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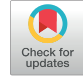
Mini-review

Viral infections and breast cancer – A current perspective



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ABSTRACT

Sporadic human breast cancer is the most common cancer to afflict women. Since the discovery, decades ago, of the oncogenic mouse mammary tumour virus, there has been significant interest in the potential aetiologic role of infectious agents in sporadic human breast cancer. To address this, many studies have examined the presence of viruses (e.g. papillomaviruses, herpes viruses and retroviruses), endogenous retroviruses and more recently, microbes, as a means of implicating them in the aetiology of human breast cancer. Such studies have generated conflicting experimental and clinical reports of the role of infection in breast cancer. This review evaluates the current evidence for a productive oncogenic viral infection in human breast cancer, with a focus on the integration of sensitive and specific next generation sequencing technologies with pathogen discovery. Collectively, the majority of the recent literature using the more powerful next generation sequencing technologies fail to support an oncogenic viral infection being involved in disease causality in breast cancer. In balance, the weight of the current experimental evidence supports the conclusion that viral infection is unlikely to play a significant role in the aetiology of breast cancer.

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1. Introduction

Breast cancer is the most common cancer to afflict women and accounts for approximately one quarter of all female cancers [1]. However, most breast cancers are sporadic and efforts to identify a unifying genetic or epigenetic cause can only explain a small proportion of disease. For instance, genetic variants which predispose to disease are present in approximately 30% of cases [2]. Intriguingly, in Queensland, Australia, the incidence of breast cancer increased from 80/100 000 in 1983 to 117/100 000 in 2002; equivalent to a 45% increase in incidence [3]. Similarly, in the United States of America, there was a 40% increase in the incidence over the 25 years to 2002 [4]. This increase in incidence may be linked to environmental factors that contribute to breast cancer development as exemplified by the increased incidence of breast cancer in Japanese women who migrated to the USA [5,6]. There are also accounts of 'cancer clusters' where high incidences of breast cancer are reported in work sites and amongst spouses [7,8]. Some of the increase in disease may be however linked to factors such as increased incidence of obesity [9]. Nonetheless, these observations have fuelled interest in a potential infectious aetiology for breast cancer.

Globally, it is estimated that 16% of all human cancers have an infectious origin [10]. Oncogenesis can be induced i) directly by viral genes, such as high-risk Human Papilloma Virus in cervical and mucosal head and neck cancer, ii) by viruses which reduce host immunity such as human immunodeficiency virus, and iii) by viruses which induce oncogenesis via chronic inflammation such as hepatitis B and C. Indeed, in 1936, it was observed that a transmissible form of mammary tumours in the mouse was caused by an extrachromosomal factor transmitted in breast milk [11], later identified as 'Mouse Mammary Tumour Virus (MMTV)' [12]. In all of these instances, tumours were associated with a high viral load which made virus discovery and analysis relatively simple.

Many different infectious agents have been investigated as potential carcinogenic agents in breast cancer, including Human Papilloma Viruses (HPV), MMTV and Epstein-Barr virus (EBV) [13]. However, significant controversy exists in the literature as to the possible role of infection with viruses or other pathogens in human breast cancer. This controversy has been fuelled by the ultralow abundance of viral DNA within the tissue. Furthermore, published

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reports which investigate the presence of virus in breast tissue vary vastly with respect to the nature of pre-analytical phase (e.g. sample type, nature of storage, sample preparation, laboratory practices) and analytical aspects (e.g. detection method, PCR or probe design, use of controls). This raises the fundamental issue of the most appropriate molecular techniques with which to detect the viruses. The debate which surrounds the putative association of viruses with breast cancer has become more polarised with the now standard use of next generation sequencing technologies.

This review will examine the evidence for viral infection as a causative agent in breast cancer and will reference both standard molecular biology techniques in addition to next generation sequencing data. Whilst breast cancer treatment has evolved significantly over the last 30 years, the identification of markers, events or indeed infection associated with disease could be exploited to develop new treatments or induce cures in patients. For this reason, it is important that a unifying rationale toward the analysis and design of pathogen-disease studies; in particular next-generation sequencing data, is used to guide sensible diagnostic and therapeutic interventions in the future.

2. Guidelines with which to critically review evidence

The original discovery in the 19th century that disease could be caused by microbes led to the development of Koch's Postulates; criteria which sought to establish a causative association between a microbe and disease. These principles were replaced by the Bradford Hill criteria, which recognise more contemporary notions in disease pathogenesis such as obligate carriers and viral infection [14]. These criteria for causality have been further refined to take into account 'molecular evidence' [15]. To truly prove disease causation by an infectious agent, these criteria must be considered. In particular, a putative pathogen genome should be detected in most disease cases, not be detected in non-diseased tissue, and the molecular evidence should be reproducible [15,16]. Thus, the first step in demonstrating causality between an infectious particle and cancer is to reproducibly detect the pathogen in the diseased tissue.

Using techniques such as *in situ* hybridisation and nested PCR to detect virus prevalence in breast cancer has produced highly variable results. For instance, high-risk oncogenic HPV prevalence has been reported to range from 0 to 86% depending on the molecular biology techniques employed and population analysed [13]. Furthermore, some of the data in the literature is lacking in experimental rigour; with regard to not using non-malignant controls or matched tissue controls, or omitting nucleic acid quality control and experimental positive and negative controls. Typically, earlier published reports used either PCR based amplification (often nested PCR) or *in situ* PCR to detect very low levels of virus DNA in breast cancer. However, few studies have generated evidence of active transcription of viral genes in breast cancer [17,18]. Viral oncogenes, such as HPV E6 and E7 are detected at high abundance and fairly ubiquitously in other virally mediated cancers [19,20], with the notable exception of 'hit and run' oncogenesis observed with bovine papilloma virus [21]. Recent advances in technology now allow for the detection of pathogens in next-generation sequencing data for both transcriptomic and genomic signatures of all known human viral pathogens. These next-generation sequencing efforts consistently failed to detect viral genomic material in breast cancer, thereby refuting a viral aetiology. However, regardless of the analysis technology or methods being employed, it is imperative that the criteria for disease causation are carefully considered in order to avoid exaggerating association without adequately proving causation.

3. Detection of viruses in breast cancer 'pre' next generation sequencing

We reviewed the literature which investigated the prevalence of four viruses – Human Papilloma Virus, Epstein-Barr Virus, Mouse Mammary Tumour and Mouse Mammary Tumour–Like Viruses and Bovine Leukaemia Virus in breast tissues using 'pre' next generations sequencing technologies. This data highlighted the disparity of prior reports which investigated the presence of viral genomic material in breast tissue. Table 1 summarises the literature, with published reports being deemed as supportive of a viral aetiology, inconclusive or refuting a viral aetiology. Supplemental data includes a more detailed review of all reports included in Table 1. For each manuscript, a judgement whether the data is inconclusive, supports or refutes a viral aetiology was made. The judgement was made on the basis of the molecular criteria for causality described above. For instance, many studies failed to examine normal tissue from non-diseased/benign breast tissue or adjacent normal tissue. These studies are inconclusive, as they do not determine the presence of pathogen in normal breast. Furthermore, studies which showed a virus prevalence in normal tissue which approximated the level in malignant tissue were also deemed inconclusive, as were studies which showed a prevalence of virus at 1 or 2% in breast cancer. Some studies were strongly supportive of a role for viruses in breast cancer, with viral DNA detected only in malignant tissue. Some studies failed to detect viral DNA in any tissue, or failed to detect it at increased prevalence in malignant breast. Some studies utilised antibodies to detect viral gene products by immunochemical methods. However, antibody based methods may not be sensitive enough to detect low level viral infection, and molecular based methods are considered more sensitive and specific.

Collectively, the literature demonstrates that in accordance with the population studied and the experimental methodologies employed, the detection of viruses in breast cancer is highly inconsistent. If one is to apply the guidelines with which to critically review evidence for an infection causing disease, many of these studies fail to provide sufficient evidence. Moreover, the volume of disparate data describing the prevalence of viral infection in breast cancer is not precedented in the literature for other truly virally mediated malignancies (such as other HPV-induced malignancies).

3.1. Human Papilloma Virus (HPV)

Hundreds of Human Papilloma Virus (HPV) subtypes have been described. The so called 'low-risk' HPV subtypes are the aetiological agent for cutaneous warts and anogenital warts [22], whilst 'high-risk' HPV (e.g. subtypes 16, 18, 11, 33) are an aetiological agent in uterine cervical cancer, anogenital carcinomas [23–25] and head and neck cancers [26]. High-risk HPV produces oncogenic proteins E6 (which promotes the degradation of p53) and E7, which bind to the Retinoblastoma protein (Rb) and disrupts Rb/E2F complexes [27]. Reports of HPV prevalence in breast cancer ranges from 0% to 86%, summarised in Suppemental Table 1.

3.2. Epstein-Barr Virus (EBV)

Epstein-Barr virus (EBV), also called human herpes virus 4 (HHV-4) is one of eight known viruses in the herpes family, and is one of the most common viruses in humans. It is the aetiological agent for infectious mononucleosis, and it is estimated that over 80% percent of 18 year olds show serological evidence of prior EBV infection [28,29]. EBV is associated with nasopharyngeal carcinoma, gastric cancer, endemic Burkitts lymphoma and a subset of

Table 1
A summary of the role for viruses in breast cancer – pre next generation sequencing. A Pubmed search identified studies which investigated viruses in breast cancer using molecular techniques such as PCR, *in situ* hybridisation, immunohistochemistry or ELISA. Studies were reviewed, and it was determined whether the data supported or refuted a role for the virus in breast cancer. Some studies were deemed inconclusive. References to support the conclusion are listed. Supplemental Tables 1-4 show the full summary from which Table 1 was derived.

Virus	Inconclusive	Support	Refute
Human Papilloma virus	*26/37 (70%)* [40–65]	*6/37 (16%)* [66–71]	*5/37 (14%)* [72–76]
Epstein-Barr virus	*19/39 (49%)* [51,62,77–93]	*7/39 (18%)* [94–100]	*13/39 (33%)* [101–113]
Mouse Mammary Tumour Virus and Mouse Mammary Tumour Virus - like	*9/29 (31%)* [62,114–121]	*8/29 (38%)* [122–129]	*12/29 (41%)* [35,96,130–139]
Bovine Leukaemia Virus	*3/4 (75%)* [140–142]	n/a	*2/4 (25%)* [143]

Hodgkin's lymphoma [30]. Detection rates of EBV in breast cancer range from 0% to 68% (summarised in Supplemental Table 2). Notably, several studies used *in situ* techniques to detect EBV and noted that a positive signal was detected in tumour associated lymphocytes only.

3.3. Mouse mammary tumour virus (MMTV) and MMTV-like (Human Mammary Tumour virus)

Mouse Mammary tumour virus (MMTV) was the agent identified in the early half of the 20th century by Joseph Bittner. It is a Betaretrovirus and induces mammary tumours in mice. A confounding factor in the detection of MMTV in humans is the presence of endogenous human retroviruses (HERVs) which are genetically similar to MMTVs. There is contradictory evidence as to whether MMTV can indeed infect human cells [31]; as they lack the transferrin receptor required for virus entry [32,33]. It has been proposed that a human retroviral analogue of MMTV, termed Human Mammary Tumour virus or MMTV-like virus is a causative agent in human breast cancer. MMTV-like virus only shares approximately 50% homology with HERVs, and a complete proviral structure has been identified from several breast cancers [34]. The prevalence of MMTV-like DNA in breast cancer has been reported to range from 0% to 57% (Supplemental Table 3). However, one study sequenced PCR amplicons which were purported to be from HMTV using published primers and showed that the amplicons represented spurious amplification of human Chromosome 3 [35]. Furthermore, unlike what is observed in the murine transmissible breast cancers, breast-feeding is not a risk factor for offspring development of breast cancer [36].

3.4. Bovine Leukaemia Virus (BLV)

Bovine Leukaemia virus (BLV) is a widespread infection of cattle. It is an oncogenic retrovirus that causes a B cell leukaemia like disease and can be transmitted to calves via milk [37]. A recent study reported the estimated prevalence in dairy herds in the USA at approximately 50% [38], whilst in Canada 78% of herds had antibodies against BLV [39]. Transmission of BLV to humans could occur via contact with animals or consumption of milk of beef products. It has been shown that 74% of humans have antibodies that react to at least one BLV antigen, suggesting that zoonotic transmission of BLV to humans is possible. Several studies have examined breast tissues for BLV, and have shown a prevalence in breast tissue from 0% to 59%, summarised in Supplemental Table 4.

4. Viral detection in next generation sequencing – sensitivity considerations

Since the advent of next generation sequencing, there have been thousands of cancer genomes and transcriptomes sequenced, primarily through efforts such as The Cancer Genome Atlas. In addition to providing critical information on the altered 'human' genetics associated with cancer, next generation sequencing can also detect non-human genetic material. One of the first examples whereby next generation sequencing was applied to a virally mediated cancer was the use of digital transcriptome subtraction technology to identify Merkel Cell Polyomavirus (MCV) in Merkel Cell Carcinoma, an aggressive neuro-endocrine skin tumour. The analysis of 'non-human' transcripts allowed for the detection of MCV, a novel polyomavirus which was clonally integrated in the Merkel Cell carcinoma genome [144]. Next generation sequencing has also been successful in applications such as the detection of viral genomes in disease outbreaks and a novel virus in organ transplant recipients [145]. Multiple viral detection bioinformatic pipelines have been described, which can detect viral transcripts, viral genomes or fusion genes [146–150], and viral integration sites in DNA [149,151–153].

An important consideration in the use of next generation sequencing is the depth at which sequencing is performed, as this is critical in the detection of low abundance transcripts, or low abundance viruses. Central to this consideration, is the typical copy number integration of viruses in cells, and the proportion of viral transcripts which are produced. Tissues such as cervical cancer show typically high expression of viral transcripts (HPV E6/E7 gene; e.g. 850 ppm; where ppm is parts per million, representing the fraction of viral reads in the total sequencing library) [154], whereas similarly HPV infected cancers such as head and neck cancer show a lower infection rate (HPV E6/E7 gene; e.g. 20–300 ppm) [63,154]. It has been proposed that a tumour can be considered 'positive' for a virus that is involved in tumour formation or maintenance, if infectivity exceeds 2 ppm [154]. This threshold is based on the consideration that a value lower than 2 ppm could be attributed to the intracellular content of an immune cell, red blood cell within the tissue analysed or arising from environmental contamination.

In the case of detection of MCV using digital transcriptome subtraction, transcripts were present in the tumour at 10 transcripts per million (10 ppm), which equates to 5 transcripts per tumour cell [144] Estimates for the detection of viral transcripts in next generation sequencing analysis are such that in RNA-sequencing at a depth of 10 million sequencing reads, if every cell is infected, there is a 99.99% probability of detecting at least one viral transcript [155,156]. This equates to 1/5 of the viral transcript load detected for the known oncogenic virus, MCV. For *de novo* assembly, i.e. in the identification of 'unknown' viruses by assembling overlapping reads end to end, it has been shown that, for very low viral load (below the limit of detection by quantitative real time PCR), *de novo* assembly was not possible without a higher level of infection, whereas viral identification can be successful using alignment to annotated viruses [157]. This study recommended

that sequencing at a depth of 7 million reads/sample performed similarly to commercially validated viral detection PCR kits would be sufficient to reliably detect credible viral transcription [157].

Other important considerations when evaluating next generation sequencing data for pathogens is the possibility of contamination from laboratory reagents or other DNA samples. Most notable was a recent report where a number of samples in the TCGA database were contaminated with HeLa cell DNA [158,159]. Another report has suggested that endometrial cancer RNA-sequencing samples in the TCGA database are contaminated with HPV38, probably due to cross-contamination of a batch of samples with DNA from one sample [160]. Contamination can also arise from inadvertent contact of specimens with patient skin, or spurious reads which arise from circulating lymphocytes which are positive for virus. This issue is also of importance for non-next generation sequencing studies. For instance, laboratories which perform frequent PCR/nested PCR for viral products can experience reagent or sample contamination from PCR amplicons. Such contamination may be prevalent even with the utilisation of positive and negative controls.

5. Next generation sequencing and viral detection in breast cancer

Several studies have interrogated next generation sequencing data in breast cancer to attempt to identify pathogenic infections. The first such study examined the transcriptomes of 810 breast cancer samples and 104 normal samples from the TCGA sequenced at an average depth of 169 million reads per sample [154]. A custom bioinformatics pipeline was used to screen for known and novel viral transcripts and viral/host fusion events. The authors found no evidence for expression of any viral transcripts in any of the cancers, with the exception of one normal tissue sample with a 3.1 ppm expression of the early and late genes of HPV2 (a cutaneous wart HPV type) [154]. Careful examination of the supplementary dataset from this study showed very low level HPV18 positivity of a maximum 0.04 ppm (8 reads) in several of the normal and malignant samples at the same prevalence in both tissue types. An additional study, similarly utilising TCGA RNA-sequencing data with a different bioinformatics analysis technique, showed no evidence of transcribed viral elements in breast carcinoma [155]. Importantly, the TCGA dataset utilised poly(A) selected mRNA fraction. EBV expresses two abundant non-coding RNA transcripts, EBER-1 and EBER-2 which lack a poly(A) tail and would not have been detected in this RNA-seq analysis. However, other EBV transcripts which are expressed during latent and lytic infection are polyadenylated and would be detected if present.

Another study comprehensively examined viral prevalence across 58 samples using RNA sequencing, exome sequencing and immunohistochemistry and PCR on tissue samples [161]. With a median sequencing read depth of 64 million paired end reads per sample, one sample (1.7% of total) showed human herpes virus 6 at 0.25 ppm and another EBV at 0.06 ppm (1.7% of total). MCV was detected at 0.04 ppm in a further sample. In the same samples, EBV presence were confirmed by exome sequencing data. However, EBV was not detected using immunohistochemistry in the EBV positive sample. Likewise, two samples were "noted" as HPV-positive using PCR techniques, however no HPV virus was detected using RNA or exome sequencing [161].

Using a different strategy, our group screened fresh breast tumour samples for HPV DNA positivity using a nested PCR-based approach [63]. Samples which were HPV DNA positive were subjected to RNA sequencing. None of the HPV positive samples showed expression of viral transcripts, nor expression of any other known virus. One explanation for the discrepancy between DNA/RNA arises from false positives or detection in non-malignant cells such as circulating blood rather than from inactive viral genomes. Thus, even biasing the sampling strategy to those samples that were positive for HPV DNA failed to show evidence of viral transcripts. These four studies all strongly suggest that human breast cancers do not contain transcriptionally active HPV, or other express any other viral transcripts.

A recent report highlighted the importance of a robust bioinformatics pipeline and adherence to a threshold of 2 ppm [162]. In this study the authors attempted to screen for HPV-positivity in TCGA breast cancer samples by a bioinformatic analysis of TCGA breast carcinoma transcriptomes, and deemed a sample positive with a minimum of one read with 98% similarity to a virus. This corresponds to 0.005 ppm fraction viral reads, or 1 read out of 169 million as viral. Unfortunately, the authors failed to analyse the greater than 100 normal breast tissue samples which are available in the TCGA archive [162]. However, if one considers the previous study by Tang et al. [154] which analysed the normal tissue samples within the TCGA then it would seem likely that this ultra-low copy number is no different from the prevalence found in normal breast tissue.

Recent reports suggest that bovine leukaemia virus (BLV) may be associated with breast cancer [141]. Analysis of 51 breast cancer whole genomes found no similarity to BLV genome [163], including screening for *in silico* generated variants of BLV. Previous reports had suggested that 59% of breast tumours should be positive for BLV – at the sequencing depth employed for the whole genome analysis at a low viral load of 0.1%, 30 BLV reads should have been detected. This data strongly suggests against clonal insertion of BLV in the breast genome [163].

Most notably, all the credible next-generation sequencing studies that have been described employed careful use of control samples (e.g. virus positive cancers such as hepatocellular carcinoma, cervical cancer and head and neck cancer) to adequately determine the sensitivity and specificity of the viral detection bioinformatics pipelines. In addition, if an attempt is made to call 'positive' samples from next generations sequencing analysis, it is imperative that normal, non-malignant samples are analysed in parallel.

6. Concluding remarks

The issue of specifying thresholds or risk is common in environmental toxicology. What we do know is that a viral load of >10 ppm is considered etiologic or an etiologic contributor in hepatocellular carcinoma and head and neck carcinoma. There is no evidence, that a viral load of <10 ppm is sufficient or capable of contributing to cancer development. However, relative viral load may not be simple to determine since it is assumed that the viral load would be homogenous across a tissue. This may not be the case and even if one considers that only a subset of cancer cells may be infected this would still seem implausible since it would assume that the virus does not replicate within the transformed cells. Whilst, as mentioned, a 'hit and run model' of viral clearance does exist for Bovine Papilloma virus, this model has not been implicated in any human cancer and as such is unlikely to occur in human breast cancer. In the age of evidence based medicine, and giving consideration to specificity and sensitivity of analysis, it seems prudent to take the viral threshold indications from other proven viral diseases such as head and neck carcinoma, cervical cancer and hepatocellular carcinoma, where the minimum proportion of viral RNA reads is > 2 ppm (more likely >10 ppm). On the basis of this assumption, there is no evidence for any virus, known or unknown, as a pathogenic agent in sporadic human breast cancer. Furthermore, the standardised nature (with respect to sample collection,

preparation, storage, diagnosis, sequencing and analysis) of large scale next generation sequencing efforts such as TCGA eliminates many of the potential causes for inconsistency which may arise during the preanalytical or analytical phases (e.g. fresh samples vs formalin fixed paraffin embedded, PCR vs in-situ hybridisation, different sensitivity and efficiency of different PCR primers).

Highly variable molecular evidence for a viral infection in breast cancer exists. The pre-next generation sequencing reports show intra-study variability which may be accounted for by different study populations, different experimental techniques or false negative/positive results. Nonetheless, it is clear that many of the PCR-based studies do not meet the molecular criteria for verifying causality between pathogen and disease. Multiple large scale, case controlled next-generation sequencing studies performed across multiple centres with different cohorts of patients (encompassing the ethnic diversity seen in developed countries) have failed to detect any viral pathogens in breast cancers, whilst showing sensitivity and specificity in the detection of viruses in known virally mediated cancers. Taking an evidence based approach, it would seem judicious to accept that the modern, molecular data does not support a causative role for viruses in breast cancer. Ultimately, an important longer–term scenario which might shed light on whether or not a commonly investigated virus can cause breast malignancy is the fact that in 2015, 78% of Australian females under the age of 15 had received the therapeutic level of 3 doses of the HPV vaccine (data – www.hpvregister.org.au/research/coverage-data/HPV-Vaccination-Coverage-2015, accessed 25/05/2017). As such, if HPV is associated with breast cancer, we would expect to see a reduction in incidence perhaps around the middle of the 21st century.

Conflicts of interest

The Authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.canlet.2018.01.076.

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