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REPORT ON CARCINOGENS

MONOGRAPH ON EPSTEIN-BARR VIRUS

RoC MONOGRAPH 07

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Foreword

The National Toxicology Program (NTP), established in 1978, is an interagency program within the Public Health Service of the U.S. Department of Health and Human Services. Its activities are executed through a partnership of the National Institute for Occupational Safety and Health (part of the Centers for Disease Control and Prevention), the Food and Drug Administration (primarily at the National Center for Toxicological Research), and the National Institute of Environmental Health Sciences (part of the National Institutes of Health), where the program is administratively located. NTP offers a unique venue for the testing, research, and analysis of agents of concern to identify toxic and biological effects, provide information that strengthens the science base, and inform decisions by health regulatory and research agencies to safeguard public health. NTP also works to develop and apply new and improved methods and approaches that advance toxicology and better assess health effects from environmental exposures.

The Report on Carcinogens Monograph series began in 2012. Report on Carcinogens Monographs present the cancer hazard evaluations of environmental agents, substances, mixtures, or exposure circumstances (collectively referred to as "substances") under review for the Report on Carcinogens. The Report on Carcinogens is a congressionally mandated, science-based, public health document that provides a cumulative list of substances that pose a cancer hazard for people in the United States. Substances are reviewed for the Report on Carcinogens to (1) be a new listing, (2) reclassify the current listing status, or (3) be removed.

NTP evaluates cancer hazards by following a multistep process and using established criteria to review and integrate the scientific evidence from published human, experimental animal, and mechanistic studies. General instructions for the systematic review and evidence integration methods used in these evaluations are provided in the *Handbook for the Preparation of Report on Carcinogens Monographs*. The handbook's instructions are applied to a specific evaluation via a written protocol. The evaluation's approach as outlined in the protocol is guided by the nature, extent, and complexity of the published scientific information and tailored to address the key scientific issues and questions for determining whether the substance is a potential cancer hazard and should be listed in the Report on Carcinogens. Draft monographs undergo external peer review before they are finalized and published.

The Report on Carcinogens Monographs are available free of charge on the NTP website and cataloged in PubMed, a free resource developed and maintained by the National Library of Medicine (part of the National Institutes of Health). Data for these evaluations are included in the Health Assessment and Workspace Collaborative. Information about the Report on Carcinogens is also available on the NTP website.

For questions about the monographs, please email NTP or call 984-287-3211.

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This report has been reformatted to meet new NTP publishing requirements; its content has not changed. The proposed substance profile is no longer part of the document because it is published in the 14th Report on Carcinogens.

About This Report

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Peer Review

Peer review of the Draft RoC Monograph on Epstein-Barr Virus (EBV) was conducted by an ad hoc expert panel at a public meeting held December 17, 2015, in the Rodbell Auditorium at the National Institute of Environmental Health Sciences, David P. Rall Building, Research Triangle Park, NC (see http://ntp.niehs.nih.gov/go/38854) for materials, minutes, and panel recommendations from the peer-review meeting). The selection of panel members and conduct of the peer review were performed in accordance with the Federal Advisory Committee Act and federal policies and regulations. The panel members served as independent scientists, not as representatives of any institution, company, or governmental agency.

The charge to the Peer-Review Panel was as follows:

(1) Comment on the draft cancer evaluation component for EBV, specifically, whether it was technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the RoC listing criteria.

(2) Comment on the draft substance profile for EBV, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of the substance (available in the 14th edition of the Report on Carcinogens).

The panel was asked to vote on the following questions:

(1) Whether the scientific evidence supports the NTP's preliminary conclusion on the level of evidence for carcinogenicity for the specific types of cancer from cancer studies in humans.

(2) Whether the scientific evidence supports the NTP's preliminary listing decision for EBV in the RoC.

This RoC monograph on EBV has been revised based on NTP's review of the panel's peer-review comments. The Peer-Review Panel Report, which captures the panel recommendations for listing status of EBV in the RoC and their scientific comments, and the NTP Response to the Peer-Review Report are available on the Peer-Review Meeting webpage for Epstein-Barr virus (http://ntp.niehs.nih.gov/go/38854).

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Abstract

Introduction: In the United States, over 50% of children aged 6–8 and over 90% of adults are infected with the Epstein-Barr virus (EBV), an enveloped, double-stranded DNA gamma-1 herpesvirus. EBV is also known as human herpesvirus 4. It is transmitted mainly by saliva, although transmission via blood is possible. In low- to middle-income countries, infection during infancy occurs at a higher rate than in higher-income countries, where infection may occur later in childhood. EBV-infected B lymphocytes can produce viral proteins, which enable those B lymphocytes to survive and proliferate indefinitely, leading in some cases to cancer.

Methods: The National Toxicology Program (NTP) conducted a cancer hazard evaluation of EBV infection and seven types of cancer for possible listing in the Report on Carcinogens (RoC). The evaluation included the findings from studies reported in the IARC monograph in Volume 100B, as well as from human cancer studies and mechanistic studies and reviews published after the IARC monograph. For each cancer site, the evidence from human and mechanistic studies was integrated considering the following guidelines: Hill's characteristics of causality, multicausality epidemiology considerations, guidance from the IARC 100B working group, and concepts of direct and indirect carcinogenesis proposed several virus experts. Finally, the RoC's listing criteria were applied to the assessment to reach an overall cancer hazard conclusion.

Results and Discussion: *NTP concluded there was sufficient evidence* of the carcinogenicity of EBV for six cancers. Four are lymphomas arising from immune cells: Burkitt lymphoma (endemic), Hodgkin lymphoma, immune-suppression-related non-Hodgkin lymphoma (NHL), and extranodal NK/T cell lymphoma (nasal type). Two are cancers arising from epithelial cells: nasopharyngeal carcinoma and stomach (gastric) cancer. Evidence of carcinogenicity is based on the collective evidence from human epidemiological and clinical cancer studies, as well as molecular studies of human tissue.

For endemic Burkitt lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma, statistically significant increased risks were found in case-control and cohort studies in different populations. A key event in Burkitt lymphoma is a chromosomal translocation of c-myc to an immunoglobin gene promoter leading to proliferation and growth of B lymphocytes. EBV-infected stomach tumors have a unique molecular profile.

Evidence that EBV is associated with immunosupression-related NHL, extranodal NK/T cell lymphoma (nasal type), and gastric cancers comes from case series data with large numbers of cases, clinical studies, or a few case-control or nested case-control studies. Limited evidence was found for sporadic Burkitt lymphoma due to the small number of cases in the studies and moderate, nonsignificant increased risk.

Molecular studies in humans for all cancer demonstrated that the EBV-related tumors were monoclonal, which provides evidence that infection preceding the cancer contained a high percentage of EBV DNA and expressed oncogenic EBV proteins. Mechanistic studies found that EBV can transform human B lymphocytes into permanently infected lymphoblastoid cell lines in culture.

NTP Hazard Conclusion and Significance: The conclusion of the cancer hazard evaluation was that EBV should be listed as *known to be a human carcinogen* in the RoC. The Secretary of Health and Human Services approved the listing of EBV in the 14th RoC. The rationale for the

listing was sufficient evidence from studies in humans (epidemiological and molecular) for six types of cancer. Globally, EBV is estimated to be responsible for 200,000 cancers per year.

Introduction and Methods

This is one of a collection of five monographs that provide cancer hazard evaluations for the following human viruses for potential listing in the Report on Carcinogens (RoC): Epstein-Barr virus, Kaposi sarcoma-associated herpesvirus, human immunodeficiency virus type 1, human T-cell lymphotropic virus type 1, and Merkel cell polyomavirus. Viruses currently listed in the RoC include human papillomaviruses: some genital-mucosal types (HPV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Each virus was selected for review for the RoC based on a large database of scientific information (including authoritative reviews), public health concerns for adverse health outcomes, and evidence that a significant number of people are infected with each virus both in the United States and worldwide.

This section provides background information on the preparation of the monographs as well as a discussion of overarching issues related to evaluating the evidence for cancer from human epidemiological studies and evaluating the causation by viruses.

Monograph Contents

The RoC monograph for each virus reviews the relevant scientific information and assesses its quality, applies the RoC listing criteria to the scientific information, and recommends an RoC listing status. Information reviewed in the monographs, with the exception of information on properties and exposure, comes from publicly available and peer-reviewed sources. All sections of the monographs underwent scientific and quality assurance review by independent reviewers.

The monograph provides the following information relevant to a RoC listing recommendation: Properties and Detection (Section 1), Human Exposure (Section 2), Human Cancer Studies (Section 3), Mechanistic and Other Relevant Data (Section 4), and Overall Cancer Hazard Evaluation and Listing Recommendation (Section 5). Because these viruses are primarily species-specific for humans, we are not conducting an evaluation of the level of evidence for carcinogenicity from studies in experimental animals and are including studies in animals that inform the mechanisms of carcinogenicity in the Mechanistic and Other Relevant Data section of the monographs, which is similar to the approach used by IARC. Also, specific details about the strains of the viruses are given only if needed to provide context, such as in the viral Properties and Detection section. The monographs relied on the information and data provided in previous IARC monographs on these five viruses in addition to newer key studies or reviews published since the IARC monographs; it is a peer-review assessment of available data through August 17, 2015. Additional publications published after that date were added to the monograph based on recommendations from the Peer-Review Panel that reviewed this document on December 17, 2015. Literature search strategies to obtain information relevant to the cancer evaluation are in Appendix A of each virus monograph; search terms were developed in collaboration with a reference librarian.

Evaluating the Evidence from Human Epidemiological Studies

The available studies of specific types of cancer for these human viruses present several challenges with respect to the evaluation of methodological strengths and limitations of the body of evidence. Large prospective cohort studies, particularly those that follow individuals for whom infection status is documented prior to follow-up or cancer diagnosis, have several potential methodological strengths, including evidence that infection precedes cancer diagnosis, adequate statistical power, and, in some studies, have the ability to analyze dose-response relationships. However, there is the potential for misclassification of exposure in studies with a long follow-up period that measure the virus once and have a long follow-up period as new infections might not be identified. For most types of cancer, only cross-sectional or retrospective cohort studies or hospital- or clinic-based case-control studies are available, all of which lack direct evidence of temporality and may lack power or adequate exposure data, e.g., on viral load. However, molecular evidence from human studies and mechanistic data can be used in the evaluation of temporality, distinguishing latent infections caused by the tumor virus and causality. For some (typically rare) outcomes (e.g., cutaneous T-cell lymphoma and human T-cell lymphotropic virus type 1, or lymphoepithelial carcinoma of the salivary gland and Epstein-Barr virus), only case-comparison studies, in which selection of comparison groups may be biased, unmatched, or inadequately described, or case series are available.

For several rare types of cancer, e.g., adult T-cell leukemia/lymphoma and human T-cell lymphotropic virus type 1, or primary effusion lymphoma and Kaposi sarcoma-associated herpesvirus, the presence of the virus in the tumor cells is used as a diagnostic criterion to define the cancer, and thus, evidence of causality relies on cases defined by this criterion and molecular evidence from human studies rather than on epidemiological population-based studies of the association of the virus with a level of cancer risk.

In addition, methodologically adequate studies should include measurement of cofactors and consider potentially confounding factors; however, relatively few studies have measured a panel of other viruses or taken into account other cofactors. Further, while studies comparing cancer risk in treated vs. untreated populations may provide indirect evidence of the role of human immunodeficiency virus type 1, these studies, in particular calendar-period analyses, may not adequately account for changes in risk attributable to improved survival rates or changes in other risk factors.

Evaluating Causality of Viruses

Approximately 12% of all human cancers have been attributed to viral infections. Although the known oncogenic viruses belong to different virus families, they often share several common traits, such as, viral cancers appear in the context of persistent infections, occur many years to decades after acute infection, and the immune system can play a deleterious or a protective role (Mesri et al. 2014). Many viruses generally increase cancer risk in the context of immunosuppression or chronic inflammation (Mesri et al. 2014). Similar to other carcinogenic agents, only a small percentage of infected or exposed individuals develop cancer, often decades after the initial infection, reflecting the complex nature of oncogenesis. Some cofactors produced by other organisms or agents in conjunction with risk modifiers such as virus-host-cell interactions, host genetic factors, immune dysfunction, or chronic inflammation often can contribute to malignant transformation. In addition, severe immunosuppression, as seen with congenital immunodeficiency syndromes, chronic human immunodeficiency virus type 1 infection, or as a result of tissue anti-rejection medication, can severely compromise the immune surveillance capabilities of the patient. There are also other challenges that are somewhat unique to the evaluation of the epidemiological studies of viruses and cancer (discussed below) and thus molecular evidence from human tissues is often considered in the evaluation of causality.

In light of these issues, IARC monographs and several other publications have recommended paths to evaluate causality, which are discussed below and incorporated into the NTP approach for evaluating causality of the viruses. What is important for public health in determination of causation of a health effect, such as risk for cancer, is whether the health effect is eliminated or mitigated by removal of the substance (Rothman and Greenland 2005).

A number of attempts have been made to develop criteria or considerations that address causal associations. However, all of them have limitations, especially when applied to infectious agents (Moore and Chang 2010). The following sections identify factors to consider for evaluating causality, some limitations arising from a strict application of the criteria in the context of virally induced cancers, some alternative approaches, and finally, the NTP's approach for evaluating the role of select viral agents in human cancer.

Hill's Characteristics of Causality

Hill proposed nine characteristics to consider when evaluating causality, primarily for epidemiological studies, although they have been expanded for evaluating mechanistic and other types of data (Table 1). Several considerations—strength of the association, consistency across studies, evidence of an exposure-response gradient, and temporality of exposure (Hill 1965)—are used to help guide the RoC evaluations of the human epidemiological data (see RoC Handbook, NTP 2015). However, it should be noted that these are not criteria; and, with the exception of temporality, each and every element is not required in order to demonstrate causality (Rothman and Greenland 2005). Hill (1965) avoided discussing the meaning of "causation," noting that the "cause" of an illness could be immediate and direct or remote and indirect. The primary question addressed by Hill was "whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A."

Table 1. Hill's Epidemiological Characteristics for Evaluating Causality

Characteristic	Description
1. Strength of association	A strong association between a virus and a cancer increases the confidence for causality unless confounded by some other exposure. However, a weak association does not give evidence against causality.
2. Consistency	Consistent findings observed among different groups of people, in different places, circumstances, and times.
3. Specificity	A viral exposure is limited only to specific types of cancer; this is considered a weak factor because there are well-established examples in which a virus might cause several types of cancer.
4. Temporality	Exposure to the virus must occur prior to the onset of the cancer, in contrast to a "passenger infection."
5. Biological gradient	The virus is more likely to be found at the tumor site than at non-tumor sites.
6. Plausibility	This characteristic should be applied with caution because it is limited by current medical knowledge (e.g., a currently implausible mechanism may gain acceptance with increased understanding of the underlying biology).
7. Coherence	A virus-cancer association should not seriously conflict with known facts on the cancer's natural history and biology.

Characteristic	Description
8. Experiment	Changing either exposure or continued infection in a randomized clinical trial should change the measure of clinical outcome (e.g., vaccination programs for HPV and HBV).
9. Analogy	Are related viruses clearly established to cause cancers in animals or humans?

Source: Moore and Chang (2014).

Evaluating Mechanistic Data from Human Studies

In its evaluation of the evidence for Epstein-Barr virus, the IARC working group noted that the large majority of people are latently infected with Epstein-Barr virus, thus, epidemiological studies may be limited in determining whether the presence of Epstein-Barr virus in tumor tissue is a cause of the cancer or an effect of the tumor. Therefore, in addition to the Hill characteristics, IARC (1997a) considered the following factors in its evaluation of Epstein-Barr virus, which are also applicable to other viruses:

- The proportion of Epstein-Barr virus-positive cases in a given tumor entity.
- The proportion of tumor cells that carry the virus.
- The monoclonality of Epstein-Barr virus in the tumor.
- The expression of Epstein-Barr virus proteins.

zur Hausen (1994; 2001) proposed consideration of the following types of mechanistic or epidemiological evidence for evaluating causality of viruses and cancer:

- The presence and persistence of viral DNA in tumor biopsies and cell lines derived from the same tumor type.
- The growth-promoting activity of specific viral genes or of virus-modified host-cell genes in tissue culture systems or in suitable animal systems.
- The continuous expression of viral oncogenes or the modification of host-cell genes containing viral sequences which maintains the malignant phenotype.
- The epidemiological evidence that the virus infection is a major risk factor.

It is difficult to prove that a virus causes cancer, and such determinations almost always generate considerable controversy and debate (Moore and Chang 2010). Viral cancers employ various mechanisms that involve both direct and indirect modes of interaction (Table 2) (zur Hausen and de Villiers 2014). Understanding and managing viral-induced cancers in humans has been hampered by a lack of suitable animal models, the disparate nature of tumor types, a long latency period between primary infection and cancer development, the different types of oncogenic viruses, and the complex nature of the virus-host-cell interactions leading to cancer (Mesri et al. 2014; zur Hausen and de Villiers 2014).

Table 2. Direct and Indirect Modes of Interaction of Viral Infections and Cancers

Type	Description
Direct carcinogenesis	Continued presence and expression of viral oncogenes usually after viral genome integration into host-cell DNA. Insertional gene activation or suppression. Continued episomal presence of viral nucleic acid and suppression or activation of cellular genes (e.g., by viral microRNA).
Indirect carcinogenesis	Induction of immunomodulation, activation of latent tumor virus genomes. Induction of oxygen and nitrogen radicals. Amplification of latent tumor virus DNA. Induction of mutations and/or translocations. Prevention of apoptosis.

Source: zur Hausen and de Villiers (2014).

Multicausality Issues

Although thousands of viruses are known to cause infection, only a few have been shown to cause cancer in humans (Moore and Chang 2010). An important consideration regarding causality (not limited to viruses) is "multicausality," that is, the concept that many determinants act together to cause a disease. Rothman and colleagues (Rothman and Greenland 2005) defined a sufficient cause as "complete causal mechanism"—not a single factor but a set of minimal factors (i.e., component causes)—that if present in an individual will cause disease. Most causes are neither necessary nor sufficient in the absence of other factors to produce the disease; however, a cause does not have to be either necessary or sufficient for its removal to result in disease prevention (Rothman and Greenland 2005; zur Hausen and de Villiers 2014).

Application of Causality Criteria and Alternative Approaches

Moore and Chang (2010) investigated the difficulties associated with strict application of the Hill characteristics for two of the most recently discovered oncogenic viruses: Kaposi sarcoma-associated herpesvirus and Merkel cell polyomavirus. Kaposi sarcoma-associated herpesvirus was shown to fulfill Hill's characteristics for causality of Kaposi sarcoma; however, the application of the characteristics was problematic in the case of Merkel cell polyomavirus and Merkel cell carcinoma (see the monographs for Kaposi sarcoma-associated herpesvirus and Merkel cell polyomavirus). These two examples illustrate the diversity in the patterns of tumor virus epidemiology. Some of the reasons Hill's characteristics worked for Kaposi sarcoma-associated herpesvirus but not Merkel cell polyomavirus is that all clinical forms of Kaposi sarcoma require infection by Kaposi sarcoma-associated herpesvirus while most studies indicate that not all forms of Merkel cell carcinoma require the presence of Merkel cell polyomavirus. In the case of Merkel cell polyomavirus, additional considerations, as suggested by IARC (1997a) and zur Hausen (1994; 2001), provide molecular evidence of the association between Merkel cell polyomavirus and Merkel cell carcinoma, such as mutation and monoclonal integration of the tumor-causing form of the virus into the cellular genome and requirement of tumor cells for the presence of viral oncoproteins for cell survival and proliferation.

While causal criteria can be helpful, there are flaws and practical limitations that restrict their use in cancer biology (Moore and Chang 2010). Therefore, a more probabilistic approach may be more useful for determining whether or not certain viruses cause human cancers. For example, instead of trying to determine if virus A causes cancer B, the probabilistic approach examines if cancer B is more probable in the presence of virus A. Although a correlation does not imply causation, it can be argued that correlations that are strong, reproducible, and predictive have a similar value as a causative conclusion. In a similar fashion, zur Hausen and de Villiers (2014) also expressed concern over all attempts to summarize criteria for "causality" of infectious agents in cancer development and proposed replacing "causal factor" with "risk factor" and grading them according to their contribution to an individual's cancer risk. This will require a greater understanding of the complexity of factors involved and their mechanistic contribution to individual cancers.

RoC Listing Criteria

Known to Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated to Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, OR

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

NTP's Approach

For each virus, the NTP applied the RoC listing criteria (see text box) to the body of literature to reach the listing recommendation. The level of evidence conclusion from studies in humans considers the evidence from epidemiological studies as well as clinical and molecular studies of tissues from exposed (i.e., infected) individuals. In evaluating the mechanistic data and determining the recommendations for its level of evidence conclusion and overall listing recommendation, the NTP considered the principles outlined by Hill (1965), IARC (1997b), zur Hausen (1994; 2001; 2014), and Rothman and Greenland (2005) in its assessment of causality for the five viruses reviewed. However, these factors were not used as a strict checklist to either prove or disprove a causal association but rather as guidance to assess the level of epidemiological or molecular evidence that a virus contributes to a carcinogenic effect.

1. Properties and Detection Methods

This section reviews the biological properties (Section 1.1) and methods for detection (Section 1.2) of the Epstein-Barr virus (EBV). The material presented in Sections 1.1 and 1.2 is summarized in Section 1.3.

1.1. Biological Properties

The following section reviews the types of EBV, its structure, life cycle, and course of infection.

1.1.1. Family and Type

EBV is a human herpesvirus in the gammaherpesvirus subfamily and is the prototype of the *Lymphocryptovirus* genus (IARC 2012). The formal designation of EBV is human herpesvirus 4 (HHV-4). EBV was the first human tumor virus to be discovered and was detected in Burkitt lymphoma cells in 1964. The two major types of EBV (EBV-1 and EBV-2) differ in their gene sequences of nuclear antigens (EBNA-2, -3A, -3B). Different viral strains within the two major types are created by DNA polymorphisms at other DNA sites.

1.1.2. Viral Structure and Genome

The Epstein-Barr virus is composed of a nucleocapsid surrounded by an envelope with glycoprotein spikes protruding from its outer surface; the nucleocapsid and envelope are separated by tegument proteins (Figure 1-1) (IARC 2012). Inside the nucleocapsid is a double stranded DNA (dsDNA) genome approximately 172 kb in length, wrapped around a protein core. The genome encodes over 85 genes; the open reading frames (ORFs) are divided into latent and lytic genes. ORF nomenclature is based on the *Bam*HI restriction fragment in which they are found. The genome has a series of 0.5 kb terminal direct repeats at each end as well as internal repeat sequences dividing the genome into long and short unique sequences that have most of the coding capacity. EBV forms multiple episomes within the cell nucleus that are circularized by joining their terminal repeats. Latent EBV infections of clonal origin have the same number of terminal repeats. The following section will discuss how EBV uses different combinations of latent viral gene expression to progress from initial infection to long-term persistence within the memory B-cell pool. Latent EBV proteins have a primary role in EBV-associated oncogenesis and are discussed in Section 4.2.

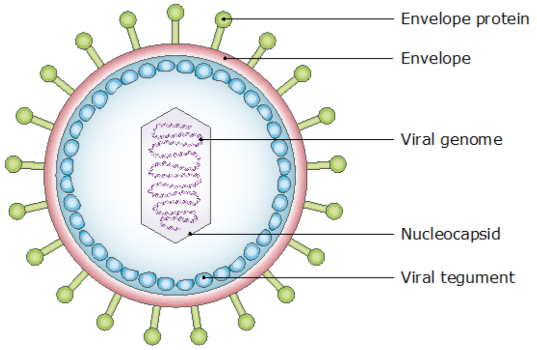

Figure 1-1. Epstein-Barr Virus Structure

Source: Provided by Wikipedia (2015).

1.1.3. Infection and Replication

Like other herpes viruses, the EBV replication cycle in B lymphocytes, also called B cells, and epithelial cells includes a latent phase and a lytic phase, corresponding to a quiescent infection and active replication, respectively. Humans are the only natural host for EBV (IARC 2012). Latent infection is divided into several phases based on the viral genes that are expressed (latency 0, I, II, and III) (Table 1-1).

Table 1-1. EBV Transcription Programs in Normal B Cells and in Associated Malignancies

Transcription Program[a]	Gene Products	Function in Normal B-cell Type[b]	Associated Malignancies
Latency 0	EBERs	Resting peripheral memory B cells; lifetime infection	None
Latency I	EBNA-1, EBERs	Dividing peripheral memory B cells	Burkitt lymphoma and gastric carcinoma[c]
Latency II	EBNA-1, LMP-1, LMP-2A, EBERs	Activated B-cell differentiates into memory cell in germinal center	NPC, Hodgkin lymphoma, NK and T-cell lymphoma, nasal type[d]
Latency III	EBNA-1, -2, -3A, -3B, -3C, -LP, LMP-1, LMP-2A, LMP-2B, EBERs	Naïve B-cell infected and activated	Immunosuppression-related NHL (AIDS-associated, post-transplant disorder, iatrogenic)
Lytic	Immediate-early, early, and late gene products[e]	Replicates in plasma cell	May be present in some malignancies[f]

Source: Adapted from IARC (2012); Yau et al. (2014).
EBER = EBV-encoded small RNA; EBNA = EBV nuclear antigen; EBNA-LP = EBV nuclear antigen leader protein; LMP = latent membrane protein; LEC = lymphoepithelial cancer; NHL = non-Hodgkin lymphoma; NPC = nasopharyngeal carcinoma.

[a] In latency I, II, III microRNAs (at least 22) are expressed in various amounts.

[b] Cell types are primarily restricted to lymphoid tissue of Waldeyer ring (i.e., tonsillar tissue in the oropharynx).

[c] Variable expression of EBNA-2, LMP-1, and BZLF1 (lytic gene) in endemic Burkitt lymphoma (Niedobitek et al. 1995); and of lytic genes and LMP-2A in gastric carcinoma.

[d] Previously called sinonasal angiocentric T-cell lymphoma.

[e] Products of immediate-early genes: *BZLF1*, *BRLF1*, *BI'LF4*; early genes: *BMRF1*, *BALF2*, *BALF5*, *BORF2*, *BARF1*, *BXLF1*, *BGLF5*, *BSLF1*, *BBLF4*, *BKRF3*; late genes: *BLLF1*, *BXLF2*, *BKRF2*, *BZLF2*, *BALF4*, *BDLF3*, *BILF2*, *BCRF1*, *BHRF1*.

[f] EBV lytic genes expressed in human lymphoblastoid cell lines (Arvey et al. 2012).

In a primary infection, EBV spreads through the saliva and infects the B cells in the tonsil, and oropharyngeal epithelial mucosa by a poorly understood mechanism (IARC 2012; Raab-Traub et al. 1991). Within the oropharyngeal epithelium the infection is primarily lytic (it is unknown whether epithelial cells support latent infection) leading to amplification of the number of viruses. Within the tonsil, EBV infects local naïve B lymphocytes entering the germinal center in the underlying lymphoid tissues by interaction of the viral envelope protein gp350/220 with the CD21 protein on B lymphocytes. Viral entry into B cells requires a complex of viral glycoproteins gH, gL, and gp42 with gp42 binding to class II human leukocyte antigen on the lymphocyte (IARC 2012; Tugizov et al. 2003). Virions containing only the gH-gL complex can infect epithelial cells while virions require the gH-gL-gp42 complex to infect naïve B cells (Tugizov et al. 2003). Inside the B lymphocytes, the virus enters the latency III phase where replication is suppressed by the expression of three EBV nuclear antigens (EBNA-3A, -3B, and -3C). The B lymphocytes then can enter a germinal center in the tonsils and, in the immunocompetent host, are destroyed by cytotoxic T cells specific for viral proteins expressed during latency III (Thorley-Lawson and Gross 2004).

Germinal centers are structures in the lymphoid tissues where antibody affinity maturation occurs through clonal proliferation of antigen-exposed B lymphocytes, diversification of antigen affinity through somatic hypermutation of immunoglobulin genes, and of antibody type through class switch recombination (Ponce et al. 2014). While in the germinal center, the EBV infection enters latency II, a phase in which gene expression is focused on survival signals. Within the germinal center, lymphocytes differentiate to memory B cells and antibody-producing plasma cells, both of which enter the peripheral circulation. Within resting B memory cells, the EBV infection is in the latency 0 phase, no genes are expressed with the exception of those coding for EBV-encoded small RNAs (EBER-1 and -2). Occasionally, memory B cells will replicate and EBV will enter latency I, where expression of EBV nuclear antigen 1 (EBNA1) allows for replication and segregation of the viral episome to daughter cells. B cells that are activated and differentiate into antibody-producing plasma cells allow EBV to express lytic genes and enter the lytic cycle of replication. Lytic genes comprise 3 immediate-early genes that initiate the lytic cycle, 10 early genes that enable virus replication, and 9 genes that enable packaging and release of the virion from the host cell (see IARC (2012) for discussion of lytic genes). Complete viral lytic replication does not occur in tissues other than mucosa-associated lymphoid tissue (MALT) and tonsillar tissue in the oropharynx (termed Waldeyer's ring). In these tissues lytic replication occurs along with cell death and shedding of virions into the saliva or re-infection of B lymphocytes repeating the cycle (Figure 1-2). While the EBV infection is in the latent I, II, or III phase, EBV-specific cytotoxic T cells and NK cells are able to recognize the expressed viral proteins and limit the infection; within resting memory B cells (latency 0 phase), the virus is able to evade immune detection and provide a site for maintenance of long-term EBV infection (Thorley-Lawson and Gross 2004).

Although EBV usually infects B lymphocytes through a CD21-dependent pathway, it also can infect some types of epithelial cells and T cells by several CD21-independent pathways (IARC 2012). Primary epithelial cells in culture can be infected with EBV only by co-culturing with EBV-producing B lymphoblastoid cells, suggesting that cell-to-cell contact is necessary for infection of epithelial cells (Imai et al. 1998). It has been demonstrated that viral envelope proteins (gH-gL) can interact with an integrin complex on the epithelial cell surface, triggering cell entry, and that gp42 interferes with binding to the integrin complex (Borza and Hutt-Fletcher

2002; Chesnokova and Hutt-Fletcher 2011). Additionally, virions released from epithelial cells express gp42 on their surface, whereas those released from lymphocytes do not have this protein marker. It is believed that this dual cell tropism enables the virus to shuttle between lymphocytes and epithelial cells. Other research using polarized basal epithelial cells identified another EBV glycoprotein, BMRF2, which enabled infection via interaction with epithelial cell marker α5β1 (Tugizov et al. 2003). Further, they showed that EBV virions could also be transmitted by direct cell-to-cell contact of B lymphocytes to apical epithelial cell membranes, and epithelial cell-to-cell infection could occur via lateral membrane transmission.

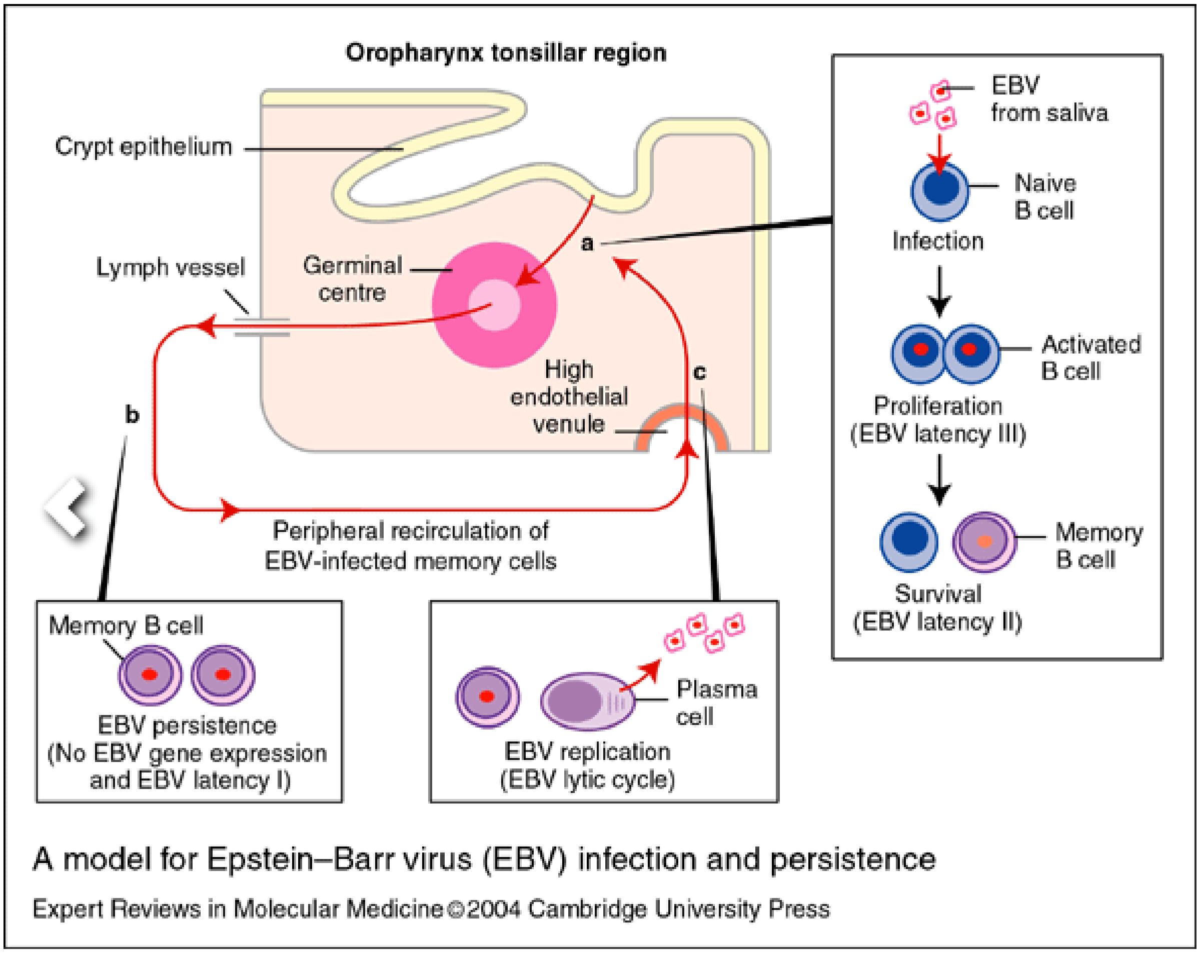

Figure 1-2. Epstein-Barr Virus Life Cycle

Source: Vetsika and Callan (2004), used with permission.

During latency, the virus can express a variable pattern of viral genes that are essential for host adaptation and in some cases also promote carcinogenesis or disease; different EBV latent gene expression patterns are associated with different types of cancers (Table 1-1) (IARC 2012). The role of latent and lytic EBV genes in the pathogenesis of cancer is an active area of investigation. In order to understand the contribution of viral and host factors in development of lymphomas, humanized mouse models using transplanted human fetal hematopoietic stem cells and lymphoid tissue are under development (Cocco et al. 2008; Ma et al. 2011).

1.2. Detection

EBV-specific serologic methods or amplification of EBV DNA from peripheral white blood cells can be used to detect EBV infection in healthy carriers (Table 1-2). In developed countries, healthy carriers are negative for EBV DNA in serum (cell-free) by the quantitative polymerase chain reaction (Q-PCR) method (IARC 2012). A positive result using the latter method indicates EBV-associated diseases or EBV reactivation. EBV infection results in production of IgG, IgM, and occasionally IgA antibodies against viral proteins and glycoproteins (e.g., viral capsid antigen [VCA] or EBNA-1). These can be detected using antigen-antibody binding assays such as enzyme immunoassays (EIA) to determine antibody titer.

Detection methods are also used to determine EBV viral load, reactivation, response to treatment, and presence in tumor cells (IARC 2012). In general, high antibody titers to some EBV antigens (e.g., VCA) are detected in patients with endemic Burkitt lymphoma. Historically, early markers used for detection of EBV in Burkitt lymphoma were antibodies to early antigen (EA) and VCA. Determination of viral load can give an indication of the degree of infection or of response to treatment and can be determined in tumor cells or in lymphocytes by Q-PCR. For example, nasopharyngeal carcinoma brushings from patients can be used to determine viral load by Q-PCR, and reverse transcriptase PCR can detect EBNA-1 or BARF1 RNA in nasopharyngeal cells in these samples. In contrast, no EBV RNA is found in healthy donors. In addition, in situ hybridization and RT-PCR are highly sensitive methods for EBV detection in Hodgkin disease.

Table 1-2. Methods of EBV Detection

Biomarker	Detection Method	Examples	Tissue
Antibodies to VCA, EBNA-1, CF/S antigens, neutralizing anti-gp350, EA	Serologic, indirect IFA, EIA	Detected in healthy EBV carriers, EA detected in some carriers; higher titers with Burkitt lymphoma	Serum
EBV DNA	PCR	Detection in healthy carriers	White blood cells
Cell-free EBV DNA	Quantitative PCR	EBV-associated diseases or EBV reactivation; healthy carriers are negative	Serum
EBV DNA	Quantitative PCR	Determination of viral load per cell	Tumor cells, white blood cells
EBER-1, EBER-2 RNAs	Reverse transcription-PCR and in situ hybridization	EBV infection; highly sensitive for Hodgkin disease detection	Tumor cells, tissue biopsy
EBNA-1 and BARF1 RNA	Reverse transcription-PCR	NPC detection	NPC biopsy or brushing

Source: Adapted from IARC (2012).
BARF1 = *Bam*HI A rightward fragment 1 (micro RNA); BL = Burkitt lymphoma; CF/S = complement-fixing soluble antigen; EA = early antigens (EA-D encoded by *BMRF-1* and EA-R encoded by *BHRF-1*); EBER = small nuclear EBV-encoded RNA; EBNA = EBV nuclear antigen; EIA = enzyme immunoassay; gp350 = glycoprotein 350; IFA = indirect immunofluorescence assay; LMP-1 = Latent membrane protein; NPC = nasopharyngeal carcinoma; PCR = polymerase chain reaction; VCA = viral capsid antigen.

1.3. Summary

Epstein-Barr virus (EBV), also called human herpesvirus 4 (HHV-4), is an enveloped dsDNA virus in the gammaherpesvirus subfamily and consists of two major types (EBV-1, and EBV-2). Like other herpes viruses, the EBV replication cycle in B lymphocytes, also called B cells, and epithelial cells includes a latent phase and a lytic phase, corresponding to a quiescent infection and active replication, respectively. Humans are the only natural host for EBV. Infection of epithelial cells is primarily lytic, which results in destruction of the infected cell with completion of the lytic cycle, whereas infection of B cells is primarily latent. Antibody-producing B cells, also known as plasma cells, allow EBV to enter the lytic phase and replicate (Ponce et al. 2014). EBV predominantly enters the host through contact with saliva and infects B cells in the tonsils. The virus circularizes upon infection of B cells and persists as an episome. During lytic replication, large DNA concatemers are formed. The latent phase is complex and changes depending on the status of the host cells (latency 0, I, II, III). EBV proteins expressed on infected cells can be recognized by cytotoxic T cells and NK cells, which attack and destroy them. However, EBV in latency 0 phase, typically found in resting memory B cells, does not express proteins on infected cells, which enables it to evade immune recognition. EBV infection can be detected by measuring anti-EBV antibodies in serum and EBV DNA or RNA in peripheral white blood cells, which can indicate viral load.

2. Human Exposure

This section discusses transmission and prevalence (Section 2.1) and non-cancer diseases, prevention, and treatment for Epstein-Barr virus (EBV) (Section 2.2). The material presented in Sections 2.1 and 2.2 is summarized in Section 2.3.

2.1. Transmission and Prevalence

Transmission of EBV is primarily via saliva, although the primary infection does not occur in the salivary glands (IARC 2012). The presence of EBV in peripheral blood suggests that transmission via blood is also possible, and transmission among transfusion recipients and organ recipients has been reported. Infected cells, primarily resting memory B cells in peripheral blood, provide a permanent reservoir for progeny to disseminate within the body and infect other hosts. EBV transmission via breast milk (Daud et al. 2015) and genital secretions (Thomas et al. 2006) has also been reported.

More than 90% of adults worldwide are infected with EBV (IARC 2012). Age at primary infection varies, occurring during infancy in developing countries and during adolescence and young adulthood in developed countries, perhaps due to better hygienic conditions, and other socioeconomic and demographic factors (e.g., household size and population density), which result in later age of exposure to infected saliva (Dowd et al. 2013; IARC 2012). The two major types of EBV (EBV-1 and EBV-2) (see Section 1) differ in geographic distribution (IARC 2012). Immunocompromised subjects more often harbor both types; EBV-2 may be more common in Africa and in men who have sex with men.

The seroprevalence of EBV antibody in the United States based on NHANES data collected in 2009 and 2010 ranged from 50% in 6-to-8-year-olds to 89% in 18-to-19-year-olds (Balfour et al. 2013; Dowd et al. 2013). Lower prevalence of EBV antibody has been shown to be associated with higher socioeconomic status within race/ethnicity groups. An analysis of 782 serum samples from Minnesota children 18 months to 19.9 years old indicated that a combination of genetics, family practices, and home environment were responsible for racial/ethnic differences in EBV antibody prevalence among young children and noted that the route of EBV transmission to preadolescents remains unclear (Condon et al. 2014). The risk for infectious mononucleosis and Hodgkin lymphoma (see Section 3.3) in younger age groups resulting from infection with EBV has been suggested to be greater in people with a higher socioeconomic background (ACS 2015b; Gutensohn 1982). One theory proposed for this relationship is that exposure to EBV later in life for children from more affluent families might somehow increase their risk for these diseases.

2.2. Non-cancer Diseases, Prevention, Treatment

Most individuals who are infected with EBV remain otherwise healthy and are asymptomatic (IARC 2012). Infection is life-long and is subclinical when it occurs in early childhood (IARC 2012); however, it results in infectious mononucleosis in at least 25% of teenagers and young adults infected with EBV (CDC 2014b). Oral hairy leukoplakia results from infection with EBV in the context of immunosuppression (e.g., human immunodeficiency virus type 1 [HIV-1]) or immunosenescence (aging) (Auwaerter 2015). Chronic uncontrolled EBV (with high EBV DNA in blood) very rarely occurs in the United States and Europe, and is more frequent but still uncommon in Asia and South America (Cohen 2009; Maia and Peace-Brewer 2000). Its etiology is unknown, but is believed to involve environmental cofactors and/or rare genetic abnormalities that impair immune control of EBV infection (Cohen 2009).

Because EBV transmission is associated with EBV shedding in saliva, avoiding salivary exposure (e.g., not kissing or sharing drinks, food, or personal items like toothbrushes with people who have EBV infection) may theoretically prevent transmission (CDC 2014a).

Some drugs have been reported to reduce or inhibit EBV shedding (e.g., see Auwaerter 2015); currently, the FDA has not approved any drugs for treatment of EBV infection. Currently, there is no vaccine against EBV; efforts to develop a vaccine are ongoing (ACS 2015a; Balfour and Jr 2014; CDC 2011; Cohen 2015; FDA 2015).

2.3. Summary

The high seroprevalence rate for Epstein-Barr virus (EBV) in the U.S. population indicates that a significant number of people living in the United States are exposed to EBV. Estimates for the seroprevalence of EBV in the United States range from 50% for 6-to-8-year-olds to 89% for 18-to-19-year-olds, based on detection of the EBV antibody; however, these levels vary based on socioeconomic status and within race/ethnicity groups. EBV is transmitted primarily via saliva, but transmission via blood is possible since EBV is present in peripheral blood and transmission among transfusion recipients and organ recipients has been reported. The infection rate worldwide is very high, likely exceeding 90%, but the age at primary infection varies geographically, with more developed countries having higher ages for primary infection due to better hygiene. EBV infections tend to be asymptomatic for most individuals, but the infection is life-long and results in infectious mononucleosis in at least 25% of teenagers and young adults infected with EBV. Prevention of transmission of EBV can theoretically be achieved by limiting exposure to saliva from kissing or sharing drinks, food, or personal items like toothbrushes between infected and non-infected individuals. There is currently no vaccine against EBV, although efforts to develop a vaccine are ongoing.

3. Human Cancer Studies

Introduction

The NTP independently evaluated the scientific evidence using the IARC monographs (1997a; 2012) on EBV as the resources for studies conducted up to and including 2008, together with any new human studies identified from 2009 to 2015. Seven tumor endpoints—Burkitt lymphoma, Hodgkin lymphoma, immunosuppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma, nasopharyngeal carcinoma, gastric cancer, and lymphoepithelial carcinoma of the salivary gland—either identified in the IARC monographs or with an adequate database, are considered in the RoC monograph. Where available, IARC data tables of the effect estimates have informed the cancer hazard assessment (IARC 2012), with links to these tables made available in the text. When tables of individual studies were not available, forest plot summaries of the data have been provided.

EBV exposure is detected in the human studies via serological measures or from DNA in the tumor. Earlier studies included in the evaluation primarily used serological measures, while later studies used tumor DNA. (See Section 1.2 above for details on EBV detection methods.)

This evaluation of the human cancer hazard associated with EBV is divided into the following three parts. The first, a summary of the approach for selection of the studies is provided in Section 3.1. Second, the cancer hazard evaluation for each endpoint is presented in Sections 3.2 to 3.8. Lastly, a summary of the evaluations across endpoints is provided in Section 3.9.

3.1. Selection of the Literature

A systematic literature search of major databases, citations, and other authoritative sources for literature from 2009 to August 2015 was conducted. The literature search strategy (including the databases, search terms, and other sources for identifying literature) and procedures and results for selecting the literature (systematic screening procedures and inclusion/exclusion criteria) are described in Appendix A. For the EBV evaluation, all post-2008 case-control and cohort studies for the seven cancer endpoints were identified and included in the evaluation. These studies may range from broadly defined, non-matched hospital or population case-control designs to formal age-, sex-, and race-matched case-control designs. Previous studies reviewed by IARC were included in the overall assessment, but not evaluated in depth. Although summaries of multiple case report or case-series studies are noted and may be considered in the overall evaluation, case reports and case series were excluded from further review.

3.2. Cancer Evaluation: Burkitt Lymphoma

3.2.1. Background Information

Burkitt lymphoma includes three subtypes defined according to their incidence in populations: endemic, sporadic, and immunodeficiency-related Burkitt lymphoma. Endemic Burkitt lymphoma (also known as the African type) occurs primarily in children aged 5 to 9 years in equatorial Africa and Papua New Guinea. It occurs with an incidence rate of 5 to 10 cases per 100,000 in children under 16, and is responsible for 30% to 70% of all childhood cancers in equatorial Africa (IARC 1997a). Among endemic Burkitt lymphoma cases, EBV is detected in the tumor in more than 95% of cases (Thompson and Kurzrock 2004). In the case-series studies reviewed in IARC (1997a), there were a total of 191 cases of endemic Burkitt lymphoma, with EBV DNA or antibodies present in 185 of the cases.

Sporadic Burkitt lymphoma is found throughout the world. It is rare, with an incidence of 2 to 3 cases per million people in the United States. Sporadic Burkitt lymphoma is associated globally with a lower EBV prevalence, with approximately 20% to 30% of cases being positive in the tumor. Among the case series and reports previously reviewed by IARC (1997a), there were a total of 383 cases of sporadic Burkitt lymphoma, with EBV DNA or antibodies present in 192 cases. In the United States, 15% to 30% of sporadic Burkitt lymphoma cases are associated with EBV (Thompson and Kurzrock 2004). Immunodeficiency-related Burkitt lymphoma has been identified in approximately 40% of HIV-1-associated lymphomas (Gloghini et al. 2013; Stefan et al. 2011) and may also be associated with other factors resulting in immune suppression such as anti-rejection therapies or congenital immunodeficiency (Carbone et al. 2008). EBV has been detected in 30% to 64% of immunodeficiency-related Burkitt lymphoma cases (Young and Rickinson 2004).

3.2.2. Case-control Studies

Twelve case-control studies conducted since 1969 were identified that have investigated the association between EBV and Burkitt lymphoma. Eleven of these were included in the IARC (1997a; 2012) reviews.

Seven case-control studies of endemic Burkitt lymphoma, with a total of 904 cases, were reviewed by IARC (1997a; 2012), all showing a statistically significant, positive association between EBV and Burkitt lymphoma (Figure 3-1). These case-control studies found that those with Burkitt lymphoma were more likely to have detectible or elevated levels of EBV titers with odds ratios (ORs) ranging from 2.9 to 52 (Carpenter et al. 2008; Henle et al. 1969; Henle et al. 1971; Hirshaut et al. 1973; Klein et al. 1970; Mutalima et al. 2008). Moreover, four of the seven studies found a dose-response relationship between EBV titer levels and Burkitt lymphoma, with ORs increasing as titer levels increased (Carpenter et al. 2008; Henle et al. 1969; Henle et al. 1971; Mutalima et al. 2008). Additionally, the geometric mean titer levels of Burkitt lymphoma patients were significantly higher than controls in the three studies that reported these findings (Henle et al. 1969; Hirshaut et al. 1973; Nkrumah et al. 1976). These studies investigated a variety of EBV antibodies including viral capsid antigen (VCA) and early antigen (EA), while other studies (Henle et al. 1969; Hirshaut et al. 1973) did not specify the type of EBV antibody under study. Regardless of the type of EBV antibody investigated, a significant, positive relationship was seen between endemic Burkitt lymphoma and EBV. Figure 3-1 shows a forest plot with the ORs of the associations between endemic Burkitt lymphoma and EBV antibodies.

Since the publication of the second IARC review (2012), there has been one additional hospital-based case-control study in Kenya on the relationship between endemic Burkitt lymphoma and EBV. This study (Mulama et al. 2014) investigated the association between cellular EBV load and endemic Burkitt lymphoma among 89 children with confirmed Burkitt lymphoma with 213 controls frequency matched on age range and malaria exposure from the Naynza and Rift Valley provinces in Kenya. These control sites were chosen to approximate malarial exposure for cases because Naynza province has high malarial transmission rates while the Rift Valley province has low rates. Though not reported in the manuscript, based on individual case and control level data reported in the figures, children with endemic Burkitt lymphoma were statistically significantly more likely to have ≥2 log EBV copies per µg of human DNA than controls (OR = 16.2; 95% CI = 8.0 to 32.5). The results of this study are included in Figure 3-1.

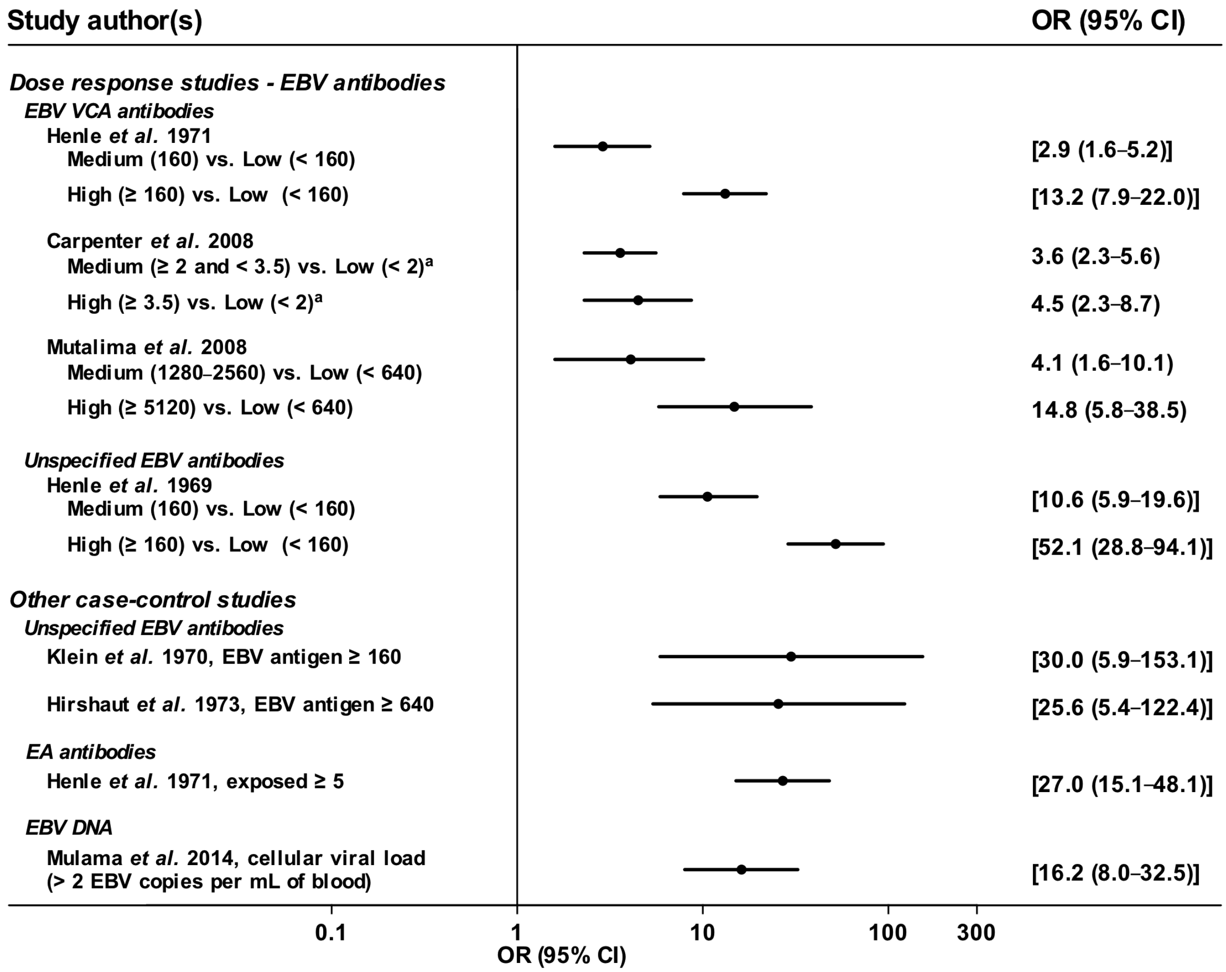

Figure 3-1. Forest Plot of Serological Case-control Studies of Endemic Burkitt Lymphoma and Epstein-Barr Virus

Sources: All endemic Burkitt lymphoma studies were conducted in sub-Saharan Africa. (Henle et al. 1969) - Kenya, Uganda, Nigeria; (Klein et al. 1970) - country not specified; (Henle et al. 1971) - Uganda, Kenya; (Hirshaut et al. 1973) - Uganda; (Carpenter et al. 2008) - Uganda; (Mutalima et al. 2008) - Malawi; (Mulama et al. 2014) - Kenya. Note: One study, Nkrumah et al. (1976), reported mean levels of EBV antibodies only but not enough information to calculate an OR.
ORs in brackets ([]) were calculated by NTP; if OR could not be calculated due to a cell size of 0, 1 was added to each cell.
CI = confidence interval; EA = early antigen; OR = odds ratio; VCA = viral capsid antigen.
^{a}Optical density (OD) measures were used as a surrogate measure for EBV VCA antigen.

Five case-control studies of sporadic Burkitt lymphoma, with a total of 113 cases, were reviewed by IARC (1997a): Ablashi et al. (1974); Cavdar et al. (1994); Gotleib-Stematsky et al. (1976); Hirshaut et al. (1973); Levine et al. (1972). Of the five studies, four investigated the relationship between Burkitt lymphoma and VCA antibodies, while one was unspecified (Hirshaut et al. 1973). Gotleib-Stematsky et al. (1976) also investigated EA antibodies in their analysis. Although four of these five case-control studies reported odds ratios of at least 2.0, only one reported a statistically significant association between the presence of EBV antibodies and

Burkitt lymphoma (OR = 4; 95% CI = 1.3 to 12.0) (Levine et al. 1972). The ORs ranged from 1 to 6.9 for those with statistically non-significant findings. In contrast to endemic Burkitt lymphoma studies, many of these studies included small numbers of cases and controls and had limited statistical power. Three of the five studies found mean EBV titers to be significantly higher in cases than in controls (Ablashi et al. 1974; Cavdar et al. 1994; Levine et al. 1972), while the other two studies found no statistically significant differences in means between cases and controls (Gotleib-Stematsky et al. 1976; Hirshaut et al. 1973). These studies are presented in Figure 3-2, which shows a forest plot with the ORs of the associations between sporadic Burkitt lymphoma and EBV antibodies.

No case-control or cohort studies on immunodeficiency-related Burkitt lymphoma were reviewed by IARC (1997a; 2012) or have been published since the more recent review by IARC (2012). See HIV-1 monograph (Sections 4.2.1 and 3.3.4) for a discussion of Burkitt lymphoma risk with severe immunosuppression.

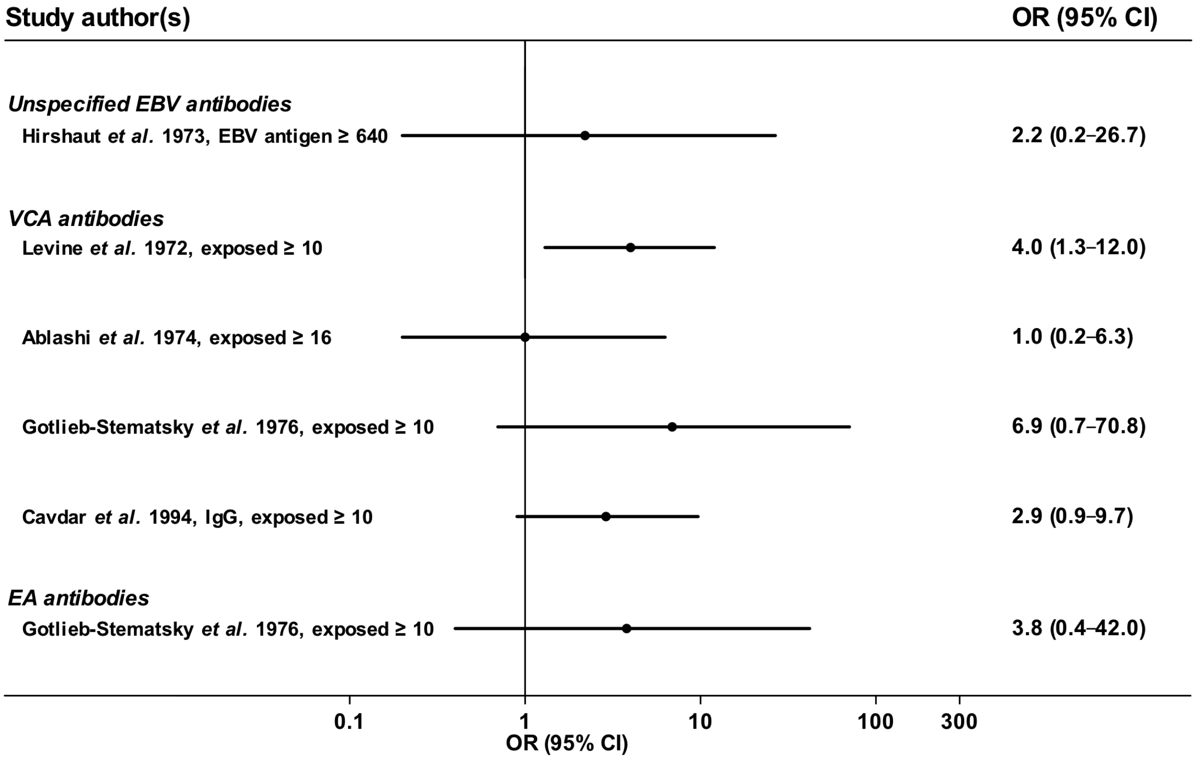

Figure 3-2. Forest Plot of Serological Case-control Studies of Sporadic Burkitt Lymphoma and Epstein-Barr Virus

Sources: Sporadic Burkitt lymphoma study locations: Levine et al. (1972) – U.S.A; Hirshaut et al. (1973) – U.S.A; Ablashi et al. (1974) – U.S.A; Gotleib-Stematsky et al. (1976) – Israel; Cavdar et al. (1994) – Turkey.
CI = confidence interval, EA = early antigen, OR = odds ratio, VCA = viral capsid antigen.

3.2.3. Cohort Studies

Only one cohort study has been identified that investigated the relationship between EBV and Burkitt lymphoma. This study was reviewed by IARC (1997a) and is briefly reviewed here. Beginning in 1972, a large-scale prospective study was begun in a Burkitt lymphoma-endemic area of northern Uganda, which collected blood samples from approximately 42,000 healthy children under age 8. The first follow-up of this cohort (1972 to 1977) was first presented by de Thé et al. (1978) which reported on 14 cases (13 histologically confirmed Burkitt lymphoma cases and one unclassified lymphoma), and the second follow-up of the cohort was presented by Geser et al. (1982) adding 2 additional cases to the analysis (1978 to 1979). Randomly selected controls, matched on age, gender, and location, were selected for a nested case-control analysis (de Thé et al. 1978). Statistically significantly higher titers of VCA antibodies were seen in the pre-diagnosis sera of the Burkitt lymphoma cases compared with the controls (geometric mean titer of Burkitt lymphoma cases = 425.5; control = 125.8, $p = 0.01$). When the additional two cases were added, the difference in VCA titers between cases and controls increased slightly ($p < 0.001$) (Geser et al. 1982). The mean values of EA and Epstein-Barr nuclear antigen (EBNA) in cases and matched controls were not provided; however, no statistically significant differences were seen in the titer levels for EA and EBNA antibodies between the Burkitt lymphoma cases and the matched controls. There were no differences between pre-diagnosis cases and controls in regard to malarial parasites or antibody titers to herpes simplex virus, cytomegalovirus, or measles reported by de Thé et al. (1978). A conditional regression analysis including all 16 cases was conducted by Geser et al. (1982) who found that the relative risk (RR) increased by a factor of 5.05 for each dilution for which the VCA titer is above the general population average. Moreover, the RR increased to 9.16 (95% CI not reported) when limited to cases that demonstrated the presence of EBV DNA in the tumor genome ($N = 9$). The results of this prospective cohort study demonstrate the temporality of the EBV/Burkitt lymphoma relationship by showing that elevated EBV antibodies, particularly VCA antibodies, precede the development and diagnosis of Burkitt lymphoma in this population.

3.2.4. Cofactors

Potential cofactors for endemic Burkitt lymphoma were reviewed by IARC (1997a; 2012). These cofactors include malaria, sickle-cell trait, and ingestion of *Euphorbia tirucalli* and other medicinal plants.

In earlier ecological studies, the geographic relationship between malaria and endemic Burkitt lymphoma was noted, with Burkitt lymphoma prevalence highest in areas with the highest malaria transmission rates (Morrow (1985) as cited in IARC (1997a)). The relationship between malaria and endemic Burkitt lymphoma was further apparent after the decline in endemic Burkitt lymphoma incidence following large-scale malaria eradication efforts. Geser et al. (1989) likewise confirmed this relationship in an intervention study designed to reduce Burkitt lymphoma incidence by reducing the prevalence of malaria. Moreover, two case-control studies published in 2008 found an increased risk of endemic Burkitt lymphoma as antibody titers to malaria increased (Carpenter et al. 2008; Mutalima et al. 2008). Based on the evidence from these studies, endemic Burkitt lymphoma is strongly associated with both EBV and with *Plasmodium* co-infection (IARC 2012); there may be a synergistic effect between malaria and EBV in the development of Burkitt lymphoma (Carpenter et al. 2008; Mutalima et al. 2008). There is additional evidence that malaria reduces the T-cell-mediated immunosurveillance of EBV-infected cells, leading to an increased viral load of EBV (Moormann et al. (2009), as cited in IARC (2012)).

A recent study (Mulama et al. 2014) did not find an association between sickle-cell trait and endemic Burkitt lymphoma (OR = 0.85; 95% CI = 0.61 to 1.17). Moreover, the lack of an association between sickle-cell trait genotype and EBV cellular viral load suggests that sickle-cell trait is not a cofactor in the relationship between EBV and Burkitt lymphoma.

The relationship between endemic Burkitt lymphoma and *E. tirucalli* and other medicinal plants is unclear, with few studies available to provide epidemiological evidence relevant to this relationship. Several case series and two case-control studies on these relationships were reviewed by IARC (1997a). Both case-control studies found a significant positive association between plant use and Burkitt lymphoma. Other studies have demonstrated that extracts of *E. tirucalli* and other related plants can induce the expression of EA and VCA antibodies, and increase EBV replication (Ito et al. (1981) and Lin et al. (1982), as cited in IARC (1997a)). No new studies on these relationships have been identified since the IARC (1997a) publication.

3.2.5. Integration of the Evidence

The epidemiological data suggest an association between EBV and both endemic and sporadic Burkitt lymphoma. All eight case-control studies and one cohort study of the relationship between endemic Burkitt lymphoma and EBV found positive, statistically significant relationships. There were five case-control studies on the relationship between sporadic Burkitt lymphoma and EBV. Although positive odds ratios ranging from 2.2 to 6.9 were seen for four of the five studies, only one OR was statistically significant. These studies on sporadic Burkitt lymphoma and EBV had limited power to detect an effect due to small numbers of cases and controls. The overall results of the individual studies are heterogeneous, particularly studies on endemic Burkitt lymphoma, for which ORs ranged from 2.9 to 52.1. One possible explanation is the variety of serological markers used by the different studies to detect EBV exposure. Another possible cause of the observed heterogeneity is the lack of variability in the exposure, particularly among cases, with up to 100% of cases exposed to EBV in some studies.

3.3. Cancer Evaluation: Hodgkin Lymphoma

3.3.1. Background Information

Hodgkin lymphoma is categorized into four histological subtypes (lymphocyte predominance, nodular sclerosis, mixed cellularity, and lymphocyte depletion). In the United States, the age-adjusted incidence rate for all types of Hodgkin lymphoma is 2.7 cases per 100,000 person-years, with a 5-year survival of 80% (SEER 2015). The relationship between EBV and Hodgkin lymphoma was first proposed in the 1960s (MacMahon 1966). Numerous case reports and case-series studies since that time have examined the association between EBV and primarily the mixed cellularity subtype, with approximately 75% of cases EBV positive; while approximately 20% of Hodgkin lymphoma cases with the nodular sclerosis subtype are EBV positive (Flavell and Murray 2000; Weiss 2000). These case reports and case series have reported that the association between EBV and Hodgkin lymphoma varies by age and geographic region. EBV-related Hodgkin lymphoma appears to be mostly highly associated with Hodgkin lymphoma incidence in middle adulthood in developed countries. In developing countries the EBV-Hodgkin lymphoma relationship shows a bimodal age distribution, with rates of EBV-related Hodgkin lymphoma highest in childhood and in older adults (Flavell and Murray 2000; Weiss 2000). EBV has been detected in 20% to 50% of Hodgkin lymphoma cases in North America and Europe, though the percentage differs by Hodgkin lymphoma subtype (Weiss 2000). EBV seropositivity in Asian Hodgkin lymphoma patients is around 65%, and 90% to 100% in South

Americans and Africans. Additionally, Hodgkin lymphoma patients with HIV have a nearly 100% EBV infection rate (Weiss 2000).

EBV has been established as the cause of infectious mononucleosis, and a large body of studies has reported an increased risk of Hodgkin lymphoma among populations with infectious mononucleosis infection (Crawford 2001). Exposure to EBV later in life (after childhood) in developed countries is more likely to lead to symptomatic infectious mononucleosis infection, Thus, this timing for infection is suggested to be a risk factor for the development of Hodgkin lymphoma, particularly in younger adults (Ambinder and Cesarman (2007) and Jarrett (2003), as cited in IARC (2012)). Several case-control and cohort studies have investigated the relationship between EBV and Hodgkin lymphoma, as well as Hodgkin lymphoma and infectious mononucleosis, as described below.

3.3.2. Case-control Studies

Thirty-eight (38) published case-control studies were identified that investigated the relationship between Hodgkin lymphoma and EBV. All but one study was previously reviewed by IARC (1997a; 2012). These studies included a total of over 7,100 Hodgkin lymphoma cases. These studies have generally fallen into two categories: those investigating the relationship between Hodgkin lymphoma and EBV serology or EBV DNA directly, and those investigating this relationship indirectly via the association between Hodgkin lymphoma and infectious mononucleosis.

Hodgkin Lymphoma and EBV Serology or EBV DNA

Twenty-seven (27) of a total of 38 case-control studies on EBV and Hodgkin lymphoma were previously reviewed by IARC (1997a; 2012), with 1 new study (Linabery et al. 2014) that examined the relationship between EBV antibodies or DNA and Hodgkin lymphoma. Nineteen studies provided an OR for the relationship between Hodgkin lymphoma and EBV serology (Figure 3-3). In general, these studies investigated the association between high VCA titer levels among Hodgkin lymphoma cases and controls, with odds ratios ranging from 0.8 to 67; the majority of ORs were between 4 and 19. Findings from studies not specifying the type of EBV antibodies were consistent with the studies of specific antibodies; most studies (5/8) reported statistically significant ORs ranging from 4 to 11. Ten of the 21 total studies (on VCA or unspecified antigens) additionally analyzed the association between Hodgkin lymphoma and EA antibodies for cases and controls, with ORs ranging from 1.2 to infinity; however, when studies with no exposure variability (studies with either no unexposed cases, or no exposed controls) were excluded, the ORs ranged from 1.2 to 15. Six case-control studies also reported risk estimates (or information to calculate estimates) for elevated titers of EBNA and Hodgkin lymphoma. These included Lange et al. (1978) with an OR of 19.3 (95% CI = 5.5 to 67.6, for 15/28 exposed cases), Mochanko et al. (1979) with an OR of 5.4 (95% CI = 1.8 to 15.8, for 18/37 exposed cases), Merk et al. (1995) with an OR of 1.7 (95% CI = 0.8 to 3.6, for 16/61 exposed cases), and Berrington de Gonzalez et al. (2006)[1] with an OR of 0.7 (95% CI = 0.3 to 1.4, for 21/83 exposed cases), and Rocchi et al. (1975), and Shope et al. (1982) reported OR of infinity (no controls had elevated titer). Three serological case-control studies did not provide

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[1] This study did not report an OR for other antibodies.

enough data to calculate an odds ratio (Lennette et al. 1993; Lennette et al. 1995; Wutzler et al. 1983).[2]

In addition to the serology studies measuring antibody, three case-control studies reported ORs between EBV DNA in serum or lymph nodes and Hodgkin lymphoma; these studies found highly statistically significant associations, with ORs ranging from 120 to infinity; however, there was little variability in exposure (Dinand et al. 2007; Gallagher et al. 1999; Lei et al. 2000; Musacchio et al. 2006). Gallagher et al. (1999) also measured EBV DNA in serum of cases and controls, but it was not possible to calculate an OR as cases were pre-classified as EBV positive or negative.

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[2] This study did not report an OR for other antibodies.

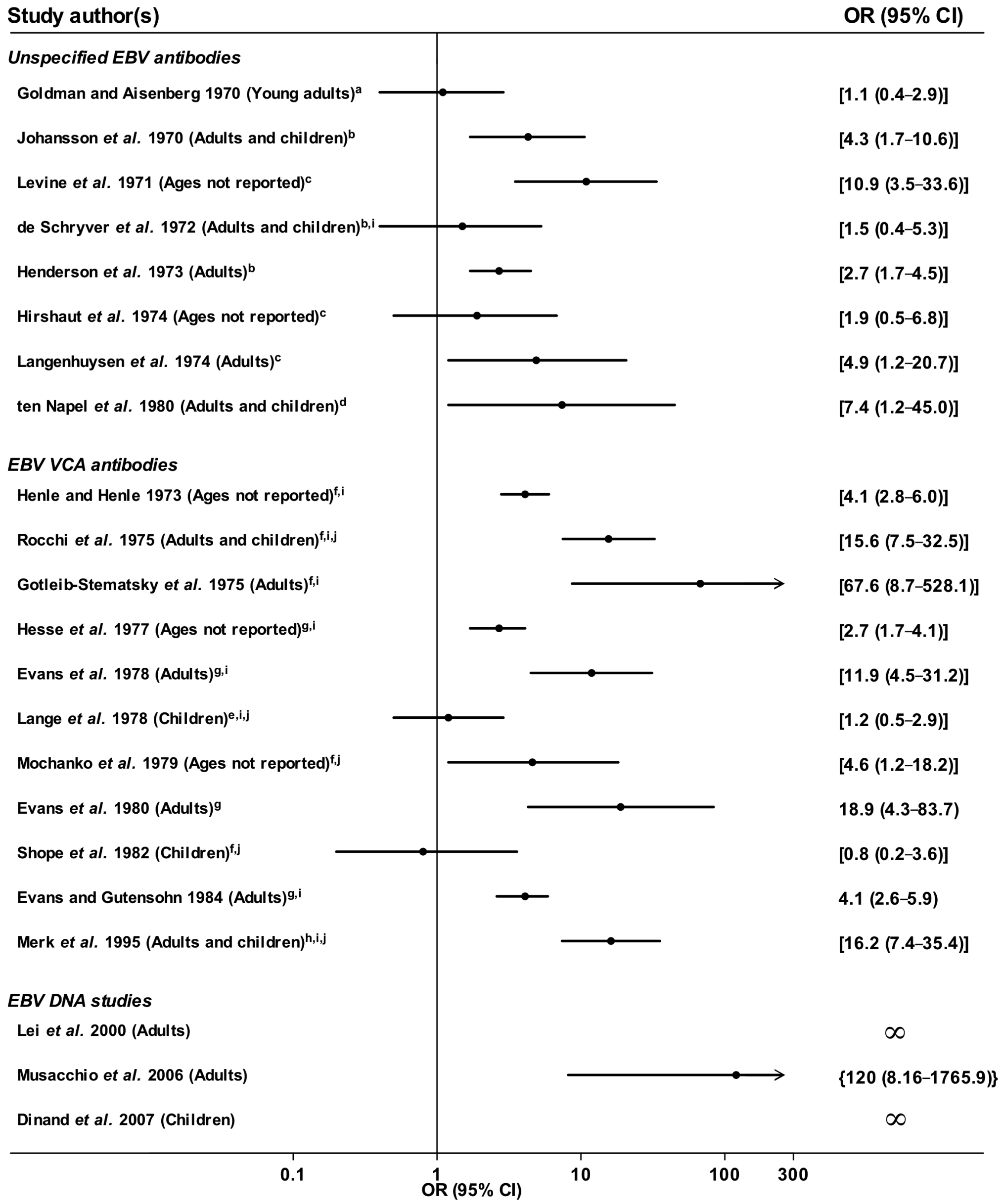

Figure 3-3. Forest Plot of Serological Case-control Studies of Hodgkin Lymphoma and Epstein-Barr Virus

Source: Table 19 in IARC (1997a); Table 2.3 in IARC (2012). Note: Hilgers and Hilgers (1976) was not included.
ORs in curly brackets ((Crawford 2001)) were calculated by IARC working group; ORs in square brackets ([]) were calculated by NTP.
CI = confidence interval; OR = odds ratio; VCA = viral capsid antigen.

[a] Exposed group – defined as any detectable EBV antibody.
[b] EBV antibody exposed group ≥160.
[c] EBV antibody exposed group ≥640.
[d] EBV antibody exposed group ≥1,280.
[e] EBV VCA antibody exposed group ≥5.
[f] EBV VCA antibody exposed group ≥160.
[g] EBV VCA antibody exposed group ≥320.
[h] EBV VCA antibody exposed group ≥1,280.
[i] Study also includes data on EA antibodies.
[j] Study also includes data on EBNA antibodies.

The study by Linabery et al. (2014) examined a subset (69%) of the 517 cases of pediatric Hodgkin lymphoma for EBV RNA in the tumor. Overall, 16% (N = 84) were found to have tumors that were EBV RNA positive. This proportion increased in the younger age groups, with 23% (N = 5) of those aged 0 to 4 years and 29% (N = 36) of those aged 5 to 9 years EBV positive. EBV status among the controls was not available; therefore, no odds ratios could be calculated.

Hodgkin Lymphoma and Infectious Mononucleosis

Eleven of the 38 case-control studies (10 reported by IARC and 1 new study, Linabery et al. (2014)) reported on the association between infectious mononucleosis and Hodgkin lymphoma. These studies generally found a positive association between infectious mononucleosis and Hodgkin lymphoma, with ORs ranging between 0.3 and 13.1 (for subtype of Hodgkin lymphoma), with most falling between 1.3 and 2.5 (Alexander et al. 2000; Alexander et al. 2003; Bernard et al. 1987; Evans and Gutensohn 1984; Glaser et al. 2005; Gutensohn and Cole 1981; Gutensohn 1982; Henderson et al. 1979; Hjalgrim et al. 2007; Linabery et al. 2014; Serraino et al. 1991). Among these studies, six found a statistically significant association between Hodgkin lymphoma and infectious mononucleosis; Bernard et al. (1987) and Serraino et al. (1991) found significant associations in subpopulations, not reported in Figure 3-4. One study (Glaser et al. 2005) found a non-significant OR of 0.3 in a population of women, ages 19 to 79, with Hodgkin lymphoma. These studies are summarized in Figure 3-4. A number of these studies had limited statistical power to detect an effect. Additionally, studies that stratified Hodgkin lymphoma patients by age found a stronger, statistically significant association among younger adults (Bernard et al. (1987) [young adult males, OR = 4.9; p = 0.04; 95% CI not available], Alexander et al. (2000); Hjalgrim et al. (2007)).

Two studies reported significant associations for cases with the nodular sclerosis subtype of Hodgkin lymphoma. Henderson et al. (1979) reported a non-significant OR of 1.5 (95% CI not reported), while Serraino et al. (1991) reported a statistically significant OR of 13.1 (1.0 to 176.6). The most recent study of children and adolescents (Linabery et al. 2014) reported a non-statistically significant increase in the odds of Hodgkin lymphoma among those diagnosed with infectious mononucleosis (OR = 1.5; 95% CI = 0.52 to 3.50 for 9/517 exposed cases); although power was limited by the small number of participants with a previous diagnosis of infectious mononucleosis (9 cases and 10 controls). When restricted to EBV-positive (EBV detected in the tumors) cases, they found a non-statistically significant 9-fold increase in the risk of Hodgkin lymphoma among those who had a history of infectious mononucleosis infection (OR = 9.1; 95% CI = 0.81 to 102.3 for 3/84 exposed cases).

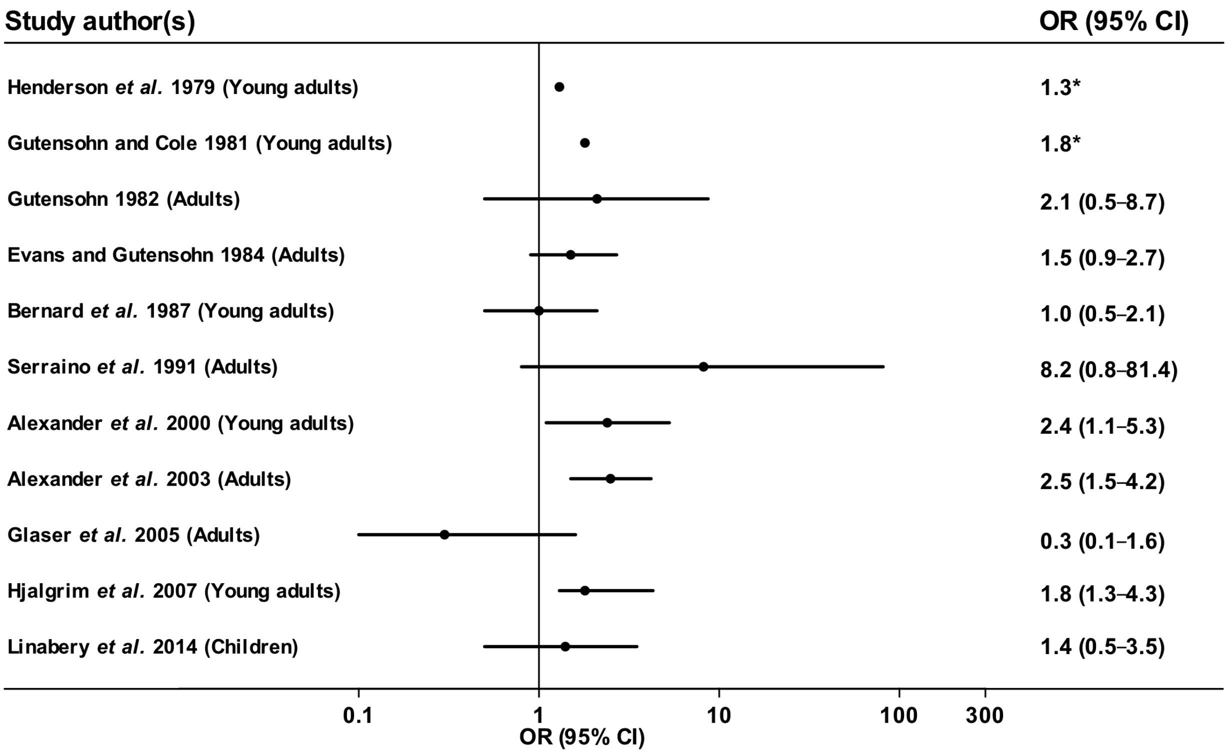

Figure 3-4. Forest Plot of Case-control Studies of Hodgkin Lymphoma and Infectious Mononucleosis

*95% confidence interval unavailable.
CI = confidence interval; OR = odds ratio.

3.3.3. Cohort Studies

Seven cohort studies and two nested case-control studies have investigated the association between EBV and Hodgkin lymphoma. These studies are summarized in Table 3-1. The seven cohort studies, conducted in the United States and Western Europe and published from 1973 to 2000, looked at the relationship between infectious mononucleosis (caused by EBV) and Hodgkin lymphoma. Six were reviewed in detail by IARC (1997a)—Carter et al. (1977); Connelly and Christine (1974); Kvale et al. (1979); Miller and Beebe (1973); Munoz et al. (1978); Rosdahl et al. (1974)—while one additional cohort study (Hjalgrim et al. 2000) was reviewed by IARC (2012). These studies included a total of over 80,000 participants with serologically confirmed infectious mononucleosis. A total of 83 cases of Hodgkin lymphoma were observed, with standardized incidence ratios (SIR) ranging from 2.0 to 5.0. All studies observed more cases of Hodgkin lymphoma than expected in the general population, with three of the seven studies reporting statistically significant SIRs (Hjalgrim et al. 2000; Munoz et al. 1978; Rosdahl et al. 1974) in the relationship between infectious mononucleosis and subsequent development of Hodgkin lymphoma. One study (Miller and Beebe 1973) did not find a statistically significant association, and the remaining studies (Carter et al. 1977; Connelly and Christine 1974; Kvale et al. 1979) did not report statistical significance in their risk estimates.

Table 3-1. Summary of Cohort and Nested Case-control Studies of Hodgkin Lymphoma and Epstein-Barr Virus

Reference	Age Group	RR[a]	Comments
Infectious mononucleosis studies[b]			
Miller and Beebe (1973)	Adults	{2.0}	NS
Connelly and Christine (1974)	Adults/children	{5.0}	NR
Rosdahl et al. (1974)	Adults/children	{2.8}	Lower CI > 1
Carter et al. (1977)	Adults	{2.3}	NR
Munoz et al. (1978)	Adults/children	4.0	Lower CI > 1
Kvale et al. (1979)	Adults/children	{3.0}[b]	NR
Hjalgrim et al. (2000)	Adults/children	2.6	Lower CI > 1
EBV serology studies[c]			
Mueller et al. (1989)	NR	VCA-IgG ≥320: 2.6	Lower CI > 1
		VCA-IgA ≥20: 3.7[d]	Lower CI > 1
		EBNA ≥80: 4.0	Lower CI > 1
		EA(D) ≥5: 2.6	Lower CI > 1
Lehtinen et al. (1993)	Adults	NR	NR

Relative risks in curly brackets ({}) were calculated by the IARC Working Group (2012).
CI = 95% confidence interval; EA(D) = early antigen-diffuse; EBNA = EBV nuclear antigen; IM = infectious mononucleosis; NR = not reported; RR = relative risk; VCA = viral capsid antigen.
[a] For IM cohort studies, RR reported is the standardized incidence ratio (SIR).
[b] SIR at least one year from IM diagnosis.
[c] All IM studies were cohort designs, while both serology studies were nested case-control designs.
[d] Risk estimate was adjusted for IgM.

Two nested case-control studies investigated EBV serology prior to a Hodgkin lymphoma diagnosis (Lehtinen et al. 1993; Mueller et al. 1989). Mueller et al. (1989) analyzed 43 Hodgkin lymphoma patients and 96 matched controls from a cohort of over 235,000 participants. They found that titers to EBV antibodies (VCA IgA and EBNA) were statistically significantly increased among those with Hodgkin lymphoma, with relative risks equaling 2.7 and 2.5, respectively. Relative risks of antibody titers to VCA-IgG and EA were elevated but not significant. Additionally, they found that these associations were generally stronger in patients with a blood draw at least three years before Hodgkin lymphoma diagnosis. Lehtinen et al. (1993) conducted a similar nested case-control study among 39,000 adults with a blood draw who were followed for up to 12 years. Data for the association between Hodgkin lymphoma and EBV were not shown, but the authors reported an increased risk of antibody response to EBV among Hodgkin lymphoma patients.

3.3.4. Integration of the Evidence

Epidemiological data provide evidence of an association between EBV and Hodgkin lymphoma with 15 of the 22 case-control studies reporting ORs showing statistically significant associations based on serologic and DNA findings. Positive associations have been reported between EBV and Hodgkin lymphoma for both adults and young adults; however, the association between EBV and childhood Hodgkin lymphoma is unclear. Moreover, infectious mononucleosis (caused by EBV) is positively associated with Hodgkin lymphoma among adults, young adults, and children; although inconsistencies in the evidence are possibly due to the fact that few infectious mononucleosis studies provided data on EBV tumor status. The temporality of this association was seen in one nested case-control study, which reported statistically significantly elevated EBV titers prior to Hodgkin lymphoma diagnosis among cases compared with controls. The strength of the observed associations varied between studies with both indirect EBV exposure measurement (infectious mononucleosis studies), and with direct EBV measurement (serological and tumor DNA studies). ORs are generally higher in the serological studies compared to the infectious mononucleosis studies, and ORs in case-control studies using tumor DNA to detect EBV exposure were highest. The heterogeneity seen in the serology and tumor DNA case-control studies may partly be explained by differential sensitivity and specificity of these exposure markers. One serology case-control study (Gotlieb-Stematsky et al. 1975) had only one exposed control, while two of the four EBV DNA studies had no exposed controls, and a third had only one exposed control.

3.4. Cancer Evaluation: Immunosuppression-related Non-Hodgkin Lymphoma

3.4.1. Background Information

Three types of immunosuppression-related non-Hodgkin lymphoma have been reported in the EBV literature and were reviewed by IARC (1997a; 2012). These lymphomas occur with severe immunosuppression and are observed with post-transplant lymphoproliferative disorders (PTLD), HIV-1-associated lymphoproliferative disorders, and congenital immunodeficiencies. PTLD is a complication of both solid organ transplant and hematopoietic stem cell transplant and is one of the most common post-transplant malignancies. The incidence of PTLD varies by type of transplant, but is generally more common in children than adults, with incidence rates ranging from <1% to 13% in children and between 1% and 8% in adults (Garfin et al. 2015). The 5-year survival rate for adults and children is approximately 60% (Hauke et al. 2001). EBV has been associated with up to 50% to 70% of PTLD cases (Al-Mansour et al. 2013; Jimenez 2015).

HIV-1-lymphoproliferative disorder is a common type of non-Hodgkin lymphoma among those diagnosed with HIV-1. Non-Hodgkin lymphoma is designated a defining acquired immune deficiency syndrome (AIDS) condition. Those with HIV-1 are 70 times more likely to be diagnosed with non-Hodgkin lymphoma (Grulich et al. 2007b) while the 5-year survival rates of those with HIV-1-related non-Hodgkin lymphoma is low, at approximately 5% (Chow et al. 2001). HIV-1-associated lymphoproliferative disorder is discussed in further detail in the HIV-1 monograph (see Sections 3.3.1 and 3.3.4 of the HIV-1 monograph, NTP (2016)). EBV is present in the tumor cells in almost all cases of HIV-1-related primary central nervous system non-Hodgkin lymphoma, and in approximately 50% of HIV-1-related diffuse large cell and immunoblastic non-Hodgkin lymphoma (Grulich et al. 2007a).

3.4.2. Studies and Evaluation

IARC reported more than 20 case-series studies relating EBV to immunosuppression and non-Hodgkin lymphoma. Detection methods for EBV (such as DNA, in situ hybridization for EBV RNA, expression of LMP) varied. In nine case-series reports (totaling 142 cases) of HIV-1-associated primary central nervous system non-Hodgkin lymphoma, EBV was found in all cases in five studies and in the majority of cases in the remaining four studies (Table 14 in IARC (1997a)). In situ hybridization studies found that EBV RNA was found in most or all of the tumor cells whereas expression of LMP was more variable. EBV was also found in HIV-1-

associated systemic non-Hodgkin lymphoma (Table 15 in IARC (1997a)). Sixteen studies identified EBV in some of the cases. In the cases positive for EBV, the number of EBV-positive cells in the tumor varied from 25% to 100%. Importantly, EBV was found to be monoclonal by terminal-repeat sequence analysis in four of these studies. In addition, seven studies investigated the presence of EBV in lymphomas from patients with congenital primary immune deficiency and all of the cases were positive for EBV (Table 16 in IARC (1997a)).

Only one case-control study has been identified that investigated the association between EBV and immunosuppression-related non-Hodgkin lymphoma. This study included cases with several types of lymphoma, including both Hodgkin and non-Hodgkin lymphomas. This study included 13 total cases of different cancer types, including two cases of PTLD and 35 healthy controls in Hong Kong (Lei et al. 2000). Plasma EBV DNA was detected in both PTLD cases, suggesting activated EBV; however, EBV plasma DNA was not detected in any of the controls.

One nested case-control study and no cohort studies were identified in which EBV titers were measured in immunosuppressed populations. In a U.K.-based nested case-control study, 67 HIV-1-positive, non-Hodgkin lymphoma patients participated in a trial of antiretroviral therapy with 67 matched controls (Newton et al. 2006). Controls were randomly selected from the trial participants among those who had not developed cancer after the same period of follow-up, and matched by trial, age group, sex, HIV-1 transmission group, treatment group, and ethnicity. Among cases, a statistically non-significant association between the risk of disease for a doubling of VCA-IgG antibodies to EBV was observed compared to controls (adjusted OR = 1.5, 95% CI = 0.9 to 2.3).

3.4.3. Integration of the Evidence

Severe immunosuppression from congenital, iatrogenic, or HIV-1/AIDS can result in EBV-associated non-Hodgkin lymphomas. Epidemiological data primarily from case studies provide consistent evidence of an association between EBV positive non-Hodgkin lymphoma and congenital immunodeficiencies. In HIV-1 patients almost all non-Hodgkin lymphomas of the central nervous system and a large number of systemic non-Hodgkin lymphomas are EBV related. There were some reports of monoclonality of the virus within the tumor, although all cells within the tumor were not positive for the activated virus. Further, EBV has been shown to be associated with over half of PTLD cases. The strength of these studies varied with detection method used, as some studies used a method that would detect EBV, but not necessarily an activated form of the virus.

3.5. Cancer Evaluation: Extranodal NK/T-cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type is a rare type of non-Hodgkin lymphoma (also known as sinonasal angiocentric T-cell lymphoma). NK/T-cell lymphoma and NK/T-cell proliferative disease most often occur in adults, are more common in males than females, are most prevalent in Asia, South America, Central America, and Mexico, and represent 7% to 40% of all non-Hodgkin lymphomas, with a 5-year survival near 50% (Chan et al. 2001; Lee et al. 2006; Suwiwat et al. 2007).

NK/T-cell lymphoma is almost universally associated with EBV in tumor cells, irrespective of the ethnic origin of the patients; however, nasal type NK/T-cell lymphomas presenting in other organ locations have been most strongly associated with EBV in Asian patients (Chan et al. 2001; IARC 2012). In recent case-series studies in Asia and South America, the presence of EBV DNA has been identified in nearly 100% of nasal type NK/T-cell lymphoma tumor cells (Barrionuevo et al. 2007; He et al. 2007). Overall, more than 400 EBV-associated NK/T-cell lymphoma cases have been identified including both these studies and studies identified by IARC (1997a) (see Table 11, sinonasal angiocentric T-cell lymphoma). No cofactors have been identified.

Two case-control studies (which included 10 cases) found a positive association between EBV DNA in plasma and/or $CD3^+$ (T) Cells and extranodal NK/T-cell lymphoma, nasal type. However, the temporal relationship between EBV and nasal extranodal NK/T-cell lymphoma has not been established. These studies are reviewed in Table 3-2.

Table 3-2. Summary of Case-comparison Studies of NK/T-Cell Lymphoma, Nasal Type and Epstein-Barr Virus

Reference	Exposure Category	OR	Exposed Cases: Exposed Controls
Lei et al. (2000) (Hong Kong)	EBV plasma DNA	∞	4/4: 0/35
Suwiwat et al. (2007) (Thailand)	EBV plasma DNA	∞	6/6: 0/45
	$CD3^+$ Cells	∞	6/6: 0/45
	$CD3^-$ Cells	∞	6/6 cases; 19/45

3.6. Cancer Evaluation: Nasopharyngeal Carcinoma

3.6.1. Background Information

Nasopharyngeal carcinoma is the predominant type of cancer in the nasopharynx. It is a rare cancer in most parts of the world. In the United States, incidence ranges from 0.5 to 2 per 100,000, with a 5-year survival of 36% to over 60% (Lee and Ko 2005). However, in areas like Southeast Asia, the Arctic, North Africa, and the Middle East, incidence rates can be much higher, ranging from 2.7 per 100,000 to 26 per 100,000 (Chin et al. 2014; Ferlay et al. 2015; Yu and Yuan 2002). Additionally, nasopharyngeal carcinoma is much more common in males than females throughout the world (Chang and Adami 2006; Chin et al. 2014). Nasopharyngeal carcinomas are classified into three types: keratinizing squamous-cell carcinoma, non-keratinizing carcinoma, and basaloid squamous-cell carcinoma (Chan et al. (2005), as cited in IARC (2012)). Nasopharyngeal carcinoma is associated with EBV, especially in EBV-endemic populations, with nearly universal EBV seropositivity among cases (Adham et al. 2012).

3.6.2. Case-control Studies

Fifteen (15) case-control studies (1976 to 2014) have been identified that investigated the association between nasopharyngeal carcinoma and EBV. These 15 studies include over 1,900 cases of nasopharyngeal carcinoma, conducted primarily in Southeast Asia, although several studies included cases from Europe (Chan et al. 1991; Lennette et al. 1993), North Africa (de Thé et al. 1978), and the United States (Chan et al. 1991; Lanier et al. 1980; Pearson et al. 1983). These studies may be divided into those that investigated the relationship between nasopharyngeal carcinoma and EBV serology, and those that investigated EBV DNA in the tumor.

Eleven (11) of the 15 case-control studies on the association between nasopharyngeal carcinoma and EBV were serological studies. Using a variety of serological markers and tumor DNA analyses, the majority of these studies generally found a strong and statistically significant association between nasopharyngeal carcinoma and EBV. These studies are summarized in Figure 3-5. The ORs ranged from 21 to ∞, although when studies with no exposure variability, i.e., studies with no non-exposed cases or no exposed controls, were removed, the ORs ranged from 21 to 138 and were all statistically significant. Three studies did not provide enough information to calculate ORs; however, the geometric mean titers of anti-EBV antibodies were statistically significantly higher in cases than in controls (de Thé et al. 1978; Hilgers and Hilgers 1976; Lennette et al. 1995). Another study, Tiwawech et al. (2008) reported on 75 nasopharyngeal carcinoma cases in Thailand and 44 matched controls. They found all cases and controls were exposed to EBNA-2 and LMP-1; however, they found the LMP-1 deletion type subtype to be more common in cases than in controls (OR = 2.5; 95% CI = 1.1 to 5.8). The six case-control studies of EBV DNA in nasopharyngeal carcinoma tumors reported statistically significant increases in EBV DNA with ORs ranging from 86 to ∞, or 86 to 820 when studies with no exposure variability are removed.

3.6.3. Cohort Studies

Two nested case-control studies and two cohort studies were identified that investigated the association between nasopharyngeal carcinoma and EBV. The two nested case-control studies included a total of 14 nasopharyngeal carcinoma cases; one was a study of 7 cases among Alaska Natives (Lanier et al. 1980) and the other among a general population in the United States (Chan et al. 1991). Both investigated whether EBV antibodies were present prior to a nasopharyngeal carcinoma diagnosis, with follow-up times ranging from 1 to 12 years. Neither study found a statistically significant relationship between EBV antibodies prior to diagnosis and nasopharyngeal carcinoma. The two prospective cohort studies (Chien et al. 2001; Ji et al. 2007) had over 51,000 participants and a total of 168 cases of nasopharyngeal carcinoma, with follow-up times up to 16 years. Both studies reported statistically significant associations and nasopharyngeal carcinoma incidence between those designated seropositive and seronegative at baseline, with relative risks of 22 (95% CI = 7.3 to 66.9) for Ji et al. (2007) and 9.4 (95% CI = 6.7 to 13.3) for Chien et al. (2001). Chien et al. (2001) also found a statistically significant relationship between EBV DNase antibodies and nasopharyngeal carcinoma with a relative risk of 3.5 (95% CI = 1.4 to 8.7). These studies are summarized in Figure 3-5.

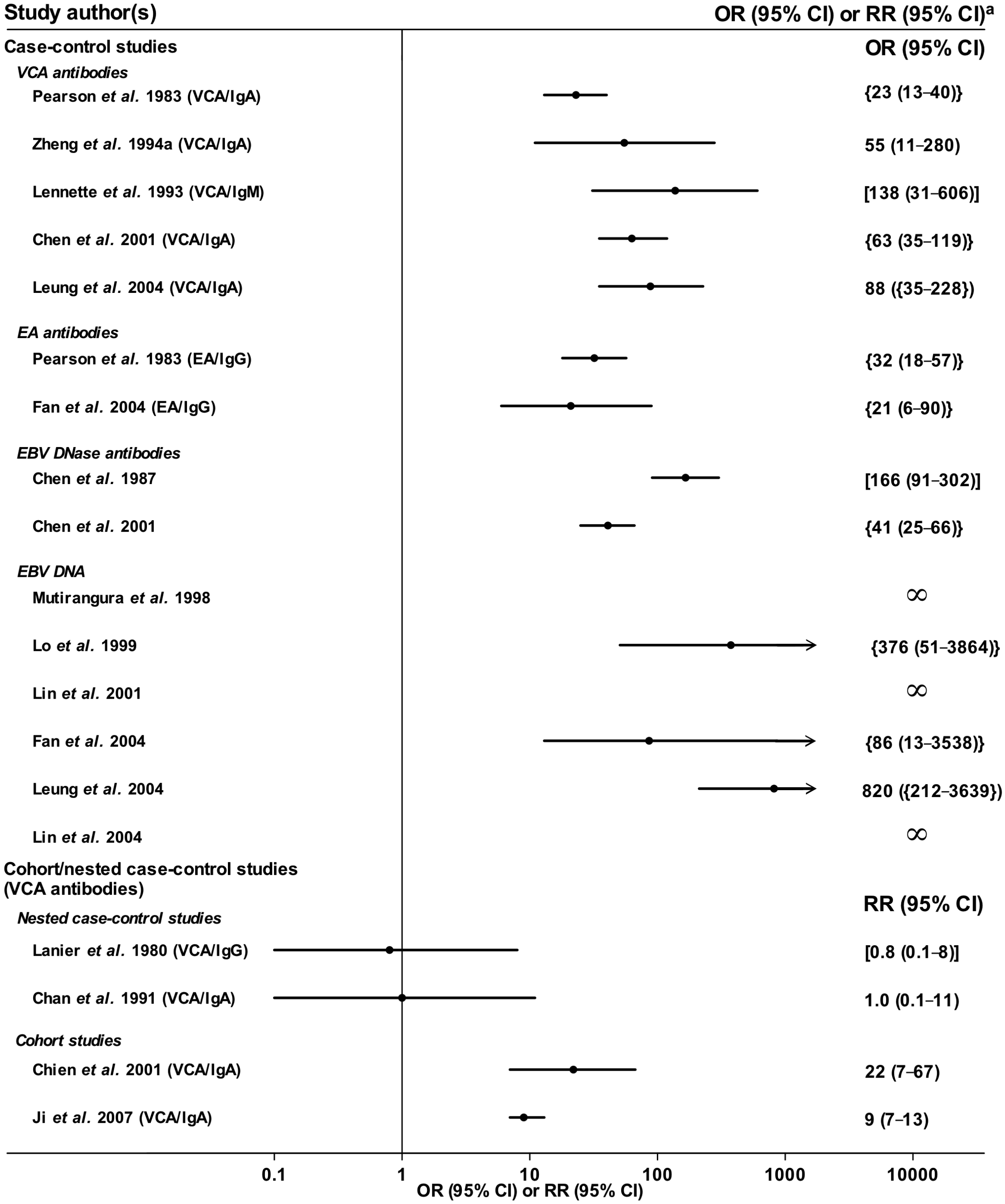

Figure 3-5. Forest Plot of Serological Case-control Studies of Nasopharyngeal Carcinoma and Epstein-Barr Virus

Source: Table 25 in IARC (1997a); Tables 2.6 and 2.7 in IARC (2012); except Chan et al. (1991); Chen et al. (1987); Lanier et al. (1980); Lennette et al. (1993).
CI = confidence interval; EA = early antigen; EBNA = EBV nuclear antigen; IgG/A/M = immunoglobulin G/A/M; OR = odds ratio; VCA = viral capsid antigen.
[a]ORs or RRs and 95% CIs in curly brackets ({}) were calculated by IARC (1997a; 2012) working groups; ORs or RRs and 95% CIs in square brackets ([]) were calculated by NTP.

3.6.4. Cofactors

Two potential cofactors in the association between EBV and nasopharyngeal carcinoma were reviewed by IARC (1997a): dietary factors (such as Cantonese-style salted fish, other preserved foods, and deficits of fruits and vegetables), and genetic factors. These cofactors are reviewed briefly here. See IARC (1997a) for an in-depth review.

No new studies on dietary factors as cofactors in the association between EBV and nasopharyngeal carcinoma have been identified since the previous IARC reviews (1997a; 2012). Earlier case-control studies found the consumption of Cantonese-style salted fish, particularly during childhood, to be associated with a diagnosis of nasopharyngeal carcinoma, with ORs ranging from 1.5 to 38; these were generally statistically significant (Armstrong and Armstrong 1983; Geser et al. 1978; Henderson and Louie 1978; Ning et al. 1990; Sriamporn et al. 1992; Yu et al. 1986; Yu et al. 1989; Yu et al. 1988; Zheng et al. 1994a; Zheng et al. 1994b). Those studies that did not find a statistically significant association did not include childhood consumption in their analysis (Chen et al. 1988; Lee et al. 1994). Other types of salted fish were not significantly associated with nasopharyngeal carcinoma; however, other preserved foods, particularly salted foods, were associated with nasopharyngeal carcinoma in several case-control studies, with ORs ranging from 1.2 to 8.6. The results of studies investigating the relationship between deficits of fresh fruits and vegetables and nasopharyngeal carcinoma were mixed, some finding no association and others finding statistically significantly lower levels of certain vitamins among nasopharyngeal carcinoma patients. Although none of the studies specifically evaluated the relationship between EBV and dietary factors, they might be potential cofactors as mechanistic studies (reviewed by IARC (1997a)) found that Cantonese-style salted fish, along with other preservatives, contained substances capable of activating EBV in latently infected cells (Poirier et al. (1989) and Shao et al. (1988), as cited in IARC (1997a)).

Genetic factors have also been suggested as cofactors for nasopharyngeal carcinoma, with multiple susceptible genetic loci identified. EBV interacts with the host-cell genes implicated in nasopharyngeal carcinoma development, influencing cell signaling and host gene regulation, and predisposing the cell for nasopharyngeal carcinoma (Aldred and Eng (2006), as cited in Lung et al. (2014)). No epidemiological studies on the associations between nasopharyngeal carcinoma, EBV, and genetic factors have been identified; however, five new studies since 2008 have demonstrated that genetic variation in certain genes is associated with the risk of nasopharyngeal carcinoma. Two of these studies (Chin et al. 2014; Zhao et al. 2012) found increased susceptibility for nasopharyngeal carcinoma associated with the HLA-A locus in Chinese cases of nasopharyngeal carcinoma. This is consistent with previous research that has found an increased risk of nasopharyngeal carcinoma associated with the HLA-A and HLA-B loci among Chinese populations. These previous studies were reviewed by IARC (1997a), along with studies in non-Chinese populations. Two new case-control studies investigated the association between nasopharyngeal carcinoma and the genes for the cytokines interleukin-2 (Wei et al. 2010) and interleukin-18 (Nong et al. 2009) among Chinese populations. Significant differences were found between the genotypes and allele frequencies of these cytokines between cases and controls in both studies. Moumad et al. (2013) studied 492 nasopharyngeal carcinoma patients in North Africa and found significant associations between nasopharyngeal carcinoma and polymorphisms of genes for pattern recognition receptors (Toll-like receptor TLR3, C-type lectin receptor CD209, retinoic acid-inducible gen I-like receptor [DDX58]).

3.6.5. Integration of the Evidence

The epidemiological data, primarily a large body of case-control studies, consistently report statistically significant, positive associations between EBV seropositivity and nasopharyngeal carcinoma. A number of these studies were conducted among populations with a high prevalence of nasopharyngeal carcinoma. ORs of 20 or higher were seen for most case-control studies, using both serological and tumor DNA EBV detection methods. Two cohort studies have also shown positive associations between EBV seropositivity and nasopharyngeal carcinoma incidence, and demonstrated the temporality of the relationship, with EBV seropositivity preceding development and diagnosis of nasopharyngeal carcinoma. Long follow-up times between study enrollment (when EBV seropositivity is determined) and diagnosis may lead to some misclassification; those developing EBV seropositivity after enrollment but before diagnosis would be misclassified as seronegative. Two cofactors, dietary factors and genetic factors, have been suggested to have an influence on the relationship between EBV and nasopharyngeal carcinoma.

3.7. Cancer Evaluation: Gastric Cancer

3.7.1. Background Information on Gastric Cancer

Gastric cancer is one of the most common cancers worldwide, with 7.5 cases per 100,000 people diagnosed each year in the United States. The 5-year survival rate for gastric cancer is 20% or less (Crew and Neugut 2006). Epstein-Barr virus was first detected (via polymerase chain reaction) in a patient with gastric cancer in 1990 (Burke et al. 1990).

3.7.2. Case-series Analyses and Pooled Analyses

EBV-related gastric cancer is defined as detection of EBV in the gastric cancer tumor, through a variety of detection methods, such as in situ hybridization or polymerase chain reaction. A case series of 138 U.S. patients (Shibata and Weiss (1992), as cited in IARC (1997a)) found the prevalence of EBV-related gastric cancer to be 16%. In a systematic review of 47 case series and case-control studies, Chen et al. (2015) found EBV DNA in 5% to 18% of gastric cancer cases when detected by in situ hybridization. A pooled analysis of case reports and case series found the global prevalence of EBV-related gastric cancer to be around 8.3% to 8.7% (Murphy et al. 2009; Sousa et al. 2008). These analyses also found the highest prevalence of EBV-related gastric cancer in North and South America (13%) and the lowest in Southeast Asia (7.8%) (Sousa et al. 2008). Additionally, in their meta-analysis based on 15,952 cases of gastric cancer worldwide, Murphy et al. (2009) noted a twofold difference in EBV-related gastric cancer by sex, with a prevalence of 11.1% in males and 5.2% in females. Pooling studies with various EBV detection methodologies, this meta-analysis also identified differences in EBV-related gastric cancer prevalence based on anatomic location of the gastric cancer tumor. Tumors originating in the gastric cardia or corpus (body) were twice as likely to be EBV positive compared with tumors in the pyloric antrum. Moreover, EBV prevalence was 4 times higher for tumors arising in postsurgical gastric stump/remnants compared to the pooled prevalence of EBV positivity. Additionally, over 90% of lymphoepithelioma-like carcinomas of the stomach were EBV positive.

3.7.3. Case-control Studies and Case-case Analyses

There have been three case-control studies and one case-case comparison study published that investigated the association between EBV and gastric cancer (de Aquino et al. 2012; Lo et al. 2001; Shinkura et al. 2000) (Table 3-3). Among the three case-control studies, there were a total of 77 EBV-positive gastric cancer cases out of 184 total gastric cancer cases. Two of these studies were reviewed by IARC (2012). In a population of 123 gastric cancer cases (64 cases with EBV-positive tumors) and 73 healthy controls in Japan, Shinkura et al. (2000) calculated the EBV seroprevalence of cases compared with controls. Cases were 7.1 (95% CI = 2.4 to 25.6) times more likely to be VCA-IgA positive and 19.9 (95% CI = 6.6 to 70) times more likely to be EA-IgG positive than healthy controls (ORs calculated by IARC working group, available in IARC (2012), Table 2.9). The authors also conducted a case-case comparison between patients with EBV-positive and EBV-negative tumors and found the geometric mean of EBV VCA-IgG ($p < 0.001$), EBV VCA-IgA ($p = 0.006$), and EA-IgG ($p < 0.001$) to be significantly higher among EBV-positive cases compared to EBV-negative cases; however, there was no difference in EBNA antibodies. EBV-positive cases were 3.4 (95% CI = 1.3 to 8.8) and 6.6 (95% CI = 2.7 to 16.3) times more likely to be seropositive for VCA-IgA and EA-IgG, respectively, compared to EBV-negative cases. It is noteworthy that cases with EBV-negative tumors were 4.9 times more likely to be seropositive for EA-IgG than healthy controls, and the geometric mean titer of VCA-IgG was significantly higher for EBV-negative cases than in healthy controls.

Table 3-3. Summary of Case-control Studies of Gastric Cancer and Epstein-Barr Virus

Reference	OR	Comments
Case-control Studies		
Shinkura et al. (2000)	VCA-IgA: {7.1}[a] EA-IgG: {19.9}[a]	Lower 95% CI > 1.0 Lower 95% CI > 1.0
Lo et al. (2001)	EBV DNA (EBV+ tumor): ∞ EBV DNA (EBV− tumor, EBV+ lymphocytes): {352.9}	5/5 EBER+ cases EBV DNA+, 13/14 EBER− cases EBV DNA+, 7/197 controls EBV DNA+ Lower CI > 1.0
de Aquino et al. (2012)	EBV DNA: ∞	8/10 cases EBV+, 0/6 control EBV+

CI = confidence interval; EA = early antigen; IgG/A = immunoglobulin G/A; OR = odds ratio; VCA = viral capsid antigen.
[a]ORs in curly brackets ({}) were calculated by the IARC Working Group (2012).

Lo et al. (2001) investigated serum EBV DNA in 51 gastric cancer cases (5 patients EBV-encoded small RNA [EBER]-positive, 14 EBER-negative but with occasional infiltrating lymphocytes that were EBER-positive, and 32 with no evidence of EBV) in Hong Kong compared with 197 healthy controls. They found that EBV DNA was detectable in all EBV-encoded small RNA (EBER)-positive cases (5/5), in all but one EBER-negative case with occasional infiltrating lymphocytes (13/14), and 0/32 EBV-negative cases, compared to 3.6% of healthy controls.

One new case-control study has been published since 2008 that investigated the prevalence of EBV DNA in the tumors of 10 gastric cancer patients in Brazil compared to a convenience sample of biopsies from 6 cancer-free control subjects obtained during endoscopies (de Aquino et al. 2012). EBV DNA, detected by polymerase chain reaction, was present in 8 of 10 gastric cancer cases and in none of the control subjects.

Boysen et al. (2011) conducted a nationwide case-case comparison study in Denmark that included 18 EBER-positive EBV gastric cancer cases out of 186 total gastric cancer cases, both with and without pernicious anemia. In comparison with gastric cancer patients without pernicious anemia, gastric cancer patients with pernicious anemia (N = 8) were 2.5 (95% CI = 0.88 to 7.14) times more likely to be EBV positive when adjusting for gender, age at diagnosis, and year of diagnosis; when further adjusted for lymphocytic infiltration, those with pernicious anemia were 2.9 (95% CI = 0.99 to 8.67) times more likely to be EBV positive.

3.7.4. Nested Case-control Studies

Levine et al. (1995) examined serum samples collected and banked prior to the diagnosis of 54 (14 EBV-positive and 40 EBV-negative) cases of gastric adenocarcinoma patients of Japanese ancestry selected from the Honolulu Heart Cohort study, along with 54 controls matched on age and date of blood collection. This study found a non-statistically significant increased risk between EBV seropositivity and subsequent development of gastric adenocarcinoma, as well as significantly elevated geometric mean titers of VCA or of EBNA in EBV-associated cases compared to controls (Table 3-4).

In another nested case-control study (Koshiol et al. 2007) among 185 cases of gastric cancer and 200 controls in China, EBV seropositivity prior to diagnosis was found to be unrelated to the incidence of gastric cancer (ORs less than 1). Follow-up time between enrollment and diagnosis was as long as 15 years. The study also found no difference in EBV seropositivity between cardia and non-cardia gastric cancer cases (see Table 3-4). However, this study did find that cardia gastric cancer cases with high baseline EBNA IgG titers (prior to diagnosis) had longer survival (hazard ratio = 0.46, 95% CI = 0.29 to 0.74) than either cardia gastric cancer cases with low baseline EBNA titers or all non-cardia gastric cancer cases. No interpretation for this finding was given.

Table 3-4. Summary of Nested Case-control Studies of Gastric Cancer and Epstein-Barr Virus

Reference	OR	Comments
Levine et al. (1995)	VCA-IgG: 1.4	NS; high (1,280+) versus low (≤640) titers
	VCA-IgA: 3.9	NS; high (20+) versus low (≤20) titers
	EBNA: 0.72	NS; high (640+) versus low (≤320) titers
	EA(D): 1.2	NS; high (5+) versus low (≤5) titers
	EA(R): 1.9	NS; high (5+) versus low (≤5) titers
	VCA-IgG (mean)	$p < 0.05$; EBV-associated cases versus controls
	EBNA (mean)	$p < 0.05$; EBV-associated cases versus non-EBV-associated tumors
Koshiol et al. (2007)	EBNA: 0.46[a]	Upper CI < 1. Survival among individuals with high vs. low EBNA.
		Seropositivity and development of gastric cancer. All non-significant.
	VCA-IgA: 0.69	
	EA-D IgG: 0.95	
	EA-R IgG: 0.52	
	High EBNA: 0.91	
Kim et al. (2009)	EBNA IgG: 0.90	NS; OR of gastric cancer risk of highest titer levels compared to lowest.
		NS; OR of gastric cancer risk of highest titer levels compared to lowest.

CI = confidence interval; EA = early antigen; EA-D = early antigen-diffuse; EA-R = early antigen-restricted; EBNA = EBV nuclear antigen; IgG/A = immunoglobulin G/A; NS = not statistically significant; OR = odds ratio; RR = relative risk; VCA = viral capsid antigen.

[a] Hazard Ratio reported.

In a third nested case-control study based in South Korea, Kim et al. (2009) studied 100 incident gastric cancer cases from a cohort of 14,000 participants in a multicenter cohort with 200 controls matched on year of enrollment, age, gender, and area of residence. Follow-up time between enrollment and gastric cancer diagnosis ranged from 0 to 9 years. The OR between EBV antibody levels prior to diagnosis and subsequent risk of gastric cancer, including among patients, was 1.37 (95% CI = 0.62 to 3.06) with the highest titers of VCA-IgG and 0.87 (95% CI = 0.51 to 1.46) for EBNA IgG. However, no dose-response relationship was observed (Table 3-4).

3.7.5. Cofactors

Currently, there are no identified cofactors for the association between EBV and gastric cancer.

3.7.6. Integration of the Evidence

The data from the three case-control studies suggest a positive association between EBV and gastric cancer, although two of those studies reported little exposure variability. In one study, all cases were EBV positive while in another there were no exposed controls. This lack of variability may account for heterogeneity seen in the results. In the three nested case-control studies, EBV titer levels prior to diagnosis were not significantly associated with an increased risk of gastric cancer; nevertheless, two studies found non-significant associations for VCA and EA antigens (Kim et al. 2009; Levine et al. 1995). None of the prospective studies typed the tumor DNA for EBV; therefore, it is unknown if those with EBV seropositivity prior to diagnosis were true EBV-positive gastric cancer cases. Also, follow-up times were long between enrollment and diagnosis for some cases resulting in non-differential exposure misclassification. Those who developed EBV seropositivity between enrollment and diagnosis would not have been counted as EBV-positive and thus would bias the findings toward the null.

3.8. Cancer Evaluation: Lymphoepithelial Carcinoma of the Salivary Gland

Lymphoepithelial carcinoma of the salivary gland is a rare carcinoma that accounts for less than 1% of all head and neck cancers and is histologically similar to nasopharyngeal carcinoma (Tsai et al. 1996; Tsang and Chan 2005). Based on the five case reports and case series published between 1982 and 1996 reviewed by IARC (1997a) 25 out of 27 total salivary gland lymphoepithelial carcinoma cases tested positive for EBV in tumor cells (IARC 1997a). Additional case-series studies of lymphoepithelial carcinoma of the parotid gland were reported in the later IARC (2012) review with 208 of 209 cases of parotid gland lymphoepithelial carcinoma reporting EBV DNA in the tumor. These EBV-positive cases of lymphoepithelial carcinoma of the salivary gland are predominantly of Eskimo/Inuit, Greenlandic, or Chinese (mainly southern) populations, which have higher incidences of nasopharyngeal carcinoma (Saku et al. 2003; Wang et al. 2004). Of the few reported cases of lymphoepithelial carcinoma of the salivary gland identified outside these geographical locations, EBV has not been consistently detected (Bialas et al. 2002; Saqui-Salces et al. 2006; Zhan et al. 2016).

3.8.1. Case-case Study

Only one case-case study of salivary gland lymphoepithelial carcinoma has been identified in the published literature. Wang et al. (2004) compared 16 cases of salivary gland lymphoepithelial carcinoma to 12 cases of other types of salivary gland tumors in Taiwan between 1977 and 2001. EBV DNA was present in the tumors of all 16 salivary gland lymphoepithelial carcinoma cases and in none of the other types of salivary gland tumors. Cases of lymphoepithelial carcinoma (all of which were EBV positive) had a better prognosis than cases of other tumor types. The lymphoepithelial carcinoma patients had a 5-year survival rate of 86% with treatment. Patients with other salivary gland tumor types who underwent treatment had a 5-year survival of only 36%.

3.8.2. Cofactors

No cofactors have been identified.

3.8.3. Integration of the Evidence

No case-control, cohort, or nested case-control studies have been identified on the association between EBV and lymphoepithelial carcinoma of the salivary gland. Thus, notwithstanding the evidence of a positive association between EBV and salivary gland lymphoepithelial carcinoma in several case reports and case series, there is insufficient epidemiological evidence to evaluate this endpoint.

3.9. Synthesis across Cancer Endpoints

A summary of the evidence for EBV infection and the different cancer endpoints from epidemiological studies is provided in Table 3-5. The level of evidence from cancer studies in humans also considers studies of tissues from humans in addition to epidemiological studies and is provided in Section 5.

Table 3-5. Summary of EBV Cancer Endpoints and Strength of the Epidemiological Evidence

Cancer Endpoint	Strength of Evidence
Burkitt lymphoma (endemic)	• Consistent evidence across multiple studies. All epidemiological studies report significant associations. • Elevated pre-diagnosis titers seen to one EBV antigen (VCA) in one prospective study. • Dose-response relationships observed in several studies.
(sporadic)	• Generally elevated, but non-significant ORs. One study found a significant association. • No prospective studies identified.

Cancer Endpoint	Strength of Evidence
Hodgkin lymphoma	• Evidence of an association between EBV and Hodgkin lymphoma in 15 of the 22 case-control studies reporting statistically significant ORs. • EBV DNA studies show a very strong association with tumor DNA. • One EBV serology nested case-control study shows temporal relationship. • Evidence for an association between infectious mononucleosis and Hodgkin lymphoma is less clear.
Immunosuppression-related NHL	• Case series indicate EBV is consistently found in cases of immunosuppression-related non-Hodgkin lymphoma. • Two epidemiological studies, one prospective, found evidence of an association, though not statistically significant.
Extranodal NK/T-cell lymphoma, nasal type	• Consistent association of nasal NK/T-cell lymphoma with EBV in tumor cells in case series; over 400 cases. • Two case-comparison studies found EBV DNA in the plasma or CD3+ (T cells) cells from cases but not from controls.
Nasopharyngeal carcinoma	• Consistent evidence of a strong association between EBV and NPC. Most ORs were 20 or higher. All case-control ORs were significant. • Two cohort studies showed a temporal association between EBV and NPC.
Gastric cancer	• Three case-control studies found strong associations with both EBV serology and DNA. • Elevated but non-statistically significant increased risks were found in two of three serological nested case-control studies.
LEC of the salivary gland	• No case-control or cohort studies of LEC of the salivary gland available although a case-case study found EBV DNA in salivary gland lymphoepithelial carcinoma tumors but not other type of salivary gland tumors; EBV DNA detected in tumors among over 200 cases of parotid salivary gland lymphoepithelial carcinoma in Asian or Eskimo populations in several case-series or case reports. • No epidemiological studies were available for review.

LEC = lymphoepithelial carcinoma; NHL = non-Hodgkin lymphoma; NPC = nasopharyngeal carcinoma.

4. Mechanisms and Other Relevant Data

Epstein-Barr virus (EBV) was the first oncogenic virus identified in humans and was found to be associated with endemic Burkitt lymphoma over 50 years ago (Epstein et al. 1964). Evidence of the oncogenic potential of EBV was demonstrated by its ability to transform human B lymphocytes in cell culture and by studies in nonhuman primates (Pope et al. 1968; Shope et al. 1973). Over 90% of the world's adult population is infected with EBV by age 20. For the most part, the result is an asymptomatic life-long infection—similar to other herpesviruses—and is held in check by immune surveillance. Several patterns of gene expression during virus latency have been shown to be associated with EBV pathogenesis of some cancers (see Table 1-1). From studies of human cancer populations and refinement of molecular techniques, several types of cancer have a clear causal association with this virus such as Burkitt lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma. However, the presence of EBV and its possible role in other cancers, such as carcinoma of the lung, skin, or various glandular tissues (e.g., breast cancer), are not as well understood and clinical studies showing a clear causative link are not available. Other tumor types, such as EBV-positive diffuse large B-cell lymphoma (DLBCL), lacked an adequate database. Investigation of the properties of the virus, as well as the cofactors and mechanisms that enable cancer formation in various tissues or are protective, is an ongoing process.

This section provides a brief review of the characteristics of EBV-associated neoplasms (Section 4.1), the roles of viral gene transcripts and proteins in malignant transformation (Section 4.2), the mode of action and evidence for cancer causation (Section 4.3), and a synthesis of this information (Section 4.4).

4.1. General Characteristics

As discussed in the previous sections, seven neoplasms—four in lymphoid tissue and three in epithelial tissue—have been primarily associated with EBV in humans, although the level of evidence for each tumor varies (IARC 2012). These neoplasms include: (1) Burkitt lymphoma (2) Hodgkin lymphoma, (3) immunosuppression-related non-Hodgkin lymphoma, (4) nasal type extranodal NK/T-cell lymphoma, (5) nasopharyngeal cancer, (6) gastric cancer, and (7) lymphoepithelial-like carcinoma of the salivary gland. General characteristics of these EBV-associated neoplasms and degree of association of the neoplasm with EBV, i.e., percentage of tumor cells containing the EBV genome are listed in Table 4-1.

Table 4-1. Characteristics of EBV-associated Neoplasms

Neoplasm	Clinical Presentation	Lineage and Primary Tumor Cell; Evidence of EBV Clonality[a]	Percent of Tumors or Tumor Cells EBV Positive; Clonality
Burkitt lymphoma	*Endemic form* - Extra nodal lymphoid tissue (jaw, kidney, bowel, adrenal gland); positive malaria titer; children	Neoplastic B cells with *c-myc* translocation to immunoglobulin locus - all forms of Burkitt lymphoma; monoclonal	*Endemic form* - 95% of tumor cells contain EBV genome
	Sporadic form - Abdomen, lymph nodes; adults and children		*Sporadic form* - at most 20% of tumors contain EBV genome
	Immunodeficiency-associated form - anti-rejection therapy; early latency with HIV infection; also, congenital cause		*Immunodeficiency-associated form* - 40% of lymphomas in HIV-1-positive patients (Gloghini et al. 2013; Stefan et al. 2011)
Hodgkin lymphoma	Nodal tissue of neck, mediastinal, axillary and paraaortic regions; lymphadenopathy with rich inflammatory background	Multinucleated, clonal Hodgkin Reed-Sternberg cells (B-cell origin; CD15, CD30 markers)	EBV primarily associated with 75% of mixed cellularity and 20% of nodular sclerosis subtypes of classical Hodgkin lymphoma; Hodgkin lymphomas in HIV-1-positive patients are 100% EBV associated
Immunosuppression-related NHL	Lymph nodes, gastrointestinal tract, lungs, liver; associated with CNS lymphomas in HIV-1-positive patients; Lymphomas may occur with anti-rejection therapy	Primarily (85%) B-cell origin, monoclonal and polyclonal forms	100% of CNS lymphomas in HIV-1-positive patients; Systemic - 90% diffuse large cell lymphomas, 40% small non-cleaved cell lymphadenopathies (Burkitt lymphomas) EBV-associated; 60% EBV associated in post-transplant lymphoproliferative disease
Extra nodal NK/T-cell lymphoma	Lymphoid tissue; extra nodal; diffuse lymphocytic infiltrate and vascular damage	NK and T cells; most cases are NK cell neoplasms, some have a cytotoxic T-cell phenotype; monoclonal	100% in nasal variant

Neoplasm	Clinical Presentation	Lineage and Primary Tumor Cell; Evidence of EBV Clonality[a]	Percent of Tumors or Tumor Cells EBV Positive; Clonality
NPC	Epithelial tissue; strong ethnic and geographic association: Inuit, Southern Asia, China; keratinizing and non-keratinizing forms	Nasal epithelial cells; monoclonal	98% in non-keratinizing carcinoma; clonal detection in precancers (Pathmanathan et al. 1995; Tsang et al. 2014; Tsao et al. 2015)
Gastric cancer	Epithelial tissue; 89% with lymphocytic infiltration; proximal stomach or associated with stomach remnant	Gastric epithelial cells; monoclonal	9% of gastric cancers
LEC of the salivary gland	Epithelial tissue and non-cancerous lymphoid cells	Salivary gland epithelial cells; monoclonal (few samples)	Primarily parotid salivary gland

Sources: Information from IARC (1997a; 2012) unless cited in the table.
LEC = lymphoepithelial cancer; NPC = nasopharyngeal carcinoma.
[a]Evidence of clonality of virus in tumor tissue.

4.2. EBV Latent Genes and Malignant Transformation

EBV in its latent phase can express different transcription programs (0, I, II, III). In an immunocompetent host, EBV persists in memory B cells as a latent infection (latency 0). Since no proteins are produced during latency 0, the presence of the virus is not recognized by the immune system, resulting in lifetime infection. EBV-encoded small RNAs (EBERs) and microRNAs are expressed in all latency phases and approximately 22 microRNAs have been identified (IARC 2012). MicroRNAs have been shown to have a role in transformed growth properties of EBV-infected cells (Marquitz et al. 2012). NF-kB and Wnt pathways, and apoptosis and immune activation processes, are known to be regulated by EBV microRNAs (Skalsky and Cullen 2015). EBERs and microRNAs as well as the full complement of latent gene proteins are expressed in latency III. Latent gene proteins consist of six nuclear antigens (EBNAs), and three latent membrane proteins (LMPs) (IARC 2012; Yau et al. 2014). EBV transcripts include coding and non-coding RNAs and proteins produced during latency phases (see Table 1-1). Primarily latency II, but also latency I and III phases, promote acquisition of various cancer hallmarks, e.g., insensitivity to antigrowth signals, avoiding cell-cycle arrest, immune evasion, genetic instability, cell proliferation, resisting apoptosis, promotion of angiogenesis, and induction of genomic instability (Mesri et al. 2014). Table 1-1 relate their expression pattern to that found in various neoplasias. The general functions of key viral proteins and transcripts important in the pathogenesis of EBV-associated cancers are described in Table 4-2.

Table 4-2. Activation of Oncogenic Pathways by Viral Genes

EBV Transcription Program and Gene Products	Some Host Pathways Affected	Potential Cancer Property	Associated Malignancies[a]
Latency 0: EBERs	–	Promote growth, anti-apoptotic	None
Latency I: EBNA-1, EBERs	Regulation of RAG-1 and RAG-2 by EBNA-1	Resisting cell death, avoiding immune destruction, genome instability, increase in reactive oxygen species	Burkitt lymphoma and gastric carcinoma[b]
Latency II: EBNA-1, LMP-1, LMP-2A, EBERs	NFkB, JNK by LMP-1	Resisting cell death, enabling replicative immortality, angiogenesis, inflammation	NPC, Hodgkin lymphoma, NK and T-cell lymphoma, nasal type[c], LEC of the salivary gland
Latency III: EBNA-1, -2, -3A, -3B, -3C, -LP, LMP-1, LMP-2A, LMP-2B, EBERs	PI3K-Akt-mTOR, ERK by LMP-2A	Inducing angiogenesis, sustaining proliferative signaling, deregulation of cellular pathways, activation of invasion and metastasis, enables replicative immortality, activation of host methyltransferase	Immunosuppression-related NHL (AIDS-associated, post-transplant disorder, iatrogenic)
MicroRNAs[d]	Repression of translation	Immune evasion	–

Sources: Grywalska and Rolinski (2015); IARC (2012); Mesri et al. (2014).
EBER = EBV-encoded small RNA; EBNA = EBV nuclear antigen; LMP = latent membrane protein; EBNA-LP = EBV nuclear antigen leader protein; NHL = non-Hodgkin lymphoma; LEC = lymphoepithelial cancer; NPC = nasopharyngeal carcinoma.
[a]General classification of disease and heterogeneous patterns may be present in different cell populations in same individual.
[b]Expression of lytic genes and LMP-2A variable.
[c]Previously called sinonasal angiocentric T-cell lymphoma.
[d]In latency I, II, III microRNAs (at least 22) are expressed in various amounts.

4.3. Mode of Action and Evidence for Cancer Causation

Direct evidence for causality of EBV in lymphomagenesis comes from in vitro studies and studies in mice. EBV has been shown to transform lymphoblastoid cells in culture and can transform epithelial cells when co-cultured with transformed lymphoblastoid cells (Imai et al. 1998). In addition, lymphoblastoid cells transfected with activated *c-myc* genes were tumorigenic in nude mice, and infected B cells have been shown to cause B-cell lymphomas in SCID mice (Lombardi et al. 1987; Mosier et al. 1989; Rowe et al. 1991). In order to understand the contribution of viral and host factors in development of lymphomas, humanized mouse models using transplanted human fetal hematopoietic stem cells and lymphoid tissue are under development (Cocco et al. 2008; Ma et al. 2011).

EBV proteins, EBNA-1, -2, -3A, -3C, and LMP-1 are all necessary for immortalization of B-lymphocytes (Grywalska and Rolinski 2015). Clearly, EBV has oncogenic potential to transform lymphoid and epithelial cells in culture and has been found associated with cancers of epithelial and lymphoid origin. EBV is a ubiquitous virus, and criteria have been outlined by IARC as well as discussed by others for judging cancer causality by viruses (IARC 1997a; zur Hausen 2001) (see the Introduction and Methods section). The key causality criteria included the following: (1) the presence of the virus in the tumor, (2) monoclonality of EBV in the tumor (suggesting the presence of latent infection prior to expansion of the malignant clone), and (3) expression of viral proteins in pre-neoplastic lesions and in malignant tissue (IARC 1997a). The epidemiological and experimental data show that EBV meets these criteria. The mode(s) of action and evidence linking EBV with cancer are briefly reviewed by tumor type in the following sections.

4.3.1. Burkitt Lymphoma

Burkitt lymphoma is a B-cell non-Hodgkin lymphoma that presents mostly as an extranodal mass, although nodal involvement is seen in sporadic cases. In normal lymphoid tissue, B-cell response to antigenic stimulation produces B cytoblasts that differentiate into plasma cells that produce antibodies. In Burkitt lymphoma, B-cell differentiation in response to antigen stimulus undergoes faulty DNA recombination in the lymphoid tissue germinal center resulting in immunoglobulin gene/c-*myc* translocation. This results in constitutive expression of the c-*myc* oncogene driven by immunoglobulin promoters and is the primary lesion in Burkitt lymphoma. From human cancer studies, it is known that endemic Burkitt lymphoma is associated with chronic antigenic stimulation found with malarial infection, and B cells infected with EBV have latency I EBV gene expression pattern. Malarial infections can promote B-cell hyperplasia and increase the chances that B-cell translocations will occur. Moreover, malarial infection has been shown to directly increase the number of germinal center translocations occurring via deregulation of activation-induced cytidine deaminase, an enzyme responsible for class switch recombination and somatic hypermutation, in the germinal center (Torgbor et al. 2014). Normally, defective cells exiting the germinal center undergo apoptosis; however, it has been shown that EBV expression of EBNA-1 rescues defective B cells from removal by apoptosis by directly upregulating survivin production by complexing with SP1 on the *survivin* gene promoter (Kennedy et al. 2003; Lu et al. 2011). This would potentially result in more Burkitt lymphoma cells forming in the germinal center with malarial infection, and EBV cells expressing EBNA-1 would be the ones that survive.

Other lines of evidence linking EBV and Burkitt lymphoma include the following:

- EBV is associated with all three clinical forms of Burkitt lymphoma (endemic, sporadic, immune suppression related) (IARC 1997a; 2012).
- EBV DNA is present in Burkitt lymphoma cells in monoclonal form (IARC 1997a).
- Both malaria and EBV cause B-cell hyperplasia, and increase in B cells could increase the probability of a faulty gene translocation (Robbiani et al. 2015; Torgbor et al. 2014).
- EBNA-1 prevents apoptosis of Burkitt lymphoma cells and enables cell survival (Kennedy et al. 2003; Lu et al. 2011).

4.3.2. Hodgkin Lymphoma

Hodgkin lymphoma is a group of lymphoid neoplasms arising from a single lymph node, spreading to contiguous lymph nodes, and containing Hodgkin Reed-Sternberg cells, which are giant multinucleated neoplastic cells of clonal B-cell origin (Stein et al. 2008). Over 90% of the tumor is characterized by non-malignant inflammatory cells (i.e., reactive lymphocytes, macrophages, granulocytes, and fibrocytes) and fibrosis. Based on histopathology, Hodgkin lymphoma is divided into classical (with four subtypes: mixed cellularity, nodular sclerosis, lymphocyte depleted, and lymphocyte rich) and nodular lymphocyte-predominant Hodgkin lymphoma, an uncommon form that is almost always EBV negative (Stein et al. 2008). Hodgkin lymphomas account for approximately 30% of all lymphomas worldwide; however, as noted in Table 4-1, the degree of EBV infection varies among different subtypes of classical Hodgkin lymphoma (IARC 1997a; 2012).

Unlike germinal center maturation of B lymphocytes to plasma cells or memory B lymphocytes, Hodgkin Reed-Sternberg cells have not undergone somatic hypermutation and do not express immunoglobulins or most B-cell specific genes. These cells do reveal deregulation of multiple signaling pathways such as NF-κB, JAK/STAT, MAP kinase, PI3-kinase/AKT and produce an abnormal pattern of release of cytokines and chemokines resulting in a local inflammatory response. LMP-1 has been shown to be a transforming oncogene in cell culture and promotes growth and survival of Hodgkin Reed-Sternberg cells through upregulation of these pathways (Mohamed et al. 2014). EBV expresses type II latency genes (Table 4-2) in Hodgkin Reed-Sternberg cells (IARC 1997a; 2012).

Further evidence that supports EBV infection as a causal agent in some forms of Hodgkin lymphoma is as follows (IARC 2012)

- Monoclonal EBV episomes are detected in Hodgkin Reed-Sternberg cells indicating that EBV infection has occurred before clonal expansion.
- Antibody titers to EBV viral capsid antigens are increased with Hodgkin lymphoma.
- The risk of Hodgkin lymphoma increases 4-fold with a previous history of infectious mononucleosis.

4.3.3. Immunosuppression-related Non-Hodgkin Lymphoma (HIV-1-positive and Post-transplant Lymphoproliferative Disease)

EBV infection in a severely immunocompromised host can lead to immunosuppression-related non-Hodgkin lymphoma. EBV-related non-Hodgkin lymphomas have been linked to immunosuppression therapies related to transplant of organs or cells (stem cells or bone marrow), and to severe immune suppression as a result of HIV-1 infection (Pietersma et al. 2008). The link between immune suppression and non-Hodgkin lymphoma caused by EBV has been characterized from studies measuring viral load and EBV-specific cytotoxic T lymphocytes in the blood of patients with severe immune suppression (acquired immune deficiency syndrome, AIDS) or with post-transplant lymphoproliferative disorders (Gulley and Tang 2010; IARC 1997a; 2012). Post-transplant lymphoproliferative disorder occurs in approximately 0.5% to 1% overall of kidney or bone marrow transplants and varies with the patient age and type of transplant (Vegso et al. 2011). Early lesions are often polyclonal and, if untreated, continued B-cell proliferation driven by active EBV will generate a neoplastic clone (Gulley and Tang 2010).

With HIV-1 infection, perturbations in the immune system and loss of lymphocytes decrease immune surveillance. Central nervous system non-Hodgkin lymphoma may result from HIV-1-related profound immunosuppression; 100% of these lymphomas are associated with EBV (IARC 1997a). In addition, there is evidence of clonality of EBV and production of LMP-1, an oncoprotein, by EBV in HIV-associated central nervous system non-Hodgkin lymphoma tissues (IARC 1997a). EBV is also associated with a large percentage of systemic AIDS-related non-

Hodgkin lymphomas with up to 90% of diffuse large cell lymphomas and in approximately 40% of small non-cleaved cell lymphadenopathies associated with EBV (IARC 1997a).

Patients receiving transplants but not previously infected with EBV, such as children, are at a greater risk of developing non-Hodgkin lymphoma from infected transplant tissue or from transmission of EBV in saliva from an infected person. Polymorphic post-transplant lymphoproliferative disease appears early after transplant procedure (<1 year) in children and is associated with a primary EBV infection (Vegso et al. 2011). Most of the post-transplant lymphoproliferative disease lesions are of B-cell origin (85%) and >90% are associated with EBV infection (IARC 2012; Taylor et al. 2005; Vegso et al. 2011). The most common EBV gene expression pattern with post-transplant patients is latency III growth pattern (Carbone et al. 2008) (see also Table 1-1).

Evidence that EBV is causal in some cases of immunosuppression-related non-Hodgkin lymphoma includes the following (Lim et al. 2006):

- Treatment with EBV-specific cytotoxic lymphocytes results in decreases in EBV viral load and in tumor size.
- Further administration of EBV-specific cytotoxic lymphocytes to an immune-suppressed individual can protect against lymphoma development.
- In organ or cell transplant cases, decreasing therapy for immunosuppression can decrease viral load and tumor size. Not all cases of post-transplant lymphoproliferative disease or lymphoproliferative disease with HIV-1 are related to EBV infection, but reactivation of a latent infection or initiation of a primary EBV infection can lead to lymphoproliferative disease.

4.3.4. Extranodal NK/T-cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, previously known as angiocentric T-cell lymphoma, is a rare EBV-associated lymphoma that has a higher prevalence in South America, Mexico, and Asia than in the United States. NK/T-cell lymphomas are classified by location of the tumor to nasal, intestinal, and subcutaneous panniculitis-like lymphomas. The amount of association of these lymphomas with EBV varies with tumor site, geographic location, and genotype of the patient (Ambinder and Cesarman 2007).

EBV expresses type II latency genes (Table 4-2) in this cancer. LMP-1, an EBV-specific oncoprotein, has been shown to be a transforming protein in cell culture and promotes cell growth and survival through upregulation of NF-κB, JAK/STAT, MAP kinase, PI3-kinase/AKT pathways (IARC 2012). Kanemitsu et al. (2012) examined 30 cases of nasal type NK/T-cell lymphoma, for expression profile of EBV-encoded protein; results show that all tissues were positive by immunohistochemistry for EBER, none were positive for EBNA-2, and LMP-1 was positive in 22 cases and correlated with a localized disease ($p = 0.06$). Furthermore, nuclear localization of phosphorylated RelA (NF-κB) and phosphorylated Akt (PI3K) were observed in conjunction with positive cases ($p < 0.002$ and $p < 0.001$, respectively). RNA silencing experiments of LMP-1 correlated with decreased phosphorylation of RelA and Akt in vitro providing evidence that EBV LMP-1 expression was in part enhancing NFκB and PI3K expression.

Additional evidence that supports EBV infection as a causal agent in some forms of NK/T-cell lymphoma is as follows:

- Nasal type NK/T-cell lymphoma presents as a localized disease with near 100% positivity for EBV (IARC 1997a).
- EBV is clonal in these nasal tumors (IARC 1997a).
- Viral proteins (LMP-1) associated with EBV latency II gene expression pattern are present in these tumors (IARC 2012).

4.3.5. Nasopharyngeal Carcinoma

Research efforts have focused on addressing biological properties of EBV that may result in differences in nasopharyngeal cancer incidence among different populations. Initial characterization relied on the use of restriction enzymes to identify DNA polymorphisms describing EBV strain variation in different populations. Genome sequence analysis identified specific genetic variants (such as in LMP-1) that could potentially enhance transforming potential and virulence of EBV and enable variants of LMP-1 to evade immune recognition (Raab-Traub 2002). In addition, multiple EBV microRNAs have immune evasion functions (Tsao et al. 2015). Whole-EBV genome sequencing studies have revealed that the nasopharyngeal carcinoma-derived EBV strains from endemic regions vary and show significant differences from the reported EBV genomes from non-endemic populations (Liu et al. 2011). A review by Lung et al. (2014) lists oncogenes and tumor suppressor genes important in nasopharyngeal carcinoma development and the effects of EBV infection on regulation of gene expression. The findings suggest the existence of disease-specific viral variations that may possess higher oncogenic properties, propensity for infection of epithelial cells, and persistence of the latency II program, or less efficiency in inducing host immune response, especially in the nasopharyngeal carcinoma endemic population (Liu et al. 2011). Linkage analysis of susceptible Chinese populations has demonstrated an association between nasopharyngeal carcinoma risk and allelic variations in human leukocyte antigen (HLA), a part of the MHC I complex of immunosurveillance. A consistent association between nasopharyngeal carcinoma and a Chinese HLA subtype, as compared to a Caucasian subtype, was detected by a genotyping study (Hildesheim et al. 2002). Multiple areas of hypermethylation are present in the nasopharyngeal carcinoma genome resulting in inactivation of tumor suppressor genes (e.g., *p16* and *RASSF1A*) and disruption of cell functions (i.e., cell-cycle controls, signal transduction, apoptosis, and DNA repair) (Kwong et al. 2002). As the efficiency of sample collection and genetic assays improve and are replicated, more details of host-virus interactions will likely be found.

Evidence that EBV is a primary causal factor in nasopharyngeal carcinoma is as follows:

- Clonal EBV episomes are detected in undifferentiated tumors (Liu et al. 2011).
- Studies showing early preneoplastic nasopharyngeal lesions (dysplastic lesions, carcinoma in situ) but not normal tissues are also infected with EBV and express latency II program gene products (IARC 2012; Pathmanathan et al. 1995; Raab-Traub 2002; Tsang et al. 2014; Tsao et al. 2015).

4.3.6. Gastric Carcinoma

Gastric cancer is a common cancer, and it is estimated that EBV is a causal factor in 5% to 10% of all gastric cancers worldwide. Latency I/II patterns of EBV gene expression are found in these cancers with approximately 50% expressing LMP-2A which activates the NF-κB survival pathway (IARC 2012).

Molecular studies in humans provide strong evidence of an association between EBV and some gastric cancers. These studies show that EBV is found as a monoclonal form in a subset of human gastric cancers. Moreover, the virus produces oncogenic proteins in gastric cancer tissue that promote cell division, cell survival, and oncogenic transformation, and produces a unique molecular profile in genomic studies of gastric tumors. Recent comprehensive molecular work by the Cancer Genome Atlas Research Network (2014) has resulted in the identification of four distinct molecular profiles of gastric cancer, as described below. Primary gastric tumors from 295 untreated patients were analyzed and blood or non-malignant gastric tissue was used as reference for somatic alterations in the tumors. Non-malignant gastric tissue was also collected for DNA methylation and expression analyses and six molecular testing platforms were used to analyze the tissue (Cancer Genome Atlas Research Network (2014)), reviewed by Gulley (2015)). Four distinct molecular profiles were discerned for gastric cancer: EBV-positive, microsatellite instability (MSI), chromosome instability (extensive somatic copy-number aberrations [SCNAs], and genomically stable. Molecular features unique to all EBV-positive gastric cancers were also identified: hypermethylation of promoter regions resulting in gene down-regulation or silencing, mutations and gene amplifications, and expression of multiple noncoding viral RNAs. The EBV-positive group had a distinctive genetic profile, marked CpG methylation, including *CDKN2A* (*p16*, tumor suppressor gene), a strong immune-cell presence, and evidence of an IL-12-mediated signaling response. Some of the more frequent genetic changes are listed in Table 4-3. Promoter hypermethylation affected genes involved in cell-cycle regulation (*CDKN2A - p16*), DNA repair (*GSTP1*), cell adhesion and metastases (*TIMP1*), apoptosis (*bcl-2*), and signal transduction (*PTEN*). JAK2 was amplified in 12% of the EBV-positive tumors. A gene locus, 9p24.1, was linked to overexpression and amplification of JAK2, and CD274 (PD-L1) and PDCD1LG2 (PD-L2) in approximately15% of the EBV tumor subgroup. PD-L1 and PD-L2 signaling cascades prevent T-cell proliferation and aid in escape of the cancer from immune surveillance. Further, EBV-positive tumors had mutations in PIK3CA (10% to 72%), ARID1A (47% to 55%), AKT2 (38%), TGFBR1 (25%), CCNA1 (25%), BCOR (23%) and MAP3K4 (21%), but rarely in *TP53*. In addition, multiple noncoding viral RNAs as well as viral LMP1, LMP2A, and EBNA1 were consistently expressed at low levels (Gulley 2015). From this unique molecular profile and the presence of activated EBV within gastric tissue, it is apparent that EBV is causal for tumor promotion. However, the pathogenesis of EBV activation in this form of gastric cancer has not been resolved.

Table 4-3. Properties of Some Known Signaling Pathways Altered with EBV-related Gastric Cancer

Signaling Pathway	Effects
MicroRNAs	Unknown
CDKN2A (p16)	Tumor suppressor gene; slows progression from G1 to S phase

Signaling Pathway	Effects
JAK2	Cell growth and division
PI3K/Akt	Cell growth and division; inhibits apoptosis, promotes genomic instability, cytoskeleton change; LMP-2 activates
ERBB2	Cell growth and division
ARID1A	Cell-cycle progression
BCOR	Transcription and chromatin regulation
CD274 (PD-L1)	Immunosuppression
PDCD1LG2 (PD-L2)	Immunosuppression
IL-12	Immune-cell stimulation in response to antigen
NF-κB	Resists apoptosis, cell proliferation; LMP-2A activates

Source: Gulley (2015).

4.3.7. Lymphoepithelial Cancer of Salivary Glands

Lymphoepithelial carcinomas and their association with EBV have been reported most frequently in gastric cancer and in cancer of the salivary glands but less frequently in some other epithelial malignancies such as lung and skin (IARC 1997a; 2012). For cancer of the salivary glands, it is hypothesized that the close proximity of the salivary glands to the oropharyngeal area would increase exposure of these glands to the lytic form of EBV in the saliva. IARC (1997a; 2012) reported a number of case-series studies detecting EBV DNA in lymphoepithelial carcinoma of the salivary glands and a case-case study presented evidence of EBV DNA in salivary tumors with lymphoepithelial histology, but not in salivary tumors of other histology (Wang et al. (2004), as reported in IARC (2012)). As reported by IARC, viral EBER RNA and LMP-1 protein were detected in tumor tissue from 10 cases of lymphoepithelial carcinoma of the salivary gland from a Chinese population (Leung et al. 1995). Clonal EBV termini were associated with undifferentiated carcinoma of the parotid glands (two tumors from American Inuit) and EBER-1 RNA, LMP-1 RNA and *Bam*HI-A rightward reading frame were expressed in the malignant cells (Raab-Traub et al. 1991). In both studies, an episomal form of EBV was detected in the tumor tissue, but no EBV was detected in normal adjacent tissue. These data provide evidence for the presence of EBV in lymphoepithelial cancer of salivary glands. However, the level of evidence from mechanistic data is inadequate to assess whether EBV is carcinogenic in epithelial cells of the salivary gland since the mechanism has not been elucidated.

4.4. Synthesis

EBV is highly prevalent and results in a life-long latent infection that is refractory to immune recognition. Activated EBV transcription programs mimic B-cell proliferation and survival and in some cases result in cancer. However, as with other oncoviruses, EBV infection alone is necessary but not sufficient for cancer development.

The latency patterns of EBV are associated with specific cancers and factors including immunosuppression, infectious agents, regional differences in diet, and host genetic susceptibility; all of which potentially have a role in cancer development. In primary EBV infection of naïve B cells, growth and differentiation occur due to the latency III transcription pattern that is highly immunogenic. Factors causing immunosuppression such as HIV-1 infection or post-transplant therapies enable the latency III pattern to continue, resulting in dysregulation of cellular pathways leading to non-Hodgkin lymphoma or post-transplant lymphoproliferative disease.

Immune pressure promotes selection to latency II or I patterns, which are less immunogenic. Endemic Burkitt lymphoma is associated with co-infection with the malaria parasite, *P. falciparum,* which further enhances B-cell proliferation and genetic instability of latency I pattern, resulting in *c-myc* translocation and overexpression. Hodgkin lymphoma, NK/T-cell lymphoma, nasopharyngeal carcinoma, and some gastric and salivary gland lymphoepithelial cancers all express EBV latency II program. Expression of EBV latent genes LMP-1 and LMP-2 result in dysregulation of host cellular pathways and promotes oncogenesis. In addition, the genotypes of both the host and the virus, as well as dietary factors, have been linked to the prevalence of nasopharyngeal carcinoma.

5. Overall Cancer Hazard Evaluation and Listing Recommendation

Epstein-Barr virus (EBV) is known to be a human carcinogen based on sufficient evidence from studies in humans. This conclusion is based on epidemiological studies showing that it causes endemic Burkitt lymphoma (Table 5-1), Hodgkin lymphoma (Table 5-2), immunosuppression-related non-Hodgkin lymphoma (Table 5-3), nasal type NK/T-cell leukemia/lymphoma, (Table 5-4), nasopharyngeal carcinoma (Table 5-5), and gastric cancer (Table 5-6) in humans, together with supporting evidence from mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans. There is also limited evidence for an association with Burkitt lymphoma (sporadic) (Table 5-1) and lymphoepithelial cancer of the salivary gland (Table 5-7) from studies in humans.

The following tables provide the level of evidence recommendations for the carcinogenicity of EBV for each tumor endpoint from studies in humans, including the key data from both epidemiological and molecular studies.

Table 5-1. Summary of the Evidence for EBV and Burkitt Lymphoma (Endemic or Sporadic) from Human Studies

Types of Studies	Burkitt Lymphoma (Endemic)	Burkitt Lymphoma (Sporadic)
Epidemiological Number of studies reporting a positive association[a]	EBV antibodies or DNA: 8/8 case-control studies (993 cases) & 1 cohort study (16 cases) All statistically significant; high RRs/ORs Dose response with viral titer in cohort study and several case-control studies	EBV antibodies: 4/5 case-control studies (113 cases) Mostly statistically non-significant; moderate ORs
Molecular (human tissue)		
Clonality for EBV	Monoclonal	NA
% EBV-infected tumors	95%	20%
EBV protein expression	EBNA-1	NA
Level of evidence	**Sufficient**	**Limited**

EBNA = Epstein-Barr nuclear antigen; EBV = Epstein-Barr virus; NA = not available; OR = odds ratio; RR = risk ratio.

[a] The number of studies is based on those reporting risk estimates.

Table 5-2. Summary of the Evidence for EBV and Hodgkin Lymphoma from Human Studies

Types of Studies	Hodgkin Lymphoma
Epidemiological Number of studies reporting a positive association (OR > 1.2)[a]	EBV DNA: 3/3 case-control studies; very high ORs EBV antibodies: 17/20 case-control studies & 1 nested case-control study; mostly statistically significant OR between 4 & 19 Infectious mononucleosis: 10/11 case-control studies and 7/7 cohort studies with modest ORs/RRs

Types of Studies	Hodgkin Lymphoma
Molecular (human tissue)	
Clonality for EBV	Monoclonal
% EBV-infected tumors	20%–50% North America and Europe; 65% Asia; 90%–100% Africa and South America
EBV protein expression	LMP-1, -2A in 50% of cases
Level of evidence	**Sufficient**

EBV = Epstein-Barr virus; LMP-1 = latent membrane protein 1; LMP-2A = latent membrane protein 2A; OR = odds ratio.
[a]The number of studies is based on those reporting risk estimates.

Table 5-3. Summary of the Evidence for EBV and Immunosuppression-related Non-Hodgkin Lymphoma (NHL) from Human Studies

Types of Studies	Immunosuppression-related NHL
Epidemiological	Consistent evidence in case-series studies Elevated statistically non-significant increase with EBV antibodies in one nested case-control study
Molecular (human tissue)	
Clonality for EBV	Monoclonal
% EBV-infected tumors	100% (CNS + HIV-1) >50% post-transplant lymphoproliferative disease
EBV protein expression	LMP-1, -2A, -2B, EBNAs; EBV-specific cytotoxic
Other	T-cells protect against or reduce viral load and tumor size
Level of evidence	**Sufficient**

CNS = central nervous system; EBNA = Epstein-Barr nuclear antigen; EBV = Epstein-Barr virus; HIV-1 = human immunodeficiency virus type 1; LMP-1 = latent membrane protein 1; LMP-2A = latent membrane protein 2A; LMP-2B = latent membrane protein 2B.

Table 5-4. Summary of the Evidence for EBV and NK/T-Cell Leukemia/Lymphoma, Nasal Type from Studies in Humans

Types of Studies	NK/T-Cell Leukemia/Lymphoma, Nasal Type
Epidemiological	Consistent evidence in case-series studies; at least 16 case series with more than 400 cases Two case-comparison studies: EBV DNA found in plasma or CD3+ cells from cases but not from controls
Molecular (human tissue)	
Clonality for EBV	Monoclonal
% EBV-infected tumors	100%
EBV protein expression	EBNA-1, LMP-1, -2A
Other	EBV found in majority of CD56+ tumors
Level of evidence	**Sufficient**

EBNA = Epstein-Barr nuclear antigen; EBV = Epstein-Barr virus; LMP-1 = latent membrane protein 1; LMP-2A = latent membrane protein 2A.

Table 5-5. Summary of the Evidence for EBV and Nasopharyngeal Carcinoma from Human Studies

Types of Studies	Nasopharyngeal Carcinoma
Epidemiological Number of studies reporting a positive association[a]	EBV antibody: 11/11 case-control and two cohort studies; high to very high statistically significant RRs; no association in two small-nested case-control studies EBV DNA: 6/6 case-control studies; very high RR
Molecular (human tissue)	
Clonality for EBV	Monoclonal in precancer/cancer
% EBV-infected tumors	98% in non-keratinizing tumors
EBV protein expression	EBNA-1, LMP-1, -2A
Level of evidence	**Sufficient**

EBNA = Epstein-Barr nuclear antigen; EBV = Epstein-Barr virus; LMP-1 = latent membrane protein 1; LMP-2A = latent membrane protein 2A; RR = risk ratio.

[a] The number of studies is based on those reporting risk estimates.

Table 5-6. Summary of the Evidence for EBV and Gastric Cancer from Human Studies

Types of Studies	Gastric Cancer
Epidemiological Number of studies reporting a positive association	3/3 case-control studies (77 EBV cases/184 gastric); statistically significant high ORs 2/3 nested case-control studies; statistically non-significant modest ORs; statistically significant elevated mean EBV antibodies for EBV-positive cases in one study compared to controls
Molecular (human tissue)	
Clonality for EBV	Monoclonal
% EBV-infected tumors	8%–11%
EBV protein expression	EBNA-1, LMP-2A (variable expression)
Other	Unique molecular profile
Level of evidence	***Sufficient***

EBNA = Epstein-Barr nuclear antigen; EBV = Epstein-Barr virus; LMP-1 = latent membrane protein 1; LMP-2A = latent membrane protein 2A; OR = odds ratio.

Table 5-7. Summary of the Evidence for EBV and Lymphoepithelial Carcinoma of the Salivary Gland from Human Studies

Types of Studies	Lymphoepithelial Carcinoma/Salivary Gland
Epidemiological	No case-control or cohort studies available to evaluate these cancers although one case-case study found EBV DNA in salivary gland lymphoepithelial carcinoma tumors but not other types of salivary gland tumors

Types of Studies	Lymphoepithelial Carcinoma/Salivary Gland
Molecular (human tissue)	
Clonality for EBV	Monoclonal (four samples from two studies)
% EBV-infected tumors	Close to 100% (208/209 cases) in Asian, Greenland, and Eskimo populations; variable in few cases in Western populations
EBV protein expression	EBNA-1, LMP-1
Other	Mechanism(s) in epithelial cells unknown
Level of evidence	**Inadequate**

EBNA = Epstein-Barr nuclear antigen; EBV = Epstein-Barr virus; LMP-1 = latent membrane protein 1

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Glossary

Affinity: A measurement of the strength of interaction between an epitope and an antibody's antigen binding site.

Case report: Detailed descriptions of a few patients or clinical cases (frequently, just one sick person) with an unusual disease or complication, uncommon combinations of diseases, an unusual or misleading semiology, cause, or outcome (maybe a surprising recovery). They often are preliminary observations that are later refuted. They cannot estimate disease frequency or risk (e.g., for lack of a valid denominator).

Case series: A collection of subjects (usually, patients) with common characteristics used to describe some clinical, pathophysiological, or operational aspect of a disease, treatment, exposure, or diagnostic procedure. A case series does not include a comparison group and is often based on prevalent cases and on a sample of convenience. Common selection biases and confounding severely limit their power to make causal inferences.

Case-comparison study (case-control study, case referent study): The observational epidemiological study of persons with the disease (or another outcome variable) of interest and a suitable control group of persons without the disease (comparison group, reference group). The potential relationship of a suspected risk factor or an attribute to the disease is examined by comparing the diseased and non-diseased subjects with regard to how frequently the factor or attribute is present (or, if quantitative, the levels of the attribute) in each of the groups (diseased and non-diseased).

Convenience sample: Samples selected by easily employed but basically non-probabilistic (and probably biased) methods. "Man-in-the-street" surveys and a survey of blood pressure among volunteers who drop in at an examination booth in a public place are in this category.

Defining acquired immune deficiency syndrome (AIDS) condition: Any HIV-related illness included in the Centers for Disease Control and Prevention's (CDC) list of diagnostic criteria for AIDS. AIDS-defining conditions include opportunistic infections and cancers that are life threatening in a person with HIV.

Diagnostic criteria: The specific combination of signs, symptoms, and test results that a clinician uses to identify a person as representing a case of a particular disease or condition.

Enzyme immunoassay: An assay that uses an enzyme-bound antibody to detect antigen. The enzyme catalyzes a color reaction when exposed to substrate.

Exposure variability: A characteristic describing whether epidemiological studies included non-exposed cases or exposed controls. Lack of exposure variability may contribute to observed heterogeneity of study results.

Germinal center: Discrete areas within secondary lymphoid tissues where B-cell maturation and memory development occur.

In situ hybridization: A technique that allows for precise localization of a specific segment of nucleic acid within a histologic section. The underlying basis of in situ hybridization is that nucleic acids, if preserved adequately within a histologic specimen, can be detected through the application of a complementary strand of nucleic acid to which a reporter molecule is attached.

EBV latency patterns: Particular EBV viral gene expression patterns that establish distinct EBV latent infection statuses (latency types III, II, and I).

Latent phase: A phase of the virus life cycle during which the virus is not replicating.

Lytic phase: A phase of the virus life cycle during which the virus replicates within the host cell, releasing a new generation of viruses when the infected cell lyses.

Monoclonal: Pertaining to or designating a group of identical cells or organisms derived from a single cell or organism.

Nude mouse (athymic nude mouse): A type of laboratory mouse that is hairless, lacks a normal thymus gland, and has a defective immune system because of a genetic mutation. Athymic nude mice are often used in cancer research because they do not reject tumor cells, from mice or other species.

Open reading frame: A portion of a DNA molecule that, when translated into amino acids, contains no stop codons.

Optical density: The absorbance of a particular substance at a specified wavelength in an enzyme-linked immunosorbent assay.

Peripheral blood: Blood circulating throughout the body; the primary method for transporting nutrients such as oxygen and carbon dioxide through the body consisting of three primary components: erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (blood platelets).

Polyclonal: Pertaining to or designating a group of cells or organisms derived from several cells.

Titer: A laboratory measurement of the concentration of a substance in a solution (e.g., an antibody titer measures the presence and amount of antibodies in the blood).

Abbreviations

AIDS	acquired immune deficiency syndrome
AKT	serine/threonine kinase *Akt* (also known as protein kinase B or PKB)
BARF1	*Bam*HI A rightward fragment 1 (micro RNA)
BL	Burkitt lymphoma
CDC	Centers for Disease Control and Prevention
CF/S	complement-fixing soluble antigen
CI	confidence interval
CNS	central nervous system
DNA	deoxyribonucleic acid
EA	early antigen
EA(D)	early antigen-diffuse
EBER	EBV-encoded small RNA
EBNA	EBV nuclear antigen
EBNA-LP	EBV nuclear antigen leader protein
EBV	Epstein-Barr virus
EIA	enzyme immunoassays
GC	germinal center
HHV4	human herpesvirus 4
HIV	human immunodeficiency virus
IARC	International Agency for Research on Cancer
HLA	human leukocyte antigen
IFA	indirect immunofluorescence assay
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
LEC	lymphoepithelial cancer
LMP	latent membrane protein
LMP-1	latent membrane protein 1
LMP-2	latent membrane protein 2
LMP-2B	latent membrane protein 2B
MALT	mucosa-associated lymphoid tissue

NHL	non-Hodgkin lymphoma
NPC	nasopharyngeal carcinoma
NHANES	National Health and Nutrition Examination Survey
NR	not reported
NS	not statistically significant
NTP	National Toxicology Program
OD	optical density
OR	odds ratio
ORF	open reading frames
PCR	polymerase chain reaction
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PTEN	phosphatase and tensin homologue
PTLD	post-transplant lymphoproliferative disorders
Q-PCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
RR	relative risk
RT-PCR	reverse transcriptase-polymerase chain reaction
SCNA	somatic copy-number aberrations
SEER	Surveillance, Epidemiology, and End Results Program
SIR	standardized incidence ratios
USA	United States of America
VCA	viral caspid anigen

Appendix A. Literature Search Strategy

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The objective of the literature search approach is to identify published literature that is relevant for evaluating the potential carcinogenicity of the Epstein-Barr Virus (EBV). As discussed in the Viruses Concept Document (https://ntp.niehs.nih.gov/ntp/roc/concept_docs/2014/virusesconcept_508.pdf), the monograph relies on the IARC monograph and studies published since the monograph (new studies). The literature search strategy was used to identify new human cancer studies and recent reviews of mechanistic data.

A.1. General Approach

Database searching encompasses selecting databases and search terms and conducting the searches. Searches of several citation databases are generally conducted using search terms for the individual viruses of interest, combined with search terms for cancer and/or specific topics, including epidemiological and mechanistic studies. A critical step in the process involves consultation with an information specialist to develop relevant search terms. These terms are used to search bibliographic databases. IARC used literature found by searching PubMed for EBV through 12/2008, so PubMed, Web of Science and Scopus were searched for new information about EBV from >2008 to August 2015. Table A-1 highlights the general concepts searched with selected example terms. To review all the terms used, please refer to the full search strings below.

Table A-1. Major Topics Searched

Topics	Example Terms
Epstein-Barr virus *NOT post-transplant	Epstein-Barr virus infections (MeSH), EBV infection, herpes virus 4, herpesvirus 4, human (MeSH)
General cancer	*Neoplasms (MeSH), tumor(s), leukemia, cancer*
Relevant cancers	Gastric cancers, stomach neoplasms (MeSH), parotid, salivary gland neoplasms (MeSH), lymphoepithelial, LELC
Study types	Case control, ecological studies, follow-up study
Epidemiology terms	cohort, epidemiologic studies (MeSH), epidemiology (Subheading)

The large and complex body of literature for EBV was searched using narrowing terms for the relevant major topics within the bibliographic databases. The results were then processed in EndNote to remove duplicates and conduct a first level of screening, before being transferred to DistillerSR for additional screening.

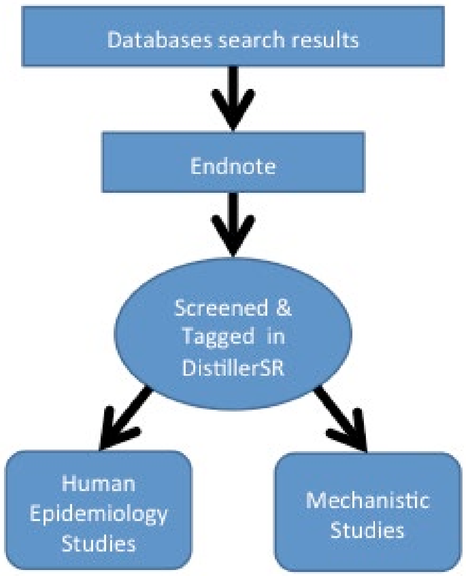

Figure A-1. Literature Processing Flow

The bibliographic database search results (2,632) were processed in EndNote then imported into DistillerSR for first and second tier screening. Relevant studies found through the citations of review articles and other secondary searched were also included. Tagging in DistillerSR categorized the useful articles into Human Epidemiologic literature (245) or Mechanistic literature (335).

A.2. Search Strings for EBV Searches

A.2.1. Cancer and Epidemiology

A.2.1.1. PubMed: 2009–2015

(Epstein-Barr virus infections[mh] OR "epstein-barr virus nuclear antigens"[mh] OR "epstein-barr"[tiab] OR EBV[tiab] OR (EBV*[tiab] NOT "epstein-barr"[tiab]) OR EBVaGC[tiab] OR Herpesvirus 4, human[mh] OR "Herpes virus 4"[tiab] OR HHV-4[tiab] OR HHV4[tiab] OR “EBV infection” OR EBV-infected OR "EBV-associated" OR "Ebv-encoded" OR "EBV-driven" OR “EBV-positive”) NOT (Posttransplant OR post-transplant OR transplant*[tiab])

AND

Neoplasms[mh] OR neoplas*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumorigenesis[tiab] OR tumour*[tiab] OR cancer*[tiab] OR carcinogen*[tiab] OR lesion*[tiab] OR adenoma*[tiab] OR adenosarcoma*[tiab] OR leiomyo*[tiab] OR leukemia*[tiab] OR lymphoma*[tiab] OR lymphangio*[tiab] OR sarcoma*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR oncogen*[tiab]

AND

Epidemiologic studies[mh] OR epidemiology[sh] OR case-control[tiab] OR case reports[ptyp] OR clinical trial[ptyp] OR cohort[tiab] OR comparative study[ptyp] OR cross-sectional[tiab] OR evaluation studies[ptyp] OR “follow-up study”[tiab] OR longitudinal[tiab] OR meta-analysis[tiab] OR meta-analysis[ptyp] OR multicenter study[ptyp] OR observational-study[tiab] OR prospective[tiab] OR randomized controlled trial[tiab] OR retrospective[tiab] OR individual*[tiab] OR man[tiab] OR men[tiab] OR patient*[tiab] OR subject*[tiab] OR woman[tiab] OR women[tiab] OR cases[mh]

A.2.1.2. Web of Science and Scopus: 2009–2015

("epstein-barr" OR EBV* OR EBVaGC OR "Herpes virus 4" OR HHV-4 OR HHV4 OR EBV-infected OR EBV-infection OR EBV-associated OR EBV-encoded OR EBV-driven OR EBV-positive) NOT (Posttransplant OR post-transplant OR transplant*)

AND

neoplas* OR tumor* OR tumour* OR cancer* OR carcinogen* OR lesion* OR adenoma* OR adenosarcoma* OR leiomyo* OR leukemia* OR lymphoma* OR lymphangio* OR sarcoma* OR carcinoma* OR adenocarcinoma* OR oncogen*

AND

Epidemiologic* OR case-control OR “case report” OR “case reports” OR “clinical trial” OR cohort OR “comparative study” OR cross-sectional OR “evaluation studies” OR “follow-up study” OR longitudinal OR meta-analysis OR multicenter study OR observational-study OR prospective OR “randomized controlled trial” OR retrospective OR individual* OR man OR men OR patient* OR subject* OR woman OR women

A.2.2. Relevant Cancers

A.2.2.1. PubMed: 2009–2015

A. (Epstein-Barr virus infections[mh] OR "epstein-barr virus nuclear antigens"[mh] OR "epstein-barr"[tiab] OR EBV[tiab] OR (EBV*[tiab] NOT "epstein-barr"[tiab]) OR EBVaGC[tiab] OR Herpesvirus 4, human[mh] OR "Herpes virus 4"[tiab] OR HHV-4[tiab] OR HHV4[tiab] OR “EBV infection” OR EBV-infected OR "EBV-associated" OR "Ebv-encoded" OR "EBV-driven" OR “EBV-positive”) NOT (Posttransplant OR post-transplant OR transplant*[tiab])

AND

Stomach neoplasms[mh] OR ((gastric OR stomach) AND (adenocarcinoma* OR adenoma*[tiab] OR adenosarcoma*[tiab] OR cancer*[tiab] OR carcinogen* OR carcinoma* OR lesion*[tiab] OR lymphoid[tiab] OR lymphoma*[tiab] OR lymphoepithel*[tiab] OR neoplas* OR tumor[tiab] OR tumors[tiab] OR tumorigenesis OR tumour*))OR stomach/virology[mh] OR ((stomach OR gastric) AND (epithelial*[tiab] OR epithelial cells/virology[mh])) OR (gammaherpesvirus-68[tiab] OR gammaHV-68[tiab]) AND (stomach[tiab] OR intestin*[tiab] OR gastric[tiab] OR gut[tiab])

B. (Epstein-Barr virus infections[mh] OR "epstein-barr virus nuclear antigens"[mh] OR "epstein-barr"[tiab] OR EBV[tiab] OR (EBV*[tiab] NOT "epstein-barr"[tiab]) OR EBVaGC[tiab] OR Herpesvirus 4, human[mh] OR "Herpes virus 4"[tiab] OR HHV-4[tiab] OR HHV4[tiab] OR “EBV infection” OR EBV-infected OR "EBV-associated" OR "Ebv-encoded"

OR "EBV-driven" OR “EBV-positive”) NOT (Posttransplant OR post-transplant OR transplant*[tiab])

AND

Salivary gland neoplasms[mh] OR salivary glands[mh] OR salivary-gland*[tiab] OR parotid[tiab] OR sublingual[tiab] OR submandibular[tiab] OR salivary-duct*[tiab] OR “von Ebner”[tiab] AND (Lymphoproliferative OR lymphoepithel* OR LEC OR LELC)

C. (Epstein-Barr virus infections[mh] OR "epstein-barr virus nuclear antigens"[mh] OR "epstein-barr"[tiab] OR EBV[tiab] OR (EBV*[tiab] NOT "epstein-barr"[tiab]) OR EBVaGC[tiab] OR Herpesvirus 4, human[mh] OR "Herpes virus 4"[tiab] OR HHV-4[tiab] OR HHV4[tiab] OR “EBV infection” OR EBV-infected OR "EBV-associated" OR "Ebv-encoded" OR "EBV-driven" OR “EBV-positive”) NOT (Posttransplant OR post-transplant OR transplant*[tiab])

AND

lymphoepithel*[tiab] OR LEC[tiab] OR LELC[tiab]

A.2.2.2. Web of Science and Scopus: 2009–2015

A. ("epstein-barr" OR EBV* OR EBVaGC OR "Herpes virus 4" OR HHV-4 OR HHV4 OR EBV-infected OR EBV-infection OR EBV-associated OR EBV-encoded OR EBV-driven OR EBV-positive) NOT (Posttransplant OR post-transplant OR transplant*)

AND

((gastric OR gut OR intestin* OR stomach) AND (adenocarcinoma* OR cancer* OR carcinogen* OR carcinoma* OR neoplas* OR tumor* OR tumour*)) OR ((gammaherpesvirus-68 OR gammaHV-68) AND (stomach OR intestin* OR gastric OR gut)

B. ("epstein-barr" OR EBV* OR EBVaGC OR "Herpes virus 4" OR HHV-4 OR HHV4 OR EBV-infected OR EBV-infection OR EBV-associated OR EBV-encoded OR EBV-driven OR EBV-positive) NOT (Posttransplant OR post-transplant OR transplant*)

AND

“Salivary gland” OR “salivary glands” OR parotid OR sublingual OR submandibular OR “salivary duct” OR “salivary ducts” OR “von Ebner” AND (Lymphoproliferative OR lymphoepithel* OR LEC OR LELC)

C. ("epstein-barr" OR EBV* OR EBVaGC OR "Herpes virus 4" OR HHV-4 OR HHV4 OR EBV-infected OR EBV-infection OR EBV-associated OR EBV-encoded OR EBV-driven OR EBV-positive) NOT (Posttransplant OR post-transplant OR transplant*)

AND

lymphoepithel* OR LEC OR LELC

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