Epstein-Barr Virus as a Disease-Causing Agent in Well-Characterized Disease States and the Broader Population

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Abstract

Epstein-Barr virus infection (EBV) affects 90% of adults and is the most common cause of infectious mononucleosis - a syndrome with fever, sore throat, enlarged lymph nodes, and fatigue. After infection, the virus remains in latent condition in host B lymphocytes. It is generally kept in check by host immune mechanisms, but in rare cases, EBV can replicate, unfettered, and lead to multitudinous reactions within the body. The uncontrolled proliferation of EBV-infected cells is highlighted in scenarios of X-linked lymphoproliferative disease (XLP), a genetic predisposition that allows young males with primary EBV infection to develop cancer, and in post-transplant cases where the virus can cause lymphoma. In broader populations, EBV has been linked to nasopharyngeal carcinoma (NPC) and has significant impacts on treatment and survival in classic Hodgkin lymphoma (cHL). EBV, a DNA virus, integrates into the genome, turning cell checkpoints into malignant systems and allowing rapid induction of carcinogenesis. This review explores factors that allow EBV to evade host immune mechanisms- resulting in cancer- and aims to address gaps in screening and prevention. Sources are primarily obtained from the PubMed Central Database. Understanding the conditions under which the virus can reactivate and the extent to which it promotes oncogenesis will foster increased awareness of avoiding triggers and further clinical research for vaccines for vulnerable groups. Furthermore, a growing body of evidence points toward the potential prognostic value of serological testing in at-risk populations.

Keywords: Epstein-Barr virus, X-linked lymphoproliferative disease, Post-transplant lymphoproliferative disorder, Classic Hodgkin lymphoma, Nasopharyngeal carcinoma.

Introduction

Epstein Barr-Virus (EBV) affects most adults worldwide. It is the most common cause of infectious mononucleosis but typically resides in a latent form in the body's lymphocytes[1]. Though this virus is consistently found to latently reside in the peripheral blood memory B lymphocytes and some bone marrow cells, in rare cases, natural error via cell malformation and repeated proliferation can allow infected cells to spread and cause cancer[2]. However, numerous studies have linked the EBV Virus to carcinogenesis as it may play a role in further suppressing

the human body's ability to correct cellular errors. The biochemical and genomic factors involved are still largely unknown, but a better understanding of the virus and its effects in normal populations is necessary and valuable in helping with immunization and protection for high-risk groups.

In certain well-characterized disease states, such as in cases of X-linked lymphoproliferative disease (XLP), a genetic predisposition that allows young males with primary EBV infection to develop cancer, as well as in cases of post-transplant lymphoproliferative disorder where the virus can cause lymphoma, the pathways that EBV takes in infecting cells and causing uncontrolled proliferation are well known[2]. Additionally, a newer body of evidence concerning EBV oncogenesis in broader populations suggests a stronger link between EBV and cancer development. In cases of classic Hodgkin lymphoma, a type of blood cancer of the lymphocytes, EBV-positive status has had both positive and negative impacts on treatment efficacy and likelihood of survival across different age groups[3]. Further, in cases of nasopharyngeal carcinoma, a head and neck squamous cell carcinoma primarily affecting Southeast Asians, EBV is an indicator of both future development and severity of cancer[4]. The presence of EBV antigens as blood markers has been used to predict whether an individual will develop nasopharyngeal carcinoma and the level of antigen presence has been used to determine the likelihood of this development[5]. Further screening for those members of high-risk populations may eventually be a very useful tool in preventing those with nasopharyngeal carcinoma from progressing in severity and may drastically increase survival rates.

Previously written literature reviews synthesize evidence regarding the links between EBV and various types of cancers, often focusing on the role that EBV plays in the development of cancers. Conversely, few reviews explore both the endogenous and exogenous factors involved in development and their contribution, as biomarkers, to screening and prevention efforts. In modern medical treatment, there are many gaps in screening and prevention technologies when it comes to EBV-associated carcinogenesis. This review study aims to look not only at the link between EBV and carcinogenesis but rather discuss the links and genomic evidence of EBV in the development of cancer to identify important biomarkers for these technologies and emphasize the importance of further clinical research for vaccines, screening, and improved preventative efforts. Improved tools will be very useful in both preventing cancer development and improving treatment efficacy and survival rates in cancer patients. This review does not however seek to answer the question of whether EBV is directly linked to carcinogenesis, nor does it look to discover what specific screening and prevention tools should be used in treatment, as not enough evidence currently exists on the subject. Sources are, in majority, obtained from the PubMed Central Database with a general inclusion criteria preference for primary research focusing on correlations between EBV and oncogenesis.

Results

Mechanisms of Immune System and Cellular Checkpoint Evasion by EBV

Epstein-Barr Virus has been directly linked to a variety of different cancers, generally transitioning infected cells to a cancerous form due to abnormal gene expression[12]. EBV presents a more unique case in viral carcinogenesis as it exists in an episomal state rather than directly integrating itself into it. EBV DNA binds to the surface of the host DNA and rewires the molecule so that it completely changes its shape[6]. This change in shape has been linked to the activation of cancer-related genes in the body.

EBV may also take other pathways in viral oncogenesis. By binding to the host DNA, EBV can cause chemical changes to the epigenome that result in switching off tumor-suppressor genes[7]. Under these circumstances, EBV is easily able to evade normal checkpoint mechanisms and result in a tumor lineage. Without the control of normal checkpoint mechanisms, cellular apoptosis cannot be activated as the cell is not aware of the incorrect integration that has happened[6]. The malformation of a single cell followed by monoclonal proliferation, results in the malignant tumors that we know to be associated with Epstein-Barr Virus.

During primary infection, EBV generally infects both lymphocytes and epithelial cells[8]. EBV is seropositive in most adults and remains latent while expressing latent genes, however, in these cases of carcinogenesis, these latent expressions begin to interact with the normal chromosomes and begin to create disturbances in the cell cycle. EBV promotes rapid phase transitions in the cell cycle, inhibits the function of apoptosis, and generates neoplasms, which further become forms of malignant lymphoma[6].

In vitro tests have shown that EBV can transform these commonly infected B lymphocytes into malformed cells; however, in this process, the cells are thus immortalized which is a vital step in the proliferation of the cancerous cells[8]. These cells can continue to multiply for an indefinite period. Many studies have also proved that EBV can infect NK, or natural killer, cells whose job it is to kill cancerous cells as part of the body's immune surveillance[9]. This means that viral carcinogenesis with EBV can become even more dangerous considering that there is potential for malignant lymphoma and severe immune compromise that comes along with the condition. This makes many treatment forms much less effective as the natural anti-tumor mechanisms are rendered ineffective.

This lack of immune response is better understood in the context of the EBV oncogene, EBNA1. The EBNA1 oncogene is responsible for maintaining the genome of EBV in latently infected cells[10]. It has more recently become very clear, however, that there is an association between tumor virology in EBV and EBNA1's suppression ability[8]. EBNA1 can inhibit NK cells' responses and apoptosis reaction to cells that were recently infected. Though there are memory B cells

that can fight against EBV based on the reaction to the initial infection, EBNA1 causes there to be significantly less reaction and surveillance from the immune system, thus allowing EBV to result in carcinogenesis without being stopped by the body's natural defense mechanisms[9]. These infected cells continue to survive for the rest of the host's life without intervention as the immune surveillance for those particular cells has been deactivated.

EBV contains many different proteins such as the EBNA-3C antigen, which allows for the transformation, proliferation, and survival of the infected lymphocytes[7]. In its integration into parts of the genome, EBV and its various proteins suppress the transcription of necessary parts of the cell cycle, and thus the cell possesses not only the infection from the virus but also lacks its essential parts and transitions for it to function as a normal cell even without the virus[11]. All such cells should be destroyed immediately and yet apoptosis reactions cannot be fueled because the virus has shut off all appropriate immune reactions. Even the pre-apoptotic tumor-suppressor genes and factors such as promotion of the G1/S phase are suppressed by these oncogenic proteins[6]. These proteins essentially inhibit each part of the cell cycle so that the cells do not proliferate and survive inappropriately. Specific medical conditions are known to render patients especially vulnerable to the previously mentioned mechanisms.

Epstein-Barr Virus Associated Carcinogenesis in Well-Characterized Disease States

X-linked Lymphoproliferative Disease

A prototype genetic immune deficiency is found in the case of X-linked lymphoproliferative disease (XLP). In this condition, the affected group is primarily young males. In XLP, a mutation within the SH2D1A (SH2 domain protein 1A) gene affects a receptor involved in T cell and natural killer (NK) cell signal transduction[14]. The SH2D1A gene is essential for lymphocyte functions including T helper (Th) cell signaling and differentiation, NK and CD8 cell killing, generation of NKT cells, and germinal center formation as well as generation of plasma cells and memory B cells[2]. This is a silent immunodeficiency, however, when a person with XLP is met with primary EBV infection, they could die from fulminant infectious mononucleosis syndrome or EBV-induced lymphoma[13]. About 50%-60% of people with XLP can develop EBV-related complications, which include malignant lymphoma in around 30% of patients. The mean age for EBV infection is typically around five years of age, and though there are no simple methods for genetic screening, XLP can be found by gene sequencing in the case of the previously mentioned conditions[2]. As mentioned above in the case of SH2D1A deficiency, the T cells and NK cells become dysfunctional and fail to control the unfettered replication of EBV-infected cells[2]. Without this gene, cell signals and receptors send incorrect signals, resulting in the failure of apoptosis to occur when necessary. This ultimately results in malignant tumors.

Post-transplant Lymphoproliferative Disorder (PTLD)

EBV-associated PTLD can occur in up to 20% of solid organ transplant recipients[15]. The risk for developing PTLD depends on several factors including the timing of EBV infection related to the transplant, the type of transplant, and the age of the recipient. Firstly, most PTLD cases occur within one year of transplantation. Primary infection in the setting of a donor being positive for EBV and the recipient being negative or when both donor and recipient are negative but EBV is environmentally acquired poses a very high risk. In both situations, the common factor is that the recipient lacks preexisting memory of EBV[2]. Certain types of transplants have a greater propensity towards PTLD. One such example is a small bowel transplant. On the other hand, kidney transplants have a very low risk[15]. Finally, age is a factor because younger children are more likely to be EBV negative than adults and thus have a higher risk of acquiring primary infection after transplant[16]. Bone marrow transplants also carry low risk, at 3%. The risk factors after a bone marrow transplant include a negative recipient, severe T-cell depleted graft, or an umbilical cord blood transplant[2]. Presentation of PTLD can consist of fever, weight loss, night sweats, abdominal pain, and fatigue. More definitive changes include lymph node enlargement and liver and spleen enlargement[16]. The principle underlying PTLD is a consequence of immune suppression given before transplantation and ongoing immune suppression after transplantation suppresses T and B cell function significantly. If a person were to develop a primary infection/reactivation of EBV during this vulnerable time, the virus can multiply unmitigated, causing B cell immortalization and tumor formation[17]. One strategy that physicians employ in managing this problem is reducing immune suppression, hoping that the host immune response may control the infection. On occasions, the transplanted organ is sacrificed to allow for the complete stopping of immune suppression and gaining control of EBV[15].

In these well-characterized disease states, the pathway for immune suppression is well known and is often able to be treated as the previously mentioned outcomes are very common amongst those in the outlined pools. However, the common cases of immune suppression and irregular behavior of cellular formation are one of many other possible pathways that the Epstein-Barr virus takes in its process of oncogenesis. In normal populations, there are many other ways in which it may influence the body, potentially taking an effect ranging in severity based on a variety of risk factors.

Epstein-Barr Virus Associated Oncogenesis in Normal Populations

Recent studies have shown notable links between the Epstein-Barr Virus and the reactivation or exacerbation of certain health conditions due to the virus's presence. The mechanisms through

which the Epstein-Barr Virus results in a tumor lineage are still relatively unknown, however, recently, more links between EBV and oncogenesis have been found in those who do not have known risk factors.

Epstein-Barr Virus in Classic Hodgkin Lymphoma(cLH) Patients

As mentioned previously, the Epstein-Barr Virus is a DNA virus and the leading cause of Infectious Mononucleosis. By the time one reaches adulthood, it is almost certain that they carry the virus in its latent form[1]. Previous literature indicated that EBV-positive status proved detrimental for the elderly and other older adults with cLH. There is no certain explanation for why this may be the case, however, the particular qualities associated with old age allow speculation into how natural processes may be the deciding factor when looking at the virus's impacts. Patients of the older age groups may also naturally have immune deficiency preventing them from receiving strong and targeted chemotherapy to remove the EBV-induced cancer cells.

In pediatric and adolescent patients, however, different results were found. Though there was generally a mild positive impact or no impact at all relating to EBV status and cLH, EBV-positive status seemed to improve treatment efficacy, increase the likelihood of survival, and prolong survival time in cases of certain death. Often, EBV-positive children were far less likely to reach more severe stages of cancer as compared to EBV-negative children[3].

There is no clear link between EBV and its impacts on different age groups, however, research has been able to conclude by observing the tumor microenvironments in different age groups to observe the potential causes for the opposite reactions that are occurring.

In pediatric patients, the tumor microenvironments were found to be significantly more cytotoxic than those of adult patients. Pediatric tumor microenvironments are Th1 dominant and therefore possess the CD8 cells necessary for killing virus-infected cells- the cells of the tumor[3]. In children, the tumor is surrounded by a minimally immunosuppressive environment and is, therefore, more responsive to treatments as the body is not working against itself when responding to chemotherapy[18]. The tumor microenvironments of adult tumors, however, contain increased Tregs as well as decreased interferon-beta production[19]. The tumor microenvironments in adults are more Th2 dominant, meaning they possess more CD4, or support, cells that do not place their focus on attacking the infected cells[3]. These environments also contain a significant number of Tregs with the FoxP3+ protein which, in normal cases, would limit a dangerously overactive immune response, however, by limiting the immune response here, it creates a suppressive environment which is not conducive to accepting and effectively receiving treatment[20]. The tumor environment in pediatric patients is constructed very effectively for responding to direct treatments, creating a positive case when someone has a positive EBV status, however, in adults, a positive status means increased immune suppression

and reduced immune response. Not all pediatric cases have had good effects, some have just been neutral, but the overall observation in adults has been an exacerbation of cLH because of its tumor microenvironment[3]. These conclusions can be drawn, but it is still unknown if EBV causes a specific tumor environment or if a specific tumor environment impacts EBV.

Serological Testing for Identifying the Risk of Developing Nasopharyngeal Carcinoma

A retrospective study on cohorts of patients with Nasopharyngeal Carcinoma has recently revealed a link between EBV expression and early signs of cancer development[21]. In an experiment involving serological testing, antibodies from patients who had nasopharyngeal cancer revealed that EBV, which is essentially ubiquitous in adults revealed that those in a risk pool for nasopharyngeal carcinoma were highly likely to develop a tumor if they had IgA antibodies that developed against EBV's EBNA1 antigen[21].

Though a direct causal relationship has not been identified, this correlation is significant in advancing scientific knowledge as IgA against EBNA1 has now been identified as a biomarker for nasopharyngeal carcinoma[22]. This is significant when it comes to screening and other potential solutions in the future because high-risk groups can undergo regular blood testing in search of this biomarker to determine if they will eventually have cancer. This serological testing allows patients to learn around four years in advance whether they will develop a tumor. This is extremely helpful in planning treatments, and prevention, and quickly identifying problems instead of allowing them to go on for years unnoticed. Essentially, blood testing will be able to quickly identify spikes in EBV antibodies and if these are found to be associated with IgA the person can very proactively take steps to prevent death and prolong survival[23].

Further links between EBV and Nasopharyngeal Carcinoma

In considering the relationship between the previously mentioned afflictions as causation or correlation, there is a clear pathway in either a causal or compounding relationship as EBV often creates a sensitive environment that is more likely to develop nasopharyngeal carcinoma. In its path of infection, EBV infects the epithelial cells in the lining of the nasopharynx, causing cellular damage and inflammation[24]. This cellular damage can many times result in the uncontrolled proliferation of malformed cells, ultimately resulting in a tumor lineage. EBV may, in this case, also take the pathway of causing the shutdown of tumor-suppressor genes, making apoptosis dysfunctional and resulting in a tumor lineage[6].

Many recent studies on the link between Epstein-Barr virus and Nasopharyngeal Carcinoma (NPC) have concluded that a significant number of NPC cases have been found to exist

concurrently with EBV in the body of the patient[4]. In a recent study observing the importance of EBV blood markers as an indication of NPC, researchers found that NPC alone is a highly treatable disease when detected early. Early detection was found to correlate with a 90% five-year disease-free survival rate, as opposed to a less than 50% chance of survival with late detection[25].

Extensive research into such a link, particularly in the case of a group of over 9,500 Taiwanese men, showed that high antibody levels, particularly of the VCA IgA antigen preceded the development of NPC quite dramatically[26]. The hazard ratio, with a 95% confidence interval, of developing nasopharyngeal carcinoma for low and high EBV antibody levels was 9.5 (2.2-40.1) and 21.4 (2.8-161.7)[5]. A positive test for significant amounts of this antigen was directly linked to a 22-fold increase in the development of NPC in later appointments. These tests were conducted in a population with a relatively high degree of genetic predisposition to NPC; each subject had at least two first or second-degree relatives who had been affected by NPC. In such populations, NPC rates have even been as high as 100 per every 100,000 cases which is 100-fold that of the rate in the United States[5].

There are a variety of factors affecting predisposition for NPC beyond that of just genetic association[27]. In a control study in nasopharyngeal squamous-cell carcinoma, interviews with over 400 subjects indicated that a higher risk was often associated with a past of ear, nose, or throat diseases, exposure to fumes and smoke, exposure to chemicals, as well as environmental carcinogens from certain food groups[28]. A different study following an NPC screening cohort of over 10000 individuals in China found that smoking can increase an individual's long-term risk for developing NPC by reactivating EBV[29]. Foods such as salted fish contain volatile nitrosamines that have caused oncogenic alterations (secondary gene alterations)[30]. Middle-aged individuals are also found to have much higher rates of NPC than other age groups[27].

Research has also found that EBV DNA found in plasma is also a potential biomarker for NPC, which when used in screening had a sensitivity of 96% and a specificity of 93%[4]. The EBV DNA that is found in plasma is in the form of short fragments that are specifically released by the nasopharyngeal carcinoma cells. The presence of this DNA is enough to indicate that NPC cells are present, thus making it a potential marker for future cancer development. The same study further indicated that early diagnosis of NPC is critical to survival, with the five-year survival of patients with stage I disease being as high as 95%, compared to a drastically lower 60% if diagnosed at stage IV[4]. Early diagnosis is critical as NPC is regarded as a relatively asymptomatic form of cancer. Most NPC patients are initially diagnosed around stage IV wherein advanced metastasis has taken place beyond the point of repair[31].

All plasma and serological tests for EBV DNA or anti-EBV IgA antibodies generally have very low positive predictive values, as is common in testing for asymptomatic diseases; however,

there is evidence to suggest that these screening methods may be beneficial for those with known predispositions and risk factors to take preventative action for future tumor development. Plasma and serological tests are found to be very cost-effective in at-risk populations, which makes them a good screening option given the limited options available within current research[32].

It is important to note that NPC is a relatively aggressive cancer with rapid metastasis, however, a three-year rate of progression-free survival in a group of NPC patients identified that those diagnosed during stage 1 had a 97% chance of survival as compared to a much lower 70% if diagnosed in a later stage (0.10 HR)[4]. NPC patients were ten times more likely to have a positive outcome with the early diagnosis than later diagnosis because there are current treatments for early-stage NPC. Late-stage NPC is very difficult to cure because of the ever-growing state of cancer, meaning that early diagnosis is critical to long-term survival[4]. Other research, using in situ hybridization methods has found that almost 100% of NPC cases have EBV-encoded small RNAs (EBER) in the nuclei of the tumor cells, which would again suggest the importance of early screening[33]. EBV is often characterized by its latent infection of cells, including NPC cells. In its general pathology, EBV then possesses the ability to restrict apoptosis and tumor suppressors in the cells, allowing the rapid proliferation of infected cells. The sooner this potential for development is identified, the quicker the rapidly escalating processes can be halted or stabilized[34].

Further studies of a population in China found that the anti-EBV antibody levels in NPC patients were elevated by 93% in NPC and were at this raised level for up to ten years before diagnosis[35]. There is evidence to suggest that screening in this window of the preclinical stage of NPC development can be a clear indicator of future tumor development. In a study of 171 people in a geographically high-risk population, within two years, 61 people developed NPC. Of these 61 people, 58(95.1%) were detected with early serological testing[35].

Though there is a relatively high rate of false positives and negatives in the broader population, as is the case when studying the link between conditions with so many potential risk factors, screening for EBV may be valuable amongst those who are identified as being predisposed to developing NPC. NPC is consistently found to be the most treatable when caught in its earlier stages and EBV may be a potential biomarker for development even before the cancer's onset[4]. Though it is difficult to say that there is a strong enough correlation to suggest any form of immunization, there is certainly evidence to suggest that serological testing and subsequent screening can be extremely beneficial.

Discussion

Epstein-Barr Virus has been repeatedly linked to carcinogenesis as it may play a role in suppressing the human body's ability to correct cellular errors[7]. In its typical pathway, EBV switches off the body's tumor-suppressor genes, and inhibits the function of apoptosis and other pre-apoptotic factors, allowing the unfettered proliferation of infected cells[6]. This proliferation is ultimately what we know as a tumor lineage.

In certain well-characterized disease states, such as in cases of X-linked lymphoproliferative disease (XLP) and cases of post-transplant lymphoproliferative disorder, the virus can cause cancer by allowing infected cells to take over the body during immunosuppressed states. In cases of oncogenesis in XLP, a deficiency in the SH2D1A gene impairs the function of the T cells and NK cells which allows the EBV-infected cells and their receptors to send incorrect signals, ultimately stopping apoptosis when needed and resulting in malignancies[2]. Similarly, in cases of post-transplant lymphoproliferative disorder, a patient can acquire EBV infection from the transplanted organ or the environment while under immunosuppressive drugs, which can cause T and B cell function suppression and result in a tumor lineage[17].

Newer evidence concerning EBV oncogenesis in broader populations shows that there are further links between EBV and cancer development. In cases of classic Hodgkin lymphoma, EBV-positive status has had positive impacts on treatment efficacy and likelihood of survival across pediatric cases[3]. It was found that because of the cytotoxic nature of the tumor microenvironments in children, the environment is minimally immunosuppressive and contains the components necessary for killing EBV-infected cells before they can result in malignancy[3]. Similarly, although there is little knowledge about the exact pathways of the pathology of Epstein-Barr Virus and Nasopharyngeal Carcinoma in association with one another, there is a clear indication that there is a strong correlation between the two. Epstein-Barr virus takes a variety of predictable as well as undiscovered pathways in oncogenesis and despite the presence of a direct causal relationship or lack thereof, in the case of Nasopharyngeal Carcinoma, the presence of certain EBV antigens, such as the IgA antigen, has through repetition appeared to be an indicator of future NPC development. Both through serological testing and extraction of plasma, testing in high-risk populations for NPC development has indicated that those who have EBV that go on to develop NPC often have certain biomarkers such as anti-EBV IgA antibodies as well as DNA strands to serve as an early indicator of a future tumor lineage[21]. Early detection in the case of such aggressive cancer has been linked to a substantive increase in the rate of survival in these patients. Further, the detection of such antibodies can allow those at high risk to take the necessary precautions and medical treatment that are required to prevent any development of cancer. Despite many false positives and negatives in a broader population pool, those with clear and identified risk factors for NPC may greatly benefit from targeted testing. There are significant gaps when it comes to the prevention and early detection of EBV-related cancers, so despite the more primitive nature of some of the

findings discussed in this study regarding these technologies, they are still the best option to begin addressing some of these health issues as they present themselves increasingly in today's world. It may be a valuable tool to perform these tests in cases of genetic predisposition or other risk factors as there are existing treatments to remove early-stage NPC, which would greatly increase the survival rates and stop continued metastasis for patients.

There are limitations to this literature review. Because of limited evidence regarding a direct relationship between the Epstein-Barr virus and oncogenesis in a variety of cases, many of the screening and prevention recommendations provided operate on a level of conjecture. However, despite this limitation, the current evidence suggests that there is enough of a correlation that we can begin the use of certain technologies accurately and effectively.

This literature review aims to discuss the genomic evidence and pathways of EBV in the development of cancer to identify important characteristics and biomarkers for screening technologies. It looks not only at the nature of EBV-associated oncogenesis in well-characterized disease states but also at similar situations in broader populations to better assess how to prevent related scenarios in normal populations. Improving existing screening and preventative technologies is critical given the multitudinous instances of EBV-related oncogenesis. Technological advances present a much healthier future as early detection and prevention will drastically improve treatment efficacy in patients and increase long-term survival rates. The important next step forward is to further clinical research for vaccines, screening, and improved preventative efforts, as an improved understanding of the extent to which EBV can result in oncogenesis may improve the lives of thousands in at-risk groups.

Methodology

This literature review primarily obtains its sources from the PubMed Central Database, or PMC. This database is an archive of biomedical literature and other life science literature. All searches outlined a scope from database inception to April of 2023. Some keywords used to conduct the searches were Epstein-Barr Virus (EBV), oncogenesis, nasopharyngeal carcinoma (NPC), X-linked lymphoproliferative disease (XLP), post-transplant lymphoproliferative disorder (PTLD), classical Hodgkin lymphoma (cHL), and serological markers.

The primary inclusion criteria for sources generally prioritized primary research and sources that focus on a discussion of the links between the Epstein-Barr Virus and either cancer development or cancer indication. Sources used were also generally published within the past 5-10 years. However, some review articles as well as older pieces were used in the process.

In data extraction, the important types retrieved included population proportions both generally and for specific demographics, data indicating the strength or direction of correlations given the

limited evidence of direct links between EBV and oncogenesis, hazard ratios and confidence intervals, and sensitivity and specificity data when analyzing the validity of biomarker tests and other serological testing. Confidence intervals assess the probability that a given parameter will fall between a certain set of values- it is used to assess the reliability of a statistic. A 90% confidence interval suggests that there is 90% confidence that the true value falls within the given range. Hazard ratios refer to a measurement of how often a given event occurs in one group compared to how often it occurs in another over a given time interval. If the hazard ratio is one, there is no link between the occurrence of an event between the two groups; however, if it is greater than one there is a link between the occurrences. When looking at testing, sensitivity refers to the ability of a test to designate an individual who is truly positive for a given factor as a positive while specificity refers to the ability of a test to designate an individual who is truly negative as negative. High sensitivity would indicate that a test misses very few positive cases while high specificity indicates that a test gives few false positives.

Following data retrieval, a narrative synthesis approach was used, analyzing, both within and between sources, for evidence to form a substantive evaluation and discussion of both the robustness of the correlation between Epstein-Barr Virus and oncogenesis and the prognostic value of EBV markers in serological testing for cancer.

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