Original Article

Association Between Hepatitis B Virus DNA Positivity and Breast Cancer: A PCR-Based Case-Control Study from Isfahan and Khuzestan Provinces, Iran

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Abstract

Background: Hepatitis B virus (HBV) has been hypothesized to contribute to breast carcinogenesis through persistent or occult infection and indirect biological mechanisms, although current evidence remains inconclusive.

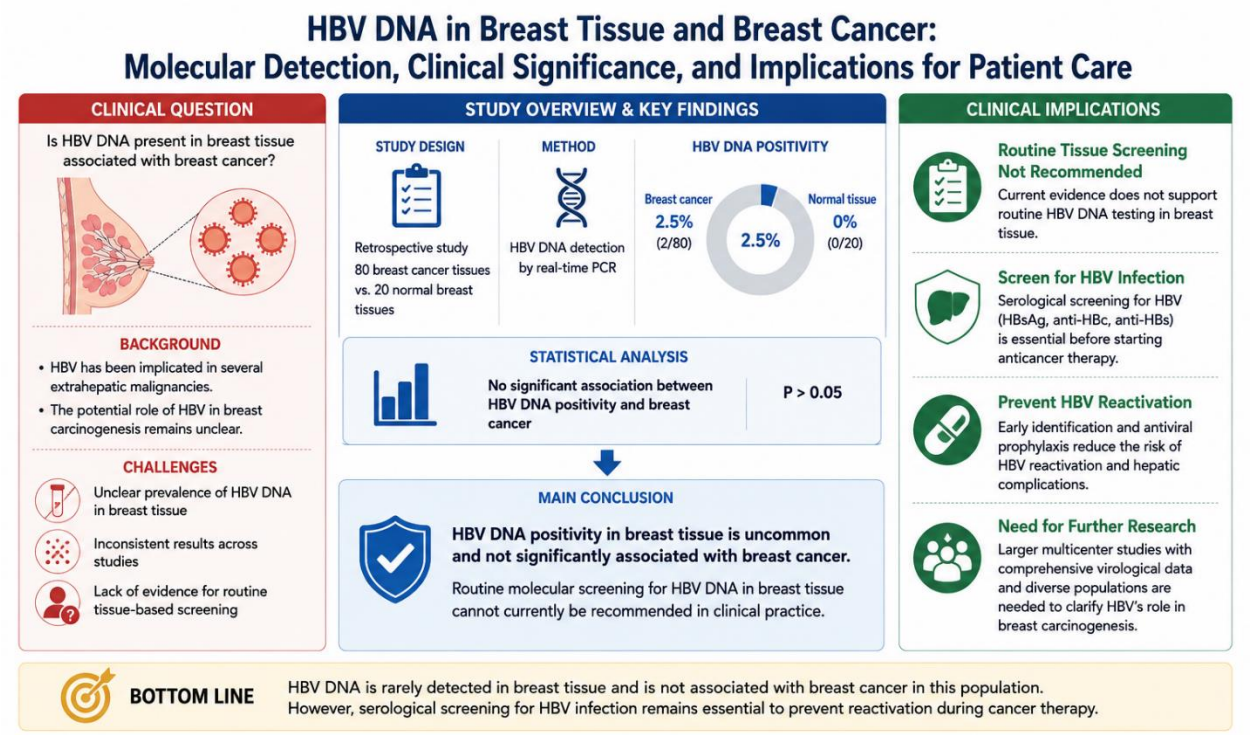
Materials and methods: Formalin-fixed paraffin-embedded (FFPE) breast tissue specimens from 80 women with breast cancer and 20 normal breast tissue specimens used as controls were collected from pathology archives in Isfahan and Khuzestan provinces, Iran. Samples were examined for the presence of HBV DNA using polymerase chain reaction (PCR). Statistical analyses were performed using SPSS version 16.0, and Cramer's V was calculated to assess the strength of the association.

Result: HBV DNA was detected in 3 of the 80 breast cancer tissue samples (3.75%), whereas none of the 20 control samples tested positive. Statistical analysis showed no significant association between HBV DNA positivity and breast cancer (P = 0.081), with a Cramer's V coefficient of 0.138.

Conclusion: HBV DNA was detected in only a small proportion of breast cancer tissue samples (3.75%) and was absent in all control specimens. These findings did not demonstrate a statistically significant association between HBV DNA positivity and breast cancer in women from Isfahan and Khuzestan provinces, Iran. Larger multicenter studies using complementary molecular and serological approaches are warranted to further clarify the potential role of HBV in breast carcinogenesis.

Implications for Patient Care: The absence of a significant association between HBV DNA positivity and breast cancer in this study does not support routine HBV DNA testing in breast tissue for breast cancer evaluation. Larger multicenter studies are needed before any changes to clinical practice can be recommended.

Keywords: Breast neoplasms; Hepatitis B virus; HBV DNA; Polymerase chain reaction; Viral oncogenesis; Iran



Graphical Abstract. The graphical abstract summarizes the study design, principal findings, and clinical implications of HBV DNA detection in breast tissue. HBV DNA positivity was uncommon and showed no significant association with breast cancer, indicating that routine molecular screening of breast tissue is not supported by the current evidence. However, the findings reinforce the importance of established serological HBV screening before chemotherapy, immunosuppressive therapy, or targeted anticancer treatment to identify patients at risk of HBV reactivation and guide appropriate antiviral prophylaxis. The figure also highlights the need for large multicenter studies to further clarify the potential role of HBV in breast carcinogenesis.

Introduction

Breast cancer is a complex and heterogeneous malignancy with the ability to spread to distant organs, including the bones, liver, brain, and lungs. It is currently the most frequently diagnosed cancer worldwide. Breast cancer remained a major global health concern in 2022, accounting for approximately 2.3 million newly diagnosed cases in women and close to 670,000 related deaths (1). The incidence of breast cancer has increased considerably during recent decades, with particularly notable increases reported in several Asian countries (2–5). Multiple factors contribute to breast cancer development, including benign breast disorders, reproductive characteristics such as parity, obesity, especially after menopause, family history, genetic susceptibility, and the use of oral contraceptives (6–9).

In addition to established genetic, hormonal, and environmental factors, infectious agents have also been suggested to play a role in cancer development. Studies by zur Hausen and other researchers have indicated that a proportion of human cancers may be associated with infectious agents, including Epstein–Barr virus (EBV), human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), Helicobacter pylori, and bovine leukemia virus (BLV) (10). These findings have led to increasing interest in investigating the possible contribution of viral infections to breast carcinogenesis (10–12).

The hepatitis B virus (HBV) is an enveloped DNA virus of the Hepadnaviridae family that

contains a partially double-stranded, circular DNA genome (13,14). HBV remains one of the leading causes of chronic viral liver disease worldwide, with evidence of previous infection observed in approximately 2 billion individuals and chronic infection affecting several hundred million people globally (15). Although HBV is recognized as a human oncogenic virus because of its strong association with hepatocellular carcinoma, the virus does not directly transform normal cells. Instead, HBV contributes to carcinogenesis through a combination of mechanisms, including chronic inflammation, immune-mediated damage, oxidative stress, and possible viral DNA integration into the host genome (16).

Beyond liver cancer, chronic HBV infection has also been associated with several extrahepatic malignancies, including non-Hodgkin lymphoma, intrahepatic cholangiocarcinoma, and other hematological and gastrointestinal cancers (17–24). In some cancers, HBV infection has been linked to unfavorable clinical characteristics and outcomes. Furthermore, because chronic HBV infection is often asymptomatic, identifying HBV carriers among cancer patients before chemotherapy or immunosuppressive treatment is important to reduce the risk of viral reactivation, which can be prevented through appropriate antiviral prophylaxis (25).

The possible relationship between HBV infection and breast cancer remains unclear. Some studies have suggested that chronic or occult HBV infection may contribute to breast carcinogenesis through indirect mechanisms, such as persistent inflammation, immune dysregulation, and alterations in hormone metabolism. Since estrogen exposure is an important factor in breast cancer development, disturbances in estrogen regulation during chronic viral infection have been proposed as a possible link between HBV infection and breast cancer progression (26). However, the presence of HBV DNA in breast tissue and its potential role in breast cancer development have not been fully established.

Therefore, the present study was conducted to investigate the potential association between HBV infection and breast cancer by analyzing HBV DNA in breast tissue specimens using polymerase chain reaction (PCR).

Materials and Methods

Sample Collection

This retrospective study included formalin-fixed paraffin-embedded (FFPE) breast tissue specimens collected from 80 women diagnosed with breast cancer and 20 normal breast tissue specimens used as controls. The archived specimens were obtained from pathology laboratories and hospitals in the Iranian provinces of Isfahan and Khuzestan. All tissue samples, including malignant and non-malignant specimens, had been collected between 2015 and 2016. Tissue sections were prepared using a microtome, mounted on glass slides, and histopathologically evaluated and confirmed by an experienced pathologist before molecular analysis. The patients included in this study were women aged 23–90 years, according to the available clinical records. Samples from patients with a previous history of other malignancies or prior therapeutic interventions were excluded. Due to the retrospective design of the study, information regarding some potential risk factors, including cigarette smoking, alcohol consumption, and illicit drug use, was not available.

Ethical Considerations

This study was performed in compliance with the ethical principles outlined in the Declaration of Helsinki. Archived FFPE tissue specimens

obtained from pathology laboratories and hospitals were used in this study, and no additional samples were collected from participants. Furthermore, no intervention or direct contact with patients was involved. Patient confidentiality was maintained throughout the study, and all clinical information was analyzed anonymously. This study was performed as part of a graduate research project and was approved by the Research Council of Lorestan University (Approval Code: 10016, first semester of the 2017–2018 academic year).

DNA Extraction and Assessment of DNA Quality and Purity

Six to ten consecutive sections (7 µm thick) were cut from each FFPE tissue block using a microtome and transferred into sterile 1.5-mL DNase/RNase-free microcentrifuge tubes. Following deparaffinization with xylene (Merck, Germany) and absolute ethanol, genomic DNA was extracted using a modified salting-out method based on previously described protocols (27,28). DNA extraction was performed using a lysis buffer containing Tris, sodium chloride, EDTA, sodium dodecyl sulfate (SDS), and proteinase K (Qiagen, Germany), followed by protein precipitation with 5 M NaCl, DNA precipitation with cold isopropanol, washing with 70% ethanol, and resuspension in TE buffer. The samples were subjected to centrifugation steps at 14,000 rpm and incubation in a water bath during the extraction procedure. The concentration and purity of extracted DNA were assessed using a NanoDrop spectrophotometer. The A260/A280 absorbance ratio was determined, and DNA samples with ratios ranging from 1.8 to 2.0 were considered acceptable for subsequent PCR amplification.

PCR Amplification of the β-Actin Gene in Tumor and Control DNA Samples

The integrity and amplifiability of extracted genomic DNA were confirmed by PCR amplification of the β-actin gene using β-actin-specific primers. The primer sequences and expected amplicon sizes for β-actin and HBV are presented in Table 1. PCR reactions were performed in a final volume of 25 µL in 0.2-mL PCR tubes containing 12.5 µL of Amplicon PCR Master Mix, 10.5 µL of deionized water, 1 µL of template DNA, and 0.5 µL of each forward and reverse primer. PCR amplification was performed under the following thermal cycling conditions: an initial denaturation step at 94°C for 5 min, followed by 30 cycles of denaturation at 95°C for 1 min, annealing at 61°C for 50 s, and extension at 72°C for 45 s. A final extension step was performed at 72°C for 10 min. The PCR products were separated by electrophoresis on a 1.5% agarose gel, and amplification of the expected 161-bp β-actin fragment was confirmed.

PCR Detection of HBV DNA in Tumor and Control Tissue Samples

Following confirmation of DNA integrity by β-actin amplification, DNA samples that passed the quality assessment were analyzed for the presence of HBV DNA using HBV-specific primers. PCR reactions were performed in 0.2-mL PCR tubes with a final reaction volume of 25 µL. The thermal cycling conditions consisted of an initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 54.9°C for 30 s, and extension at 72°C for 45 s. A final extension step was performed at 72°C for 10 min. The amplified products were separated by electrophoresis on a 1.5% agarose gel, and the presence of the expected 412-bp HBV-specific amplicon was determined. The primer sequences used for PCR amplification of the β-actin and HBV genes, together with the expected amplicon sizes and

corresponding references, are presented in Table 1.

Statistical Analysis

HBV DNA was detected in 3 of the 80 breast cancer tissue samples (3.75%), whereas none of the 20 control samples were positive. Statistical analysis showed no statistically significant association between HBV DNA positivity and breast cancer (P = 0.081). The strength of the association was weak (Cramer's V = 0.138).

Target Gene	Primer Sequence (5′–3′)	Amplicon Size (bp)	Reference
β-Actin	F: AGACGCAGGATGGCATGGG	161	(29)
	R: GAGACCTTCAACACCCCAGCC		
HBV	F: TTGTCCTCCAACTTGTCCTG	412	(30)
	R: CCAATACCACATCATCCATATAGC		

Table 1. Primer sequences used for PCR amplification

Results

DNA Extraction and Quality Assessment

All extracted DNA samples were of sufficient quality for downstream molecular analysis. Successful amplification of the β-actin gene was observed in all samples, confirming the integrity and amplifiability of the extracted genomic DNA. The expected 161-bp β-actin amplicon was visualized by electrophoresis on a 1.5% agarose gel, as shown in Figure 1**.**

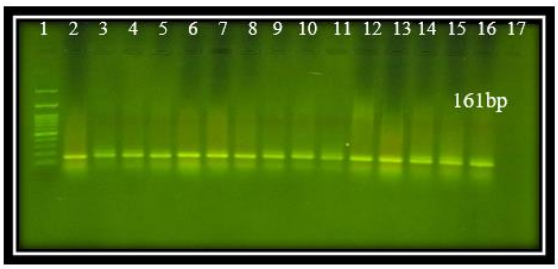


Figure 1. Agarose gel electrophoresis of the PCR-amplified β-actin gene in tumor and control tissue samples. Lane 1: 100-bp DNA ladder; lanes 2–11: breast tumor tissue samples; lanes 12–16: normal breast tissue samples (controls); lane 17: negative control (nuclease-free water).

PCR Detection of HBV DNA in Breast Tumor and Control Tissue Samples

PCR amplification using HBV-specific primers revealed the presence of HBV DNA in 3 out of 80 breast tumor specimens (3.75%), while all 20 control breast tissue specimens were negative for HBV DNA (Figure 2). The distribution of HBV DNA positivity between breast cancer cases and control samples is summarized in Table 2. Statistical analysis demonstrated no statistically significant association between HBV DNA positivity and breast cancer (P = 0.081). The strength of the association was weak, with a Cramer's V coefficient of 0.138.

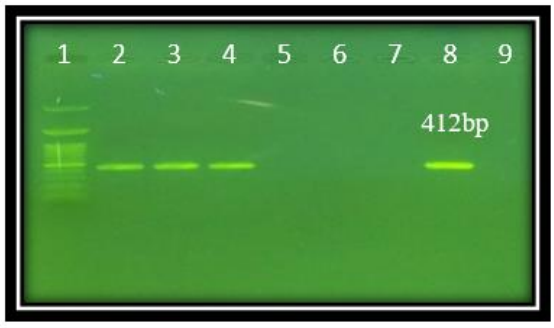


Figure 2. Agarose gel electrophoresis of PCR products amplified with HBV-specific primers. Lane 1: molecular weight marker; lanes 2–4: HBV DNA-positive breast tumor samples; lanes 5–7: control breast tissue samples; lane 8: positive control; lane 9: negative control (water).

Discussion

In the present study, HBV DNA was detected in only 3 of 80 breast cancer tissue samples (3.75%), These findings did not demonstrate a statistically significant association between HBV DNA positivity and breast cancer in women from Isfahan and Khuzestan provinces. Despite advances in cancer prevention and treatment, breast cancer remains the leading cause of cancer-related death among women worldwide. Increasing evidence indicates that oncogenic viruses may play a role in breast carcinogenesis through the expression of viral oncogenes, interference with cell-cycle regulation, and the induction of malignant transformation (31–34).

Group	HBV DNA Positive	HBV DNA Negative	Total
Breast cancer	3	77	80
Control	0	20	20

Table 2. Distribution of HBV DNA positivity among breast cancer cases and controls.

Previous studies have suggested that HBV may contribute to breast carcinogenesis through both indirect and direct mechanisms (35). Previous studies have suggested that HBV may contribute to breast carcinogenesis through both indirect and direct mechanisms. Chronic HBV infection may impair hepatic estrogen metabolism, leading to increased circulating estrogen levels, which could represent a potential link between HBV infection and breast cancer development (36,38). In addition, HBV may exert direct oncogenic effects through viral genome integration, genomic instability, and induction of mutations in cancer-related genes (18, 35). The detection of HBV DNA in human breast milk and its identification in extrahepatic tissues, including peripheral blood mononuclear cells, bone marrow, spleen, and lymphoblastoid cells, further support the possibility of HBV persistence beyond the liver (39, 40). A systematic review of gynecological malignancies reported that chronic HBV infection was significantly associated with cervical cancer but not endometrial or ovarian cancer, although hospital-based studies have suggested possible associations with cervical and endometrial cancers (41).

HBXIP, a protein expressed in breast tissue, has been implicated in HBV-related molecular pathways and breast cancer progression through regulation of oncogenic signaling pathways, including LMO4/Sp1 and angiogenic pathways involving FGFs and VEGF (42–45). However, the relationship between HBV infection and breast cancer remains controversial. A study by Su et al. in 2011 among Taiwanese patients found no significant association between chronic HBV infection and breast cancer risk (46). Conversely, He-Lu et al. reported in 2017 a higher prevalence of HBV infection among Chinese patients with breast cancer, suggesting a potential association between HBV infection and breast cancer (47). Furthermore, a study conducted in an HBV-endemic region indicated that chronic HBV infection may represent an independent prognostic factor in patients with stage II/III breast cancer, but not in those with stage I disease (48). Therefore, further investigations in diverse populations and geographic regions are required to clarify the potential role of HBV in breast carcinogenesis.

In the present study, we investigated the presence of HBV DNA using PCR in 80 FFPE breast tumor

tissue samples and 20 normal breast tissue samples as controls. HBV DNA was detected in only 3 tumor samples (3.75%), whereas none of the control samples were positive. These findings did not demonstrate a statistically significant association between HBV DNA positivity and breast cancer in the studied population. Given that several oncogenic viruses, including EBV, HPV, and HBV, have been proposed as potential contributors to breast carcinogenesis, and previous studies have generally evaluated individual viruses separately with inconsistent findings, the present study used previously extracted DNA samples from breast tissues collected in Khuzestan and Isfahan provinces, which had also been evaluated for EBV and HPV-16/18 genomes by PCR. Previous analyses of these samples demonstrated regional differences in oncogenic viral distribution. In Khuzestan Province, breast cancer was significantly associated with HPV-16/18 infection (49), whereas no significant association was observed with EBV infection (27). In contrast, in Isfahan Province, significant associations were reported between breast cancer and EBV (50) and HPV-18 infection, while HPV-16 showed no significant association (51). Overall, the present findings do not support a significant association between HBV DNA positivity and breast cancer in the studied population. Nevertheless, further large-scale studies using molecular diagnostic approaches alongside conventional methods and including diverse geographic and ethnic populations are warranted to better characterize the epidemiological distribution and potential contribution of oncogenic viruses to breast carcinogenesis. Such investigations may help identify high-risk populations and, if causal relationships are confirmed, support the development of targeted preventive strategies, including preventive strategies against established oncogenic viruses where applicable.

Study Limitations

Several limitations should be considered when interpreting the findings of this study. First, the relatively small sample size, particularly the limited number of control specimens, may have reduced the statistical power to detect weak associations. Second, the retrospective design and the use of formalin-fixed paraffin-embedded (FFPE) tissue samples may have introduced limitations related to sample quality, although successful β-actin amplification confirmed the suitability of extracted DNA for PCR analysis. Third, only HBV DNA detection by PCR was performed, and additional markers of HBV infection, such as serological parameters and viral load, were not evaluated. Fourth, the geographic distribution of samples was limited to two provinces, which may restrict the generalizability of the findings to other populations. Therefore, larger multicenter studies incorporating complementary molecular and serological approaches are warranted to further clarify the potential association between HBV DNA positivity, HBV infection status, and breast cancer.

Conclusion

In conclusion, HBV DNA was detected in only 3 of the 80 breast tumor samples (3.75%), whereas none of the control samples tested positive. No statistically significant association was observed between HBV DNA positivity and breast cancer among women from Khuzestan and Isfahan provinces. Nevertheless, given the heterogeneous findings reported in previous studies, further large-scale investigations involving genetically and ethnically diverse populations are warranted

to clarify the potential role of HBV and other oncogenic viruses in breast carcinogenesis.

Implications for Patient Care

The findings indicate that HBV DNA positivity in breast tissue is uncommon and was not significantly associated with breast cancer in the studied population. Therefore, routine molecular screening for HBV DNA in breast tissue "is not currently supported by the available evidence as part of the diagnostic work-up or clinical management of patients with breast cancer. Nevertheless, these findings should not diminish the importance of identifying chronic HBV infection in oncology patients. Screening for HBV infection using established serological markers remains essential before the initiation of chemotherapy, immunosuppressive therapy, or targeted anticancer treatments, as early identification and appropriate antiviral prophylaxis can substantially reduce the risk of HBV reactivation and its potentially serious hepatic complications. Furthermore, additional multicenter studies involving larger populations, comprehensive virological assessments, and diverse ethnic groups are required to better define the potential role of HBV in breast carcinogenesis and determine whether specific patient subgroups may benefit from targeted viral investigations.

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Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

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Author Contributions

Study conception and design were performed by Faranak Hadi and Seyed Hesamaldin Hejazi. Data collection, laboratory investigations, and preparation of the initial manuscript draft were carried out by Pegah Hosseinpouri. Manuscript review, critical revision, and final approval of the manuscript were performed by Faranak Hadi.

Ethics approval and consent to participate and Ethics Statement

The study was approved by the Research Council of Lorestan University (Approval No. 10016; Academic Year 2017–2018).

Ethics Statement

The authors confirm that all ethical principles of research and scientific publication, including plagiarism prevention, data integrity, and avoidance of duplicate publication, were fully observed.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Publisher's Note

The graphical abstract was prepared by the journal's editorial team using artificial intelligence-assisted design tools and was reviewed and approved by the authors prior to publication.

Reference

1. World Health Organization. Breast cancer. Geneva: World Health Organization; 2024 [cited 2024 Mar 13]. Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer

2. Leong SPL, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, et al. Is breast cancer the same disease in Asian and Western countries? World J Surg. 2010; 34(10):2308–2324. https://doi.org/10.1007/s00268-010-0683-1.

3. Pollán M. Epidemiology of breast cancer in young women. Breast Cancer Res Treat. 2010 Sep;123 Suppl 1:3-6. https://doi.org/10.1007/s10549-010-1098-2.

4. Huang CS, Lin CH, Lu YS, Shen CY. Unique features of breast cancer in Asian women--breast cancer in Taiwan as an example. J Steroid Biochem Mol Biol. 2010 Feb 28;118(4-5):300-3. https://doi.org/10.1016/j.jsbmb.2009.12.017.

5. Lim SE, Back M, Quek E, Iau P, Putti T, Wong JEL. Clinical observations from a breast cancer registry in Asian women. World J Surg. 2007;31(7):1387–1392. https://doi.org/10.1007/s00268-007-9086-3.

6. Casey PM, Cerhan JR, Pruthi S. Oral contraceptive use and risk of breast cancer. Mayo Clin Proc. 2008 Jan;83(1):86-90; quiz 90-1. https://doi.org/10.4065/83.1.86.

7. Hamilton R, Williams JK, Bowers BJ, Calzone K. Life trajectories, genetic testing, and risk reduction decisions in 18-39 year old women at risk for hereditary breast and ovarian cancer. J Genet Couns. 2009 Apr;18(2):147-59. https://doi.org/10.1007/s10897-008-9200-1.

8. Lajous M, Boutron-Ruault MC, Fabre A, Clavel-Chapelon F, Romieu I. Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. Am J Clin Nutr. 2008;87(5):1384-1391. https://doi.org/10.1093/ajcn/87.5.1384.

9. Terry KL, Willett WC, Rich-Edwards JW, Michels KB. A prospective study of infertility due to ovulatory disorders, ovulation induction, and incidence of breast cancer. Arch Intern Med. 2006 Dec 11-25;166(22):2484-9. https://doi.org/10.1001/archinte.166.22.2484.

10. Zur Hausen H. The search for infectious causes of human cancers: where and why. Virology. 2009;392(1):1-10. https://doi.org/10.1016/j.virol.2009.06.001.

11. Glaser SL, Hsu JL, Gulley ML. Epstein-Barr virus and breast cancer: state of the evidence for viral carcinogenesis. Cancer Epidemiol Biomarkers Prev. 2004 May;13(5):688-97.

12. De Villiers EM, Sandstrom RE, zur Hausen H, Buck CE. Presence of papillomavirus sequences in condylomatous lesions of the mamillae and in invasive carcinoma of the breast. Breast Cancer Res. 2005;7(1): R1-11. https://doi.org/10.1186/bcr940.

13. Asandem DA, Segbefia SP, Kusi KA, Bonney JHK. Hepatitis B Virus Infection: A Mini Review. Viruses. 2024 May 3;16(5):724. https://doi.org/10.3390/v16050724.

14. Rajbhandari R, Nguyen VH, Knoble A, Fricker G, Chung RT. Advances in the management of hepatitis B. BMJ. 2025; 389:e079579. https://doi.org/10.1136/bmj-2024-079579.

15. Kuhns MC, Busch MP. New strategies for blood donor screening for hepatitis B virus: nucleic acid testing versus immunoassay methods. Molecular Diagnosis & Therapy. 2006;10(2):77-91.
https://doi.org/10.1007/BF03256447.
16. Rosenberg M, Poluch M, Thomas C, Sindaco P, Khoo A, Porcu P. Hepatitis B Virus and B-cell lymphoma: evidence, unmet need, clinical impact, and opportunities. Front Oncol. 2023 Oct 20;13:1275800.
https://doi.org/10.3389/fonc.2023.1275800.
17. Lemaitre M, Brice P, Frigeni M, Hermine O, Arcaini L, Thieblemont C, Besson C. Hepatitis B virus-associated B-cell non-Hodgkin lymphoma in non-endemic areas in Western Europe: Clinical characteristics and prognosis. J Infect. 2020 Feb;80(2):219-224.
https://doi.org/10.1016/j.jinf.2019.12.005.
18. Mahale P, Engels EA, Koshiol J. Hepatitis B virus infection and the risk of cancer in the elderly US population. Int J Cancer. 2019 Feb 1;144(3):431-439.
https://doi.org/10.1002/ijc.31643.
19. Clements O, Eliahoo J, Kim JU, Taylor-Robinson SD, Khan SA. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A systematic review and meta-analysis. J Hepatol. 2020 Jan;72(1):95-103.
https://doi.org/10.1016/j.jhep.2019.09.007.
20. Yang F, Ma L, Yang Y, Liu W, Zhao J, Chen X, Wang M, Zhang H, Cheng S, Shen F, Wang H, Zhou W and Cao G (2019) Contribution of Hepatitis B Virus Infection to the Aggressiveness of Primary Liver Cancer: A Clinical Epidemiological Study in Eastern China. Front. Oncol. 9:370.
https://doi.org/10.3389/fonc.2019.00370.
21. Liang JH, Gao R, Dai JC, Gale RP, Li W, Fan L, Hu ZB, Xu W, Li JY. The prognostic role of HBV infection in chronic lymphocytic leukemia. J Cancer Res Clin Oncol. 2018 Jul;144(7):1309-1315.
https://doi.org/10.1007/s00432-018-2663-z.
22. Cui H, Jin Y, Chen F, Ni H, Hu C, Xu Y, Xuan H, Hu D, Deng W, Zhang Y, Liu Y. Clinicopathological evidence of hepatitis B virus infection in the development of gastric adenocarcinoma. J Med Virol. 2020 Jan;92(1):71-77.
https://doi.org/10.1002/jmv.25584.
23. Weng JJ, Wei JZ, Li M, Lu JL, Qin YD, Jiang H, et al. Effects of hepatitis B virus infection and antiviral therapy on the clinical prognosis of nasopharyngeal carcinoma. Cancer Med. 2020;9(2):541-551.
https://doi.org/10.1002/cam4.2715.
24. Desai R, Patel U, Sharma S, Singh S, Doshi S, Shaheen S, Shamim S, Korlapati LS, Balan S, Bray C, Williams R, Shah N. Association Between Hepatitis B Infection and Pancreatic Cancer: A Population-Based Analysis in the United States. Pancreas. 2018 Aug;47(7):849-855.
https://doi.org/10.1097/MPA.0000000000001095.
25. Maung ST, Deepan N, Decharatanachart P, Chaiteerakij R. Screening for viral hepatitis B infection in cancer patients before receiving chemotherapy - A systematic review and meta-analysis. Asia Pac J Clin Oncol. 2024 Jun;20(3):335-345.
https://doi.org/10.1111/ajco.14055.
26. Adhikari VP, Lu LJ, Kong LQ. Does hepatitis B virus infection cause breast cancer? Chin Clin Oncol. 2016 Dec;5(6):81.
https://doi.org/10.21037/cco.2016.08.04.
27. Saeedi Z, Hadi F, Hejazi SH, Salahshournia Z. The relationship between EBV virus and breast cancer in Khuzestan Province of Iran. J Appl

Biotechnol Rep. 2018;5(1):37–41. https://doi.org/10.29252/jabr.01.01.07.

28. Rivero ERC, Neves AC, Silva-Valenzuela MG, Sousa SOM, Nunes FD. Simple salting-out method for DNA extraction from formalin-fixed, paraffin-embedded tissues. Pathol Res Pract. 2006;202(7):523–529. https://doi.org/10.1016/j.prp.2006.02.007.

29. Ahangari G, Emruzi Z, Babaheidarian P, Arshad M. Effect of hyperlipidemia on cell mediated immunity; could it be as predisposing factor of cancer risk. Biomed J Sci Tech Res. 2018;12(3). https://doi.org/10.26717/BJSTR.2018.12.002240.

30. Nakhaei Sistani R. The designation of PCR test to detect hepatitis B virus and evaluate the performance of this test in screening applicants of blood transfusion organization. J Cell Mol Res (Iranian J Biol). 2018;30(4):430-438 (In Persian).

31. Romieu I, Hernandez-Avila M, Lazcano-Ponce E, Weber JP, Dewailly E. Breast cancer, lactation history, and serum organochlorines. Am J Epidemiol. 2000 Aug 15;152(4):363-70. https://doi.org/10.1093/aje/152.4.363.

32. Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ, Speed D, Lynch AG, Samarajiwa S, Yuan Y, Gräf S, Ha G, Haffari G, Bashashati A, Russell R, McKinney S; METABRIC Group; Langerød A, Green A, Provenzano E, Wishart G, Pinder S, Watson P, Markowetz F, Murphy L, Ellis I, Purushotham A, Børresen-Dale AL, Brenton JD, Tavaré S, Caldas C, Aparicio S. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012 Apr 18;486(7403):346-52. https://doi.org/10.1038/nature10983.

33. Richardson A. Is breast cancer caused by late exposure to a common virus? Med Hypotheses. 1997 Jun;48(6):491-7. https://doi.org/10.1016/s0306-9877(97)90118-3.

34. Lawson JS, Gunzburg WH, Whitaker NJ. Viruses and human breast cancer. Future Microbiol. 2006;1(1):33–51. https://doi.org/10.2217/17460913.1.1.33.

35. Zhang Y, Zhao Y, Li H, Li Y, Cai X, Shen Y, Shi H, Li L, Liu Q, Zhang X, Ye L. The nuclear import of oncoprotein hepatitis B X-interacting protein depends on interacting with c-Fos and phosphorylation of both proteins in breast cancer cells. J Biol Chem. 2013 Jun 28;288(26):18961-74. https://doi.org/10.1074/jbc.M113.458638.

36. Hankinson SE, Eliassen AH. Endogenous estrogen, testosterone and progesterone levels in relation to breast cancer risk. J Steroid Biochem Mol Biol. 2007 Aug-Sep;106(1-5):24-30. https://doi.org/10.1016/j.jsbmb.2007.05.012.

37. Meilahn EN, De Stavola B, Allen DS, Fentiman I, Bradlow HL, Sepkovic DW, Kuller LH. Do urinary oestrogen metabolites predict breast cancer? Guernsey III cohort follow-up. Br J Cancer. 1998 Nov;78(9):1250-5. https://doi.org/10.1038/bjc.1998.663.

38. Chen X, Chen J, Wen J, Xu C, Zhang S, Zhou YH, Hu Y. Breastfeeding is not a risk factor for mother-to-child transmission of hepatitis B virus. PLoS One. 2013;8(1):e55303. https://doi.org/10.1371/journal.pone.0055303.

39. Montoya-Ferrer A, Zorrilla AM, Viljoen J, Molès JP, Newell ML, Van de Perre P, Tuaillon E. High Level of HBV DNA Virus in the Breast Milk Seems not to Contraindicate Breastfeeding. Mediterr J Hematol Infect Dis. 2015 Jul 1;7(1):e2015042. https://doi.org/10.4084/MJHID.2015.042.

40. Joshi SS, Coffin CS. Hepatitis B virus lymphotropism: emerging details and challenges. Biotechnol Genet Eng Rev. 2018 Apr;34(1):139-151. https://doi.org/10.1080/02648725.2018.1474324.

41. Peng, L., Dou, Z., Yu, S. et al. Hepatitis B virus infection and the risk of gynecologic cancers: a systematic review and meta-analysis. Discov Onc 15, 340 (2024). https://doi.org/10.1007/s12672-024-01213-8.

42. Liu Q, Bai X, Li H, Zhang Y, Zhao Y, Zhang X, Ye L. The oncoprotein HBXIP upregulates Lin28B via activating TF II D to promote proliferation of breast cancer cells. Int J Cancer. 2013 Sep 15;133(6):1310-22. https://doi.org/10.1002/ijc.28154.

43. Zhang Y, Zhao Y, Li L, Shen Y, Cai X, Zhang X, Ye L. The oncoprotein HBXIP upregulates PDGFB via activating transcription factor Sp1 to promote the proliferation of breast cancer cells. Biochem Biophys Res Commun. 2013 May 3;434(2):305-10. https://doi.org/10.1016/j.bbrc.2013.02.123.

44. Liu F, You X, Wang Y, Liu Q, Liu Y, Zhang S, et al. The oncoprotein HBXIP enhances angiogenesis and growth of breast cancer through modulating FGF8 and VEGF. Carcinogenesis. 2014;35(5):1144–1153. https://doi.org/10.1093/carcin/bgu021.

45. Ziegler RG, Fuhrman BJ, Moore SC, Matthews CE. Epidemiologic studies of estrogen metabolism and breast cancer. Steroids. 2015 Jul; 99(Pt A):67-75. https://doi.org/10.1016/j.steroids.2015.02.015.

46. Su FH, Chang SN, Chen PC, Sung FC, Su CT, Yeh CC. Association between chronic viral hepatitis infection and breast cancer risk: a nationwide population-based case-control study. BMC Cancer. 2011 Nov 24;11:495. https://doi.org/10.1186/1471-2407-11-495.

47. Lu LJ, Adhikari VP, Zhao CX, Wu H, Dai W, Li X, Li HY, Ren GS, Wu KN, Kong LQ. Clinical study on the relationship between hepatitis B virus infection and risk of breast cancer: a large sized case-control and single center study in southwest of China. Oncotarget. 2017;8(42):72044–72053. https://doi.org/10.18632/oncotarget.19132.

48. Xiao W, Zhou Y, Yu P, Yang A, Zheng S, Tang H, Xie X. Prognostic value of chronic hepatitis B virus infection in patients with breast cancer in a hepatitis B virus endemic area. Ann Transl Med. 2020 Mar;8(5):180. https://doi.org/10.21037/atm.2020.01.97.

49. Hosseinpouri P, Hejazi SH, Hadi F. Relationship between human papillomavirus and breast cancer in women with this cancer in Khuzestan province. Iran J Obstet Gynecol. 2020;23(8):66-74 (In Persian).

50. Salahshor Z. The Study of Relationship Between Epstein - Barr virus and Breast Cancer in Isfahan Province. Iran J Breast Dis. 2018;11(02):16–24 (In Persian).

51. Hosseinpouri P, Hadi F, Hejazi SH, Talei GR. Presence of human papillomavirus-16 and -18 among women with breast cancer in Isfahan province. Yafteh. 2019;21(3):84-94 (In Persian).