

Letter to the Editor

Is Epstein–Barr virus associated with aggressive forms of breast cancer?

G Khan^{*1}, PS Philip¹ and M Al Ashari²¹Department of Microbiology and Immunology, Faculty of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates;²Department of Laboratory Medicine, Tawam Hospital, Al Ain, United Arab Emirates

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Sir,

We read with great interest the paper by Mazouni *et al* (2011) recently published in the *British Journal of Cancer* linking Epstein–Barr virus (EBV) to aggressive forms of breast cancer.

EBV is a lymphotropic herpesvirus aetiologically associated with a number of human malignancies of both epithelial and lymphoid origin. Although numerous studies have been published over the last 10–15 years looking at the possible link between EBV and the pathogenesis of breast cancer, the association remains controversial and reports from both corners of the arena continue to be published (reviewed in Amarante and Watanabe, 2009). It is possible that the discrepancies between the different reports are due to the differing methodologies used for the detection of EBV, the histological types of tumours examined, and the ethnic/geographical background of the cases studied. For example, using PCR-based techniques, a number of studies have reported a positive correlation between EBV and breast cancer, with up to 50% of cases giving a positive signal (Murray *et al*, 2003; Preciado *et al*, 2005; Fawzy *et al*, 2008). However, owing to the fact that EBV is a ubiquitous virus present asymptotically in over 90% of the world population, its mere detection in tumour tissue cannot be used to imply disease association. In this context, the findings

reported by Marzouni *et al* have to be interpreted with caution. Indeed, several studies that have used the EBER-*in situ* hybridisation (EBER-ISH) approach have failed to show an association, even in cases that were EBV PCR positive (Deshpande *et al*, 2002; Herrmann and Niedobitek, 2003; Murray *et al*, 2003; Thorne *et al*, 2005). Similarly, PCR studies on microdissected tumour cells have also led to contradictory findings. While Fina *et al* (2001) reported the presence of EBV in microdissected tumour cells, Murray *et al* (2003) did not find any evidence of the presence of EBV in the microdissected tumour cells of their cases, even though 21% of the cases were EBV positive by quantitative real-time PCR.

We too have recently examined the association of EBV with the pathogenesis of breast cancer in a large series of cases in the Arab population from the United Arab Emirates. A total of 219 samples from 61 cases were examined using an EBER-ISH method capable of detecting as little as a few EBV-infected lymphocytes in an entire tissue section (Khan *et al*, 1992). All but four cases had multiple tissues (both benign and malignant) that were studied. We found that, although EBV can be detected in approximately 50% of breast cancer cases, the virus is not present in the malignant cells. Rather, the virus is localised to occasional infiltrating lymphocytes (Figure 1), which could give rise to ‘false’ interpretations

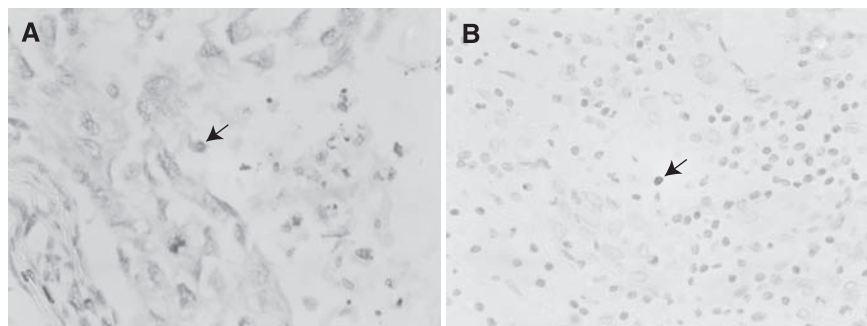


Figure 1 EBER-*in situ* hybridisation for the detection of EBV in breast cancer tissues. (A) A metastatic ductal carcinoma from a 39-year-old Emirati woman. This case was triple negative (ER–, PR–, HER2–), but an occasional EBV-positive non-malignant cell could be detected using EBER-*in situ* hybridisation (arrow). (B) A case of invasive intraductal breast carcinoma with significant inflammatory reaction from a 43-year-old Emirati woman. EBER-*in situ* hybridisation revealed the presence of EBV in an occasional non-malignant lymphoid cell (arrow).

*Correspondence: Dr G Khan; E-mail: g_khan@uaeu.ac.ae

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linking the virus to the pathogenesis of the disease. Furthermore, we did not find any correlation between the presence of EBV in infiltrating lymphocytes and ER, PR, HER2 expression or

metastasis status. We believe that our findings of EBV in infiltrating lymphocytes could explain some of the controversies relating to the role of EBV in the pathogenesis of breast cancer.

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