR** Odd ratio > 1 (at risk)

Other studies[29,30] confirmed the findings of Fina and his colleagues. This may be due to the heterogeneity of the study designs, patient characteristics, and methodology used to detect EBV, as well as geographical location. The interaction between EBV and BC is likely to be complex and influenced by multiple factors, including hormonal factors, immune status, other viral infections, genetic factors, and environmental factors. In the present study, there was a statistically significant difference between age and EBV. Women aged 30-39 years have a significantly higher odds ratio of positive EBV infection compared to those below 30 years (OR=6.914, $p$=0.013), and women aged 40 years and above also have significantly higher odds of positive EBV infection compared to those below 30 years (OR=11.082, $p$=0.003). This result was in agreement

with Mofrad *et al.*[6]. However, this result was in disagreement with Alinezhad *et al.*[31]. This difference could be due to the development of the immune system. The immune system undergoes changes and maturation as individual's age. Different age groups may engage in varying behaviors that influence the risk of EBV infection. For example, individuals in their 30s and 40s may have different social behaviors compared to those below 30 years old. Hormonal changes that occur during different stages of life, such as puberty, pregnancy, or menopause, can impact the immune response and potentially influence the susceptibility to EBV infection.

The results of this study indicate a significant association between residence and breast cancer risk within the case group compared to the control group. Specifically, residents of rural areas in the case group were found to have a significantly higher risk of breast cancer ($p$ value=0.02). A similar trend has been observed in Poland[32] and India[33]. However, in the USA, they reported that no significant rural-urban differences were observed[34]. Also, Nagrani *et al.*,[35] reported that living in a rural area has a protective effect against breast cancer. This difference could be due to differences in screening rates between rural and urban areas. In addition to some factors such as lifestyle, socioeconomic status, environmental exposures, and healthcare access in different geographical areas, which can also play a role,. Furthermore, divorced and widowed women in the case group exhibited a higher risk of breast cancer compared to those in the control group ($p$ value=0.002). In a same vein, numerous studies found that divorced women were more likely than married women to die from BC[36,37]. Additionally, Buja *et al.*,[38] reported that individuals who are separated, divorced, or widowed are more likely to have advanced-stage disease when they receive a breast cancer diagnosis, whereas Hahn *et al.*[39], found no discernible difference in the cancer stage at diagnosis between patients who were never married and those who were married. This difference could be due to the fact that the association may be influenced by confounding factors such as socioeconomic status, lifestyle factors, and access to healthcare.

The findings of the study revealed an unexpected result regarding the association between a family history of breast cancer and the occurrence of breast cancer among the women studied. The analysis showed a significant negative association, indicated by an odds ratio of 3.7 and a $p$-value of 0.002. This result contradicts the findings of previous studies[40-43], which have consistently reported a positive association between a family history of breast cancer and the risk of developing the disease. One possible explanation for this disparity could be attributed to the characteristics of the study participants. It is essential to note that the participants in this study specifically sought consultation at the National Cancer Control Foundation to ascertain their breast cancer status. Furthermore, the study included their relatives who already had breast cancer. The observed association might have been influenced by factors such as environmental exposures or other unidentified confounding variables.

**Limitations of the study**

Being a single-center study, this research has certain limitations in that its findings cannot be generalized to the entire country. More accurate results might have been obtained from a bigger population size, as the current study's sample size was insufficient. It is important to monitor patients with EBV infection to determine whether they are at risk of developing BC. It is important to promote routine breast cancer screenings, particularly for high-risk age groups, as these can help with early detection, save lives, and save treatment costs. To properly comprehend the processes behind the correlation between EBV and BC subtype, more investigation is required.

## CONCLUSIONS

There was a statistically significant association between EBV and BC. Also, the results suggest that EBV may play a role in breast cancer development, particularly among older age individuals, residing in rural areas, and divorced and widowed women. There was no statistically significant association between risk factors (smoking, education level, feeling stressed and malnutrition) and EBV infection.

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## AUTHOR'S CONTRIBUTIONS

**Reham Khaled Al-Shaibani:** Writing the original draft, method, investigation**. Ahmed Y Al-Jaufy:** Formal analysis, data organization, visualization**. Khaled Abdul-Karim Al-Moyed:** Writing, review and editing, methodology**. Hassan Abdel-wahab Al-Shamahy:** Formal analysis, data organization, visualization. All authors revised the article and approved the final version.

## DATA AVAILABILITY

The data will be available to anyone upon request from the corresponding author.

## CONFLICT OF INTEREST

There is no conflict of interest around this work.

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