Global burden of deaths from Epstein-Barr virus attributable malignancies 1990-2010

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Gulfaraz Khan1* and Muhammad Jawad Hashim2

Abstract

Background: Epstein-Barr virus (EBV) is an oncogenic virus implicated in the pathogenesis of a number of human malignancies of both lymphoid and epithelial origin. Thus, a comprehensive and up-to-date analysis focused on the global burden of EBV-attributable malignancies is of significant interest.

Methods: Based on published studies, we estimated the proportion of Burkitt’s lymphoma (BL), Hodgkin’s lymphoma (HL), nasopharyngeal carcinoma (NPC), gastric carcinoma (GC) and post-transplant lymphoproliferative disease (PTLD) attributable to EBV, taking into consideration age, sex and geographical variations. This proportion was then imputed into the Global Burden of Disease 2010 dataset to determine the global burden of each EBV-attributable malignancy in males and females in 20 different age groups and 21 world regions from 1990 to 2010.

Results: The analysis showed that the combined global burden of deaths in 2010 from all EBV-attributable malignancies was 142,979, representing 1.8% of all cancer deaths. This burden has increased by 14.6% over a period of 20 years. All 5 EBV-attributable malignancies were more common in males in all geographical regions (ratio of 2.6:1). Gastric cancer and NPC accounted for 92% of all EBV-attributable cancer deaths. Almost 50% of EBV-attributed malignancies occurred in East Asia. This region also had the highest age-standardized death rates for both NPC and GC.

Conclusions: Approximately 143,000 deaths in 2010 were attributed to EBV-associated malignancies. This figure is likely to be an underestimate since some of the less prevalent EBV-associated malignancies have not been included. Moreover, the global increase in population and life-expectancy will further increase the overall burden of EBV-associated cancer deaths. Development of a suitable vaccine could have a substantial impact on reducing this burden.

Keywords: EBV, Viral-associated cancers, Global cancer mortality, Cancer risk factors

Introduction

Cancer is one of the leading causes of death worldwide and research focused on understanding the etiology and pathogenesis of cancer is a major challenge. It has previously been estimated that oncogenic viruses play an etiological role in the development of approximately 12% of all human malignancies [1,2]. The vast majority of these malignancies are caused by just five different viruses of which Epstein-Barr virus (EBV) is arguably one of the most extensively studied [3].

EBV is a large dsDNA lymphotropic herpesvirus historically associated with Burkitt’s lymphoma, from which the virus was first isolated 50 years ago [4]. However, ever since its isolation, EBV has continued to attract considerable attention, primarily due to its oncogenic properties and its association with a number of human malignancies, including Burkitt’s lymphoma (BL), nasopharyngeal carcinoma (NPC), post-transplant lymphoproliferative disease (PTLD), Hodgkin’s lymphoma (HL) and gastric carcinoma (GC) [3]. EBV is primarily transmitted via saliva and in healthy immunocompetent individuals it infects and establishes life-long latency in memory B-lymphocytes [5,6]. In these cells, the virus limits its gene expression to 1 or 2 viral proteins only, thus escaping the immune surveillance [7]. This is referred to as type 0/1 latency. In some EBV-associated malignancies, such as NPC and HL, at least 3 viral genes have been shown to be expressed, including...
the oncogenic membrane protein LMP-1 [3]. This is referred to as type 2 latency. How the viral infected cells in these malignancies escape the immune system is unclear. In contrast, in vitro infection of B-lymphocytes results in their immortalization and establishment of lymphoblastoid cell lines (LCLs) [8]. In these cells, at least a dozen different EBV latent products are expressed, including 6 Epstein-Barr nuclear antigens (EBNAs), 3 latent membrane proteins (LMPs) and 2 non-protein coding small RNAs (EBERs) [3]. In addition to these, a number of micro-RNAs have also been shown to be expressed [9]. This is referred to as type 3 latency or growth program [10,11]. A substantial body of evidence indicates that a number of these latent viral products are central for EBV-associated malignancies, all three patterns of latency have been detected, suggesting that EBV induces oncogenesis by different mechanisms in different malignancies. Although EBV is carried asymptomatically by over 90% of adults worldwide, induction of cancer by this virus is nevertheless a very rare event. This clearly indicates that EBV on its own is not sufficient and other co-factors are necessary [12-14]. Thus, in order to link EBV in the etiology of a malignancy it is essential to demonstrate the presence of viral genome and/or gene expression directly in the tumor cells. This approach has revealed that the virus is not necessarily etiologically involved in all cases of a malignancy with which EBV has been implicated [15,16]. For example, only about 40% of Hodgkin’s lymphoma cases have EBV in the malignant cells and the prevalence varies with age [17]. In this study we provide the most up-to-date and detailed descriptive epidemiology of EBV-attributable malignancies using the Global Burden of Disease, Injuries and Risk Factors Study 2010 (GBD 2010) dataset. GBD 2010 is the largest and most comprehensive study ever conducted to measure the global health metrics [18,19]. As far as we are aware, the present study is the first to use GBD 2010 data to estimate the burden of EBV-associated malignancies in different age and sex groups in 21 world geographical regions from 1990 to 2010. It is hoped that the findings of this study will high-light the need for potential preventative measures and the global regions where implementation of such measures would have the greatest impact.

Methods

EBV associated malignancies

EBV is an accepted carcinogen [20] and experimental studies have clearly demonstrated that it is present in the tumor cells of several malignancies, including NPC, BL, HL, GC and PTLD [3,21]. There is substantial evidence that EBV has a causative role in the pathogenesis of these malignancies. However, the association is not universal and not all cases from all regions are linked to EBV. Our first step in this study was to estimate the proportion of these malignancies that can be reliably attributed to EBV based on published studies.

Estimation of the proportion of EBV-attributable cases

Since EBV is ubiquitous in the general population, EBV-attributable cancers are defined as those in which viral DNA/RNA and/or viral gene expression can be demonstrated in the tumor tissues. Based on published studies, we estimated the proportion of NPC [1,2], GC [22,23], HL [17,24-29], BL [1,2] and PTLD [30,31] that are attributable to EBV, taking into consideration any established variations that have been reported in different age, sex and ethnic groups (Table 1). For GC, the proportion of EBV-attributable cases has been reported to be similar in different world regions [22,32], but varies significantly with gender [22,33,34]. Based on two large meta-analysis studies, we have used EBV-attributable estimates of 11% and 6% for males and females respectively [22,23]. For HL, there is a general consensus that the EBV-attributable fraction varies significantly between different age groups. From the published studies, we estimated 62%, 30% and 55% of the cases to be attributable to EBV for the age groups 0-14 years [17,24,27,29], 15-54 years [17,25,27-29], and 55-80+ years [17,26-29] respectively. For PTLD, we estimated that 80% of PTLD cases to be attributed to EBV [30,31] (Table 1).

Estimation of the mortality from NPC, GC, HL, BL and PTLD

Data files for mortality estimates of all cancer cases were obtained from the Institute of Health Metrics Evaluation (IHME), University of Washington [35]. Detailed descriptions of how mortality figures were estimated has been previously published as part of the GBD 2010 study [36,37]. Briefly, mortality estimates were based on several different sources, including surveys, censuses, sample registration data and vital registration data, and final estimates derived using a range of statistical models [36-38]. All mortality figures and rates were estimated with 95% confidence intervals.

Age and sex-specific mortality estimates in 21 geographical regions were directly available for NPC, GC and HL from the GBD 2010 dataset. For BL, mortality data was not directly available as this malignancy was part of a broader category of non-Hodgkin’s lymphomas (NHL). Based on a previous study on the global burden of infection-associated cancers [1], the proportion of BL within the larger NHL category in the age group 0-14 years was estimated to be 90.5%, 33.3% and 15.2% for regions where BL is endemic, intermediate or sporadic respectively (Table 1). For age group 15-80+, irrespective of geographical region, the proportion of BL in HIV-negative
adults was conservatively estimated to be 2% of all NHL [39]. BL is approximately 3-4 times more common in males as compared to females [40-45]. In this study we used male:female ratio of 3:1 in calculating the prevalence of BL. Thus, all proportions were stratified by age, sex and geographical region. For estimating the prevalence of PTLD, we used data from Global Observatory on Donation and Transplantation (GODT), produced by the WHO-ONT collaboration [46]. In 2010, a total of 101,990 transplants (kidney, heart, liver, lung and pancreas) were performed, approximately 60% of which were on males [47]. Based on previous reports [30,48], we estimated that approximately 1.5% of transplant recipients develop PTLD and 50% of these died within the first year of lymphoma development [30,48,49]. It was assumed that the risk of developing PTLD and dying from it was the same for both sexes.

Estimation of the mortality from EBV-attributed NPC, GC, HL, BL and PTLD

The estimates of the proportion of EBV-attributable death for each malignancy established from the published literature (Table 1) were imputed into GBD 2010 data, adjusted for age, sex and geographical region. For example, for BL in East Sub-Saharan Africa, GBD 2010 dataset shows 227 deaths from NHL in males aged 1-4 years. In this region, 90.5% of all NHL are BL cases in this age group [1]. It was assumed that the risk of developing BL was 3-4 times more common in males [41-43,45]. In this study we have used male:female ratio of 3:1. In adults (age group 15-80+), irrespective of region, BL was estimated to constitute 2% of all NHL [39].

Post-transplant lymphoproliferative disease (ICD10:D47.Z1)

- Endemic
  - 90.5% of all NHL are BL in 0-14 age group [1].
  - Intermediate
  - Non-endemic
  - 15.2% of all NHL are BL in 0-14 age group [1]. In adults (age group 15-80+), irrespective of region, BL is estimated to constitute 2% of all NHL [39].

Post-transplant lymphoproliferative disease (ICD10:D47.Z1) includes all cases of PTLD caused by EBV, regardless of the sex of the patient. In this study, we assumed that the risk of developing PTLD and dying from it was the same for both sexes.

Results

Overall global burden of EBV-attributed malignancies

Over a period of 20 years, global mortality from cancer has increased from 5.779 million in 1990 to 7.978 million in 2010.
million in 2010. This is an increase of approximately 2% per year. However, the collective global number of deaths from NPC, BL, HL, GC and PTLD has remained fairly constant (a modest increase of only 0.2%). Of the total of 842,674 deaths from these 5 malignancies in 2010, 142,979 (17.0%) were calculated to be from EBV-attributed cases (Table 2). This represents 1.8% of all cancer deaths in 2010 worldwide. The largest number of deaths from EBV-attributed malignancies was for gastric carcinoma (69,081 cases), closely followed by NPC (63,118 cases). The proportion of cases of NPC, BL, HL, GC and PTLD, specifically adjusted for age, sex and geographical region, attributable to EBV was 97.2%, 51.2%, 44.7%, 9.2% and 80% respectively (Table 2).

Patterns of EBV-attributed malignancies by geographical region and time
Analysis of EBV-attributed malignancies in 21 world regions revealed that the highest mortality was in East Asia (Figure 1). In fact 47% of all EBV-attributed malignancies occurred in this region. This in turn is a reflection of the fact that this region, which includes China, Democratic People’s Republic of Korea and Taiwan, has by far the highest prevalence of both gastric and

### Table 2 Global burden of deaths from EBV-attributed malignancies in 2010

| Type of malignancy | Global deaths: All cases | Global deaths: EBV-attributed cases | % deaths from EBV-attributed cases (both) |
|--------------------|--------------------------|-------------------------------------|----------------------------------------|
|                    | Males  | Females  | Both  | Males  | Females  | Both  | Males  | Females  | Both  | Males  | Females  | Both  |
| NPC                | 45,640 | 19,264   | 64,904 | 44,418 | 18,700   | 63,118 | 97.2   |
| BL                 | 3,575  | 821      | 4,396  | 1,820  | 431      | 2,251  | 51.2   |
| HL                 | 10,208 | 7,510    | 17,718 | 4,507  | 3,410    | 7,917  | 44.7   |
| Stomach            | 475,759| 279,132  | 754,891| 52,333 | 16,748   | 69,081 | 9.2    |
| PTLD               | 459    | 306      | 765    | 367    | 245      | 612    | 80.0   |
| Total              | 535,641| 307,033  | 842,674| 103,445| 39,534   | 142,979| 17.0   |

![Figure 1](https://example.com/Figure1.png)
nasopharyngeal carcinoma in the world (Additional file 1: Figure S1). Age-standardized mortality rates for these malignancies in East Asia are also the highest in the world (Figure 2a and b). Furthermore, unlike the other malignancies, the burden of mortality due to NPC has increased from 43,828 in 1990, to 63,118 in 2010, an average annual increase of 2.2% (Figure 3). Although the age-adjusted death rate of NPC in East Asia is by far the highest in the world (2.5/100,000 in 2010), the rates have not increased over the 20 years (Figure 2a). This indicates that the increase in burden of NPC observed over the 20 years is most likely due to an increase in the population at risk.

Patterns of EBV-attributed malignancies by sex and age
Global deaths from EBV-attributed cases of all 5 malignancies were up to 2.6 times higher in males as compared to females (Figure 4). This difference is likely to be an underestimate, since we did not take into account the accumulating data which indicates that males are more likely than females to have EBV-attributable HL [29,50-52].

![Figure 2](image.png)

Figure 2 Global burden of age standardized death rates of (a) nasopharyngeal carcinoma and (b) gastric cancer, 1990-2010.
Furthermore, this male predominance was common in virtually all world regions (Additional file 1: Figure S1). The reason for this male preponderance is not known, but male genetics and male lifestyle are plausible risk factors. Analysis of deaths from these malignancies by age revealed that the vast majority of the cases occurred in adults, primarily after the age of 35 years (Figure 5). An exception to this was BL, which as expected, peaked in children between the ages of 1-5 years. Interestingly, the prevalence of NPC, unlike GC and HL did not continue to increase with age. Rather, it peaked in the age group 55-60 year-olds and thereafter decreased at an average of 2.75% annually (Figure 5). This trend is consistent with previous reports [53,54].

Discussion

Epstein-Barr virus is a well-recognized carcinogen implicated in the etiology of several malignancies of both epithelial and lymphoid origin. In this study, we present descriptive epidemiology of EBV-attributable malignancies using the GBD 2010 data. In contrast to previous studies [1,2,55], we focused exclusively on EBV-attributable
cancers with an aim to provide an in-depth analysis of the malignancies associated with this virus. In addition to NPC, BL and HL, the current report also includes mortalities from GC and PTLD, both of which are known to be associated with EBV [42,56,57]. In this analysis, we present the global burden of mortality from EBV-attributed malignancies, stratified by age, sex and geographical region from 1990-2010. The results of this study demonstrate that the global burden of mortality from EBV-attributed malignancies accounts for 1.8% of all cancer deaths in 2010. This is a 14.6% increase from 1990 and the trends indicate that this burden will continue to increase as the world population and life-expectancy increase [37]. Gastric cancer and NPC accounted for 92% (132,199 cases) of all EBV-attributed cancer deaths, with the vast majority occurring in developing countries, in particular East Asia. Indeed, the age-standardized rates of both of these malignancies are also considerably higher in East Asia compared to western countries, consistent with previous reports [58,59]. The reason for this elevated incidence in certain Asian countries remains unknown, as does the male preponderance [58]. Epidemiological studies on NPC and GC have shown that individuals who migrate from high-risk countries to low-risk countries have incidence rates intermediate to their country of origin and their host country [53,59]. This implies that the etiology of these malignancies is complex and most probably involves multiple factors including, environmental, genetic and dietary. One factor in particular, namely EBV, has been consistently shown to be involved in the development of these malignancies [53,56,60], but the molecular mechanism(s) involved is not well understood. The fact that virtually all adults worldwide are infected with EBV, and yet only a very small fraction of individuals actually develop these malignancies, clearly indicates that EBV alone is not sufficient. For NPC, it has been hypothesized that infection with EBV early in childhood, which is typical of high-incidence regions, is important [53]. For GC, in particular non-cardia type, *Helicobacter pylori* is generally accepted to be one of the prime risk factors [61,62]. Of the dietary and lifestyle factors, increased intake of salts or salt preserved food, alcohol and smoking have been implicated, although the attributable risk is at best only modest [53,63,64].

In contrast to NPC and GC, the role of EBV in the development of BL, PTLD and HL is to some extent better understood. Burkitt’s lymphoma is primarily a childhood malignancy endemic in Sub-Saharan Africa. Three factors have been shown to be important in the development of this malignancy: EBV, malaria and deregulated activation of the c-myc oncogene [65]. In the case

![Figure 5 Global burden of deaths from EBV-attributed malignancies by age in 2010.](http://www.infectagentscancer.com/content/9/1/38)
of PTLD, EBV is thought to be the primary driving force. EBV infected cells express several viral latent products [66,67], including the viral oncogene LMP-1 [68]. These cells would normally be eliminated by the immune system, but in immunocompromised individuals such as transplant recipients, the infected cells proliferate unchecked. Reversal of immunosuppression or infusion of EBV-specific cytotoxic T-cells can prevent the development of PTLD [69,70]. In HL, there is restricted EBV-gene expression in the malignant cells, but crucially LMP-1 is expressed [71] and thought to be central in the oncogenic process [72].

Although this study presents the most comprehensive and most up-to-date estimates of the global mortalities from EBV-associated malignancies, it has several limitations inherent in any study of this kind. First, our estimates rely on the accuracy of the dataset from the GBD 2010 study. GBD 2010 is the largest and most comprehensive project ever conducted to measure global health metrics and as expected, this ‘super-human’ effort had its own limitations which have been described in detail elsewhere [19,37,38]. Second, in calculating the mortality of EBV-attributable fraction of NPC, GC, HL, BL and PTLD, it was assumed that the risk of death from EBV-positive and negative cases is the same. This may not always be the case for all EBV-associated malignancies [25,28,73]. Indeed, some studies have reported a better prognosis for EBV-positive cases compared to negative cases [25,74]. Third, to calculate the mortality of EBV-attributable cases of BL, we first had to determine the number of deaths from BL, as this was not directly available from GBD 2010 data. In the GBD 2010 data, BL was grouped in the larger category of non-Hodgkin’s lymphoma (NHL). In calculating the mortality of BL, it was assumed that the mortality of BL was the same as other lymphomas in the NHL group. Once again, this assumption is strictly speaking not true, since NHL represent a heterogeneous group of lymphomas with differing prognoses [75]. Fifth, for calculating the proportion of EBV-attributable malignancies at different time points i.e. 1990, 1995, 2000 and 2005, we used EBV-attributable proportions of 97.2% for NPC, 80% for PTLD, 51.2% for BL, 44.7% for HL and 9.2% for GC, estimated for 2010, with the assumption that these proportions have not changed over time. Finally, our estimate of 142,979 global deaths from EBV-associated malignancies is likely to be an underestimate since a few other EBV-associated malignancies such as central nervous system malignancies occurring in AIDS patients, for which there is substantial evidence for causality [76] have not been considered in this analysis.

Conclusion
Cancer is amongst the leading causes of death. In 2010, cancer accounted for 7.978 million deaths, and this figure appears to be rising at a rate of approximately 2% per year [38]. Thus, understanding the risk factors or causes of cancer is of paramount importance for any future prevention strategies. The analysis presented here indicates that 1.8% of all cancer deaths in 2010 were associated with EBV. This is a sizable number of deaths and developing an effective vaccine would not only reduce this burden, but could also prevent infectious mononucleosis, which is also known to be caused by EBV [77].

Additional file

Additional file 1: Figure S1. Global burden of death from EBV-attributed malignancies in 2010 by region. (A) Gastric cancer (B) Nasopharyngeal carcinoma (C) Hodgkin’s lymphoma (D) Burkitt’s lymphoma.

Competing interests
Both authors declare that they have no competing interests.

Authors’ contributions
GK: Study conception and design, data acquisition, analysis and interpretation, writing the first draft and critical revision. MJH: Statistical analysis and interpretation, drafting of manuscript and critical revision. Both authors read and approved the final manuscript.

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References
1. Parkin DM: The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006, 118:3030–3044.
2. De Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M: Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012, 13:607–615.
3. Longnecker R, Keef E, Cohen JI: Epstein-Barr Virus. In Fields Virology. Volume 2. 6th edition. Edited by Knipe DM, Howley PM. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.
4. Epstein MA, Achong BG, Barr YM: Virus particles in cultured lymphoblasts from Burkitt’s lymphoma. Lancet 1964, 1:702–703.
5. Khan G, Miyashita EM, Yang B, Babcock GJ, Thorley-Lawson DA: Is EBV persistence in vivo a model for B cell homeostasis? Immunity 1996, 5:173–179.
6. Babcock GJ, Decker LL, Volk M, Thorley-Lawson DA: EBV persistence in memory B cells in vivo. Immunity 1996, 5:395–404.
7. Tierney RJ, Steven N, Young LS, Rickinson AB: Epstein-Barr virus latency in blood mononuclear cells: analysis of viral gene transcription during primary infection and in the carrier state. J Virol 1994, 68:7374–7385.
8. Pope JH, Horne MK, Scott W: Transformation of foetal human leukocytes in vitro by filtrates of a human leukaemic cell line containing herpes-like virus. Int J Cancer 1968, 3:857–866.
9. Marquitz AR, Mathur A, Chugh PE, Dittmer DP, Raab-Traub N: Expression profile of MicroRNAs in Epstein-Barr virus-infected AGS gastric carcinoma cells. J Virol 2014, 88:1389–1393.
10. Thorley-Lawson DA, Miyashita EM, Khan G: Epstein-Barr virus and the B cell: that’s all it takes. Trends Microbiol 1996, 4:204–208.
Glaser SL, Lin RJ, Stewart SL, Ambinder RF, Jarrett RF, Brousset P, Pallesen G, Khan G, Philip PS, Al Ashari M, Houcini Y, Daoud S: The story of GBD 2010: a meta-analysis of the relationship between Epstein-Barr virus infection and clinicopathological features of patients with gastric carcinoma. Sci China Life Sci 2010, 53:524–530.

Global Burden of Disease Study 2010 (GBD 2010) Results by Cause 1990-2010 - Country Level. Seattle, Washington, United States: Institute for Health Metrics and Evaluation (IHME) [http://ghdx.healthdata.org/record/global-burden-disease-study-2010-gbd-2010-results-cause-1990-2010-country-level] (2012).

Murray CJL, Lopez AD, Cogliano V, Straif K, Grosse Y, raging, Cogliano V, Straif K, Grosse Y, Romieu I,这是因为这与EBV感染与反应化疗和生存的关系。1. 肿瘤学和胃肠癌。Science 2009, 326:74–78.

Bacsich J, Agarwal R, Al-Ashari M, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DM, Basilion M-G, Baxter A, Bell ML, Benjamin EL, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012, 380:2197–2223.

Wang H, Dwyer-Lindgren L, Lojgren KT, Rajanatham J, Marcus JR, Levin-Rector A, Levin-CZ, Lopez AD, Murray CJL. Age-specific and sex-specific mortality in 197 countries, 1970–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012, 380:2071–2074.

Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Smith G, Vos T, Makela T, Murray CJL. Disability-adjusted life years (DALYs) for 253 causes of death in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012, 380:2095–2128.

Spina M, Tirelli U, Zagonel V, Ghisetti A, Volpe R, Babere R, Abbruzzese L, Talambini R, Vaccari E, Carbone A. Burkitt's lymphoma in adults with and without human immunodeficiency virus infection: a single-institution clinicopathologic study of 75 patients. Cancer 1998, 82:668–714.

Magraith I. African Burkitt's lymphoma. History, biology, clinical features, and treatment. Am J Pediatr Hematol Oncol 1991, 13:222–246.

Philip T. Burkitt's lymphoma in Europe. JARC Sci Publ 1986, 60:107–118.

Hsu JL, Glaser SL. Epstein-Barr virus-associated malignancies: epidemiologic patterns and etiologic implications. Cit Rev Hematol Oncol 2003, 3427–53.

Queiroga EM, Gualkio G, Weiss LM, Dittmer DP, Araujo I, Kumb CEN, Harrington WI, Bacsich J. Burkitt lymphoma in Brazil is characterized by geographically specific clinical pathologic features. Cit J Pathol 2008, 138:496–505.

Boerma EG, van Imhoff GW, Appel IM, Veege NGM, Kluin PM, Kuij-Kleeman JC. Gender and age-related differences in Burkitt lymphoma—epidemiological and clinical data from the Netherlands. Eur J Cancer 2004, 40:2781–2787.

Stefan DC, Luterman R. Burkitt lymphoma: epidemiological features and survival in a South African centre. Infect Agent Cancer 2014, 9:19.

Global Observatory on Donation and Transplantation (GDOT) data, produced by the WHO-ONC collaboration [http://www.transplant-observatory.org/Pages/Organs-Activity-Data.aspx]

Organ Procurement and Transportation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN / SRTR 2010 Annual Data Report [http://srtr.transplant.hrsa.gov/annual_reports/2010/]

Mucha K, Forczewicz B, Ziarziewicz-Wroblewska B, Krawczyk M, Lenert J, Paczek L. Post-transplant lymphoproliferative disorder in view of the new WHO classification: a more rational approach to a protein disease? Nephrol Dial Transplant 2010, 25:2089–2098.

Opelz G, Döhler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004, 4:222–230.

Flavell RJ, Billingham LJ, Biddulph JP, Gray L, Flavell JR, Constantini CM, Young LS, Murray PG. The association of Epstein-Barr virus status on outcome in age- and sex-defined subgroups of patients with advanced Hodgkin's disease. Ann Oncol 2003, 14:292–290.

Claviez A, Tiemann M, Luders H, Kraus M, Parwaresch R, Schellong R, Dörffel W. Impact of latent Epstein-Barr virus infection on outcome in children and adolescents with Hodgkin's lymphoma. J Clin Oncol 2003, 21:4038–4056.
The curious case of the tumour virus: Gastric cancer epidemiology and risk factors. J Clin Epidemiol 2003; 56:1–9.

Joossens JV, Hill MJ, Elliott P, Stamler R, Lesaffre E, Dyer A, Nichols R, Kesteloot H: Hepatitis B virus and stomach cancer: a meta-analysis of cohort studies. J Natl Cancer Inst 2000; 92:1175–1183.

Kelley JR, Duggan JM: Gastric cancer epidemiology and risk factors. J Clin Epidemiol 2003; 56:1–9.

Joossens JV, Hill MJ, Elliott P, Stamler R, Lesaffre E, Dyer A, Nichols R, Kesteloot H: Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECOP) and the INTERSALT Cooperative Research Group. Int J Epidemiol 1996; 25:404–504.

Thorley-Lawson DA, Allayi MI: The curious case of the tumour virus: 50 years of Burkitt's lymphoma. Nat Rev Microbiol 2008; 6:913–924.

Young L, Alferi C, Hennessy K, Evans H, D’Hara C, Anderson KC, Ritz J, Shapiro RS, Rickinson A, Kieff E: Expression of Epstein-Barr virus latent genes in tumour tissue. J Natl Cancer Inst 2006; 98:1445–1452.

Kelley JR, Duggan JM: Gastric cancer epidemiology and risk factors. J Clin Epidemiol 2003; 56:1–9.

Joossens JV, Hill MJ, Elliott P, Stamler R, Lesaffre E, Dyer A, Nichols R, Kesteloot H: Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECOP) and the INTERSALT Cooperative Research Group. Int J Epidemiol 1996; 25:404–504.

Thorley-Lawson DA, Allayi MI: The curious case of the tumour virus: 50 years of Burkitt's lymphoma. Nat Rev Microbiol 2008; 6:913–924.

Young L, Alferi C, Hennessy K, Evans H, O'Hara C, Anderson KC, Ritz J, Shapiro RS, Rickinson A, Kieff E: Expression of Epstein-Barr virus latent genes in tumour tissue. J Natl Cancer Inst 2006; 98:1445–1452.