

MATTERS ARISING

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Viral zoonosis and human cancer: further perspectives and considerations

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Abstract

A recent review by Aguayo appearing in *Infectious Agents and Cancer* gave a timely overview of viruses that have been associated with human breast cancer. In this Matters Arising article, we discuss some critical additional points and concerns that are pertinent for this important and contentious research focus, in particular as it pertains to the involvement of the retrovirus mouse mammary tumor virus and its closely related human betaretrovirus form. This includes additional evidence for zoonotic as well as horizontal transfer of the virus and also odds ratio data on the likelihood of an involvement of the viruses proposed to be involved in human breast cancer. In our opinion, this information redresses the balance of the Aguayo review article and make a much more compelling case for this retrovirus being one of the causes of human breast cancer.

Clinical trial number Not applicable.

We read with interest the recent review article “Viral zoonosis and human cancer: a perspective” by Aguayo [1] which provides a balanced overview of all of the zoonotic viruses that are postulated to be implicated in human cancers. Of particular interest is the notion that such viruses may be involved in human breast cancer, which has been intensely studied and gained traction over the last decade (for recent review see [2]). Mouse mammary tumor virus (MMTV) was first described as possibly playing a role in human breast cancer over 50 years ago [3, 4] and the debate about breast cancer and the human form of the virus previously referred to as human mammary tumor virus (HMTV) that is highly homologous (90–98% identical) to the mouse mammary tumor virus (MMTV), and

that is now called Human Betaretrovirus (HBRV), has continued ever since [2, 5, 6]. Some key additional points and issues are addressed here in response to the review by Aguayo [1].

The evidence for a role for HBRV’s involvement in human breast cancer is more nuanced than proposed in Aguayo’s article [1]. It is not just that MMTV is capable of entering and integrating into human breast cells in vitro [7]– at least two mouse variants of the virus have also been shown to replicate and spread in human breast derived cell lines. Persistently infected human breast cells produce infectious virions that are capable of infecting naïve human breast cells in culture and this transmission can be specifically inhibited by neutralizing antibodies raised against MMTV produced by mouse cells [8, 9]. Moreover, upon infection of human breast cells, the resulting proviral DNA integrates into the human cell DNA and shows the hallmarks of MMTV specific retroviral integration [10].

This brings us to a second related issue. - If MMTV can infect and replicate in human cells why has insertional

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mutagenesis followed by clonal expansion not been identified as the mechanism by which the related HBRV, causes human breast cancer since this is clearly the mechanism by which MMTV causes mammary cancer in mice (for reviews see [5, 11]). Crucially, this mechanism needs very large amounts of virus to be produced by infected cells to generate very large numbers of integrations. However large amounts of free virus has yet to be detected in human breast cancer – indeed the virus can only be detected by sensitive techniques such as PCR. Thus, insertional activation of cellular genes seems to be an unlikely mechanism of action. Even though Civita and colleagues [12] have proposed that the high prevalence of HBRV PCR positivity in early stage ductal carcinoma in situ, compared to the lower positivity in invasive tumors [13], would be consistent with a hit-and-run insertional activation type mechanism this would again require the production (and detection) of large amounts of free virus, or at least lymphoid associated virus, at early stages in the tumorigenesis process such as during the early infection of mammary stem cells [6]. So, if HBRV plays a role in human breast cancer, it may involve other mechanisms such as the direct and indirect mechanisms that have been previously proposed for MMTV [14, 15]. Also, it cannot be ruled out that endogenous human retroviral sequences play a role, or indeed that other enveloped viruses, e.g. those mentioned by Aguayo [1], may co-infect breast epithelial cells and form pseudotyped virions that then play a role in the genesis of breast cancer [15].

Since the review article by Aguayo [1] focusses on zoonosis, it evaluates proposed transmission pathways. While in vitro experiments clearly show that virus generated from a cloned murine MMTV provirus can infect human cells [8, 9], true zoonosis requires demonstration of in vivo transmission. In the review, Aguayo [1] concludes “proposed transmission pathways - such as contact with rodents - are largely speculative” but, curiously, cites a publication where evidence supporting zoonotic transfer is summarised [16]. Another oft cited publication appearing in *Infectious Agents and Cancer* by Etkind and colleagues [17], documents late onset breast cancer in a father, mother, and daughter living in the same house. All three family members were shown to carry amplified HBRV *env* gene sequences in their tumor DNA that was over 98.0% homologous to the HBRV *env* sequences found in commonly studied lab mouse strains, and at least two other groups have suggested another route of zoonotic transmission of the virus – namely that MMTV may be transmitted to humans via pets [18, 19] resulting in HBRV. Even though it cannot yet be irrevocably concluded that zoonotic transmission occurs, this evidence is strongly suggestive. Similarly, whilst not zoonotic transmission, it is also of interest to note that Lessi

and colleagues reported the presence of MMTV/HBRV sequences in human remains dating back to the Copper Age, 4500 years ago [20] and Mazzanti et al. identified MMTV/HBRV sequences in human saliva [13]. Together, these observations raise the possibility that one or more initial zoonotic events may have occurred in ancient times, resulting in cross-species transmission and subsequent adaptation to the human host. Once the virus became adapted to efficiently infect humans, it may have been then transmitted between humans, potentially via saliva droplets (as reviewed by Bevilacqua and colleagues in [5]).

Etkind et al.'s familial clustering of cases [17] might thus reflect person-to-person spread, rather than repeated mouse-to-human contact. Other epidemiological factors lend credence to this idea. For one, urban areas in Europe and North America—where breast cancer rates peak—rarely involve intimate, ongoing human-mouse living arrangements. However, urban populations reliably show elevated breast cancer incidence compared to rural ones, a long-recognized pattern. The dense crowding of cities probably aids the spread of pathogens, which may underlie this disparity.

Another important finding on viruses and breast cancer published by James Lawson and Wendy Glenn in 2024, also appearing in *Infectious Agents and Cancer* [21], that was omitted in the review [1], compares the odds ratios for the prevalence of some of the same candidate causal viruses in breast cancer as are discussed by Aguayo [1], compared to normal and benign breast controls. Based on case control studies they report odds ratios for MMTV/HBRV of 13.40, as compared to 5.56 for HPV, 4.43 for EBV and 2.57 for BLV. Thus, Lawson and Glenn conclude that the odds ratios for the involvement of MMTV/HBRV in human breast cancer are much greater than for the other three viruses [21].

Clearly more research is needed not only to elucidate routes of virus transfer but also the mechanisms by which these viruses cause cancer. A greater insight into the contribution of HBRV and other breast cancer associated viruses as well as their mechanism(s) of action are desperately needed, also for potential future therapies and even for preventative measures.

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Competing interests

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