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Global and regional incidence, mortality and disability-adjusted life-years for Epstein-Barr virus-attributable malignancies, 1990-2017

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ABSTRACT

Objective To determine the global and regional burden of EBV-attributable malignancies.

Design An international comparative study based on the Global Burden of Disease (GBD) Study estimates.

Setting Global population by age, sex, region, demographic index and time.

Methods and outcome measures The burden of EBV-attributable Burkitt lymphoma (BL), Hodgkin lymphoma (HL), nasopharyngeal carcinoma (NPC) and gastric carcinoma (GC) was estimated in a 2-step process. In the first step, the fraction of each malignancy attributable to EBV was estimated based on published studies; this was then applied to the GBD estimates to determine the global and regional incidence, mortality and disability-adjusted life-years (DALYs) for each malignancy by age, sex, geographical region and social demographic index (SDI) from 1990-2017.

Results The combined global incidence of BL, HL, NPC and GC in 2017 was 1.442 million cases, with over 973,000 deaths. An estimated 265,000 (18%) incident cases and 164,000 (17%) deaths were due to the EBV-attributed fraction. This is an increase of 36% in incidence and 19% in mortality from 1990. In 2017, EBV-attributed malignancies caused 4.604 million DALYs, of which 82% was due to NPC and GC alone. The incidence of both of these malignancies was higher in high- and middle-high SDI regions and peaked in adults aged between 50-70 years. All four malignancies were more common in males and the highest burden was observed in East Asia.

Conclusions This study provides comprehensive estimates of the burden of EBV-attributed BL, HL, NPC and GC. The overall burden of EBV related malignancies is likely to be higher since EBV is etiologically linked to several other malignancies not included in this analysis. Increasing global population and life expectancy is expected to further raise this burden in the future. The urgency for developing an effective vaccine to prevent these malignancies cannot be overstated.

Strengths and limitations of this study

- This study examined the burden of EBV-attributed malignancies using the most up-to-date and reliable data from the GBD Study.
- This is the first study of its kind to quantitate the global and regional incidence, mortality and DALYs of EBV-attributed malignancies by age, sex, geographical region and SDI from 1990-2017.
- Although EBV is linked to a number of malignancies, this study assessed only four EBV-associated malignancies.
- The GBD estimates, albeit the most comprehensive and most refined, have their own drawbacks and limitations.

INTRODUCTION

Cancer is one of the leading causes of death worldwide. The latest estimates indicate that in 2017, there were nearly 17 million new cases and over 9 million deaths worldwide.[1] Alarmingly, the overall burden due to cancer is on the rise, primarily due to population growth and increasing life expectancy.[1] Cancer is a complex and multi-factorial disease and strategies to reduce its burden will require not only basic research, but also a global action plan targeting early detection, control and prevention. One fundamental aspect of prevention is to understand the causes of cancers. It is now well-established that infectious agents, either on their own or in combination with genetic and environmental factors, play a role in the pathogenesis of approximately 15-20% of all human malignancies.[2–4] Most of these malignancies are linked to only a handful of infectious agents.[4,5] One such agent is Epstein-Barr virus (EBV).

EBV is a very common virus asymptomatically infecting over 90% of the population.[6] In most cases, the infection is acquired early in childhood, often before the age of 5 years.[7] Once infected, the virus persists in B-cells for life.[8] Depending on the pattern of EBV gene expression in the infected cells, four latency programs, referred to as latency 0 to 3, have been recognized. Different latency programs are associated with different pathologies.[9] Moreover, the fact that EBV is very common in the general population, and yet only a very small fraction of infected individuals develop EBV-associated pathologies, indicates that other risk factors such immune deficiencies, genetic predisposition and environmental factors are also essential in the development of these pathologies.[10–12] Thus, to establish a causal link, it is necessary to directly demonstrate the virus in the affected tissues. With the advancement in technology and detection methods, the virus has now been unequivocally demonstrated in the tumour cells of a several different malignancies.[9] EBV is now firmly linked to the development of Burkitt's lymphoma (BL), nasopharyngeal carcinoma (NPC), Hodgkin lymphoma (HL) and gastric carcinomas.[9] Additionally, EBV is also clearly implicated in the pathogenesis of several other malignancies, including lymphomas arising in immunocompromised individuals, such as allograft recipients, AIDS patients and individuals with congenital immunodeficiencies.[13,14]

Although EBV was the first virus identified to be etiologically associated with human malignancies, no effective anti-viral drug or approved vaccine is available for its elimination or prevention. An accurate estimate of the burden of EBV-attributed disorders is unknown. The purpose of this study was to partially fill this gap by providing estimates of EBV-attributed BL, HL, NPC and GC, using the Global Burden of Disease (GBD 2017) estimates.

METHODS

Definition and prevalence of EBV-attributable cases of BL, HL, NPC, GC

For the purpose of this study, we define EBV-attributed cancers as those in which viral nucleic acid, and/or viral proteins can be demonstrated directly in the malignant cells (Table 1). This has been confirmed for BL, HL, NPC and GC by numerous studies (Table 1). However, not all of the cases of these malignancies are EBV-attributable. Moreover, the EBV-attributable fraction appears to vary with age, gender and geographical region. Taking these variables into account, we first estimated the fraction of EBV-attributable malignancies based on published studies as described in our previous study.[15] Table 1 summarizes the outcome of this analysis.

Estimation of the incidence, mortality and DALYs for BL, HL, NPC, GC

Estimates of incidence, mortality and DALYs for HL, NPC and GC were obtained from the GBD 2017 study. GBD methods are described extensively elsewhere.[1,32,33] Briefly, estimates are based on multiple data sources, including vital registration systems, cancer registries and verbal autopsy data.[1,32,33] A range of statistical models were used to derive the final estimates. Since each GBD study re-estimates the entire data sets annually, the results presented here are the most refined and up-to-date.

Data sets of age and sex-specific estimates of incidence, mortality and DALYs for 21 global regions from 1990-2017 were directly available from the GBD results database for HL, NPC and GC (http://ghdx.healthdata.org/gbd-results-tool, downloaded on 24th of March 2019). For BL, no direct estimates were available. The GBD study includes BL under the broader category of non-Hodgkin lymphomas (NHL). Based on previous studies,[2,15] we estimated the percentage of BL cases within the NHL category in the age group 0-14 years 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 percentage of BL in HIV-negative adults was conservatively estimated to be 2% of all NHL cases.[34] BL is approximately 3-4 times more common in males compared to females.[16,20,21] In this study we used male:female ratio of 3:1 in calculating the prevalence of BL. Thus, for BL, we first estimated the incidence, mortality and DALYs by age, sex and geographical region, before calculating the fractions attributable to EBV.

Estimation of the incidence, mortality and DALYs of EBV-attributable fraction of BL, HL, NPC, GC

The EBV-attributable proportion of BL, HL, NPC and GC estimated from published studies (Table 1) was applied to the GBD 2017 estimates. For example, for BL in East Sub-Saharan Africa, GBD 2017 estimates show 1526 incident cases of NHL in the age group 1-4 years. In this region, 90.5% of NHL cases have been estimated to be BL in this age group,[2] with a male predominance of 3:1.[16,17,20] Based on this, 1526 × 0.905 × 0.75 gives an estimate of the incidence of BL in males in the 1-4 year age group in East Sub-Saharan Africa in 2017 to be 1036. Since 95% of BL cases in this age group and in this region are EBV associated, [2,3] the incidence of EBV-attributed BL cases was estimated to be 984 cases (1036 x 0.95). Using this approach, we calculated the incidence, mortality and DALYs for each of the four EBV-associated malignancy in males and females in 23 different age groups and 21 different geographical regions from 1990-2017.

Estimation of the burden of EBV-attributable fraction of BL, HL, NPC, GC by socio-demographic index

To assess the influence of demographic development on the burden of EBV-attributable malignancies, we used each country's socio-demographic index (SDI) to estimate EBV-attributable fraction of BL, HL, NPC and GC. SDI is a summary measure of the lag distributed income (LDI) per capita, educational attainment and fertility rate and it is regarded as a good indicator of a country's socio-demographic development.[1] We assessed the burden of EBV-attributable malignancies by five SDI categories: low, low-middle, middle, middle-high and high.[1]

RESULTS

Global burden of EBV-attributable malignancies

In 2017, there were 1.442 million incident cases and 973,000 deaths from BL, HL, NPC and GC, contributing to 22.958 million DALYs (Table 2). The overall global burden of EBV-attributable fraction of these four malignancies contributed to over 265,000 (18%) of the incident cases, 164,000 (17%) of deaths and 4.6 million (20%) of DALYs (Tables 2 and Supplementary Figure 1). The individual contribution of each of these four malignancies to the overall burden of EBV-attributable fractions varied considerably. NPC and GC together accounted for over 218,000 (82%) incident cases, 146,000 (89%) deaths and 3.8 million (82%) DALYs (Tables 2). Over the period of 27 years (1990-2017), the burden of mortality from these EBV-attributable malignancies increased by 19%.

EBV-attributable malignancies by sex and age

The incidence and mortality of all four malignancies (BL, HL, NPC and GC) was higher in males than in females in all world regions. The EBV-attributable fraction of these malignancies was also higher in males compared to females (Figure 1). The combined incidence of EBV-attributed BL, HL, NPC and GC in 2017 was 196,000 in males and 69,000 in females (2.8:1.0) (Tables 2). Incidence and mortality of EBV-attributed malignancies also varied with age (Supplementary Figures 2-3). Burkitt lymphoma was primarily seen in children, peaking in the 5-10 year age group (Supplementary Figure 2A). By contrast, NPC and GC occurred in adults, peaking in the 45-60 (Supplementary Figure 2C) and 65-80 (Supplementary Figure 2D) age group, respectively. The distribution of EBV-attributable incidence of HL revealed more than one age group to be affected (Supplementary Figure 2B). For men, incidence peaked in three age groups, 5-15, 25-40 and 55-70 years. Interestingly, for women, only two peaks were noted; a large peak in the 25-40 year age group and a smaller peak in the 55-70 year group.

EBV-attributable malignancies by region and time

There was considerable regional variation in the burden of EBV-attributable BL, HL, NPC and GC (Supplementary Figures 4-6). This ranged from less than 1000 incident cases in Southern Sub-Saharan Africa to more than 100,000 cases in East Asia (Supplementary Figure 1). In fact, 43% of all global incident cases of these four malignancies and 40% of all deaths were in East Asia (Figure 1). This high burden is primarily due to the high incidence of NPC and GC in East Asia (Supplementary Figure 6-7), particularly in China (Supplementary Figure 1).

The combined incidence of the four EBV-attributable malignancies has increased from 195,000 in 1990 to 265,000 in 2017. This increase is particularly evident for males (Figure 2A). For females, the increase has been either moderate, or in the case of NPC, actually decreased slightly (277,000 in 1990 to 274,000 in 2017). In terms of the burden of deaths, absolute numbers declined only for HL (Figure 2B). Since the global population has increased over the same timeframe, the rate of death per 100,000 for HL has decreased significantly from 0.67 in 1990 to 0.43 in 2017.

EBV-attributable malignancies by socio-demographic index

Since a country's socio-economic development is an important driver of the burden of disease, we assessed the impact of SDI on the burden of EBV-attributable malignancies. Countries were grouped into five categories, low, low-middle, middle, middle-high and high SDI. As expected, there was considerable

heterogeneity in both incidence and mortality by SDI status (Figure 3). For EBV-attributed BL, low and low-middle SDI regions had the highest burden of incidence and deaths, whilst for EBV-attributed HL, incidence appeared to directly correlate with the SDI index; the highest burden was observed in the high SDI region (Figure 3B). The burden of deaths from EBV-attributed HL on the other hand, did not follow the pattern seen for incident cases. The burden of deaths was greater in low and low-middle SDI regions, possibly reflecting less resources for treating HL in these regions compared to the affluent high SDI countries (Figure 3B). The burden of DALYs for EBV-attributable cases also varied by SDI; low and low-middle countries had the highest burden for BL and HL, but for NPC and GC, the highest burden was observed in middle and middle-high countries (Supplementary Figure 8).

DISCUSSION

Improvements in life expectancy and population growth has led to an increase in the global burden of cancer, which now ranks second after cardiovascular diseases.[1] To address this growing global health problem, a multi-pronged approach is needed. It is essential not only to find better therapies for cancer, but importantly, to prevent cancer from occurring in the first place. Thus, understanding the causes and risk factors involved in the development of cancer is of central importance. In this study, using the GBD 2017 estimates, we provide a detailed epidemiological profile of EBV-attributable malignancies. We estimated the incident, deaths and DALYs of these malignancies by age, sex, geographic region, and socio-demographic status from 1990-2017.

Our analysis revealed that in 2017, BL, HL, NPC and GC accounted for 1.44 million incident cases and almost 1 million deaths. Of these, just over 265,000 incident cases and 164,000 deaths were attributed to EBV infection. This is an increase of 19% and 36% respectively from 1990. Since the global prevalence and pattern of EBV infection has not changed, the drivers of the increase in burden of EBV-attributed cancers appear to be due to an increase in the life expectancy, population growth and changing age structure.[1] The contribution of these drivers varies with socio-economic development. Whist, population growth is a major driver of the increased burden in low SDI regions, increased life expectancy appears to be more important in middle-high and high SDI regions.[1] As previously reported, all four malignancies were more common in males.[1] The reasons for the male preponderance is not known, but genetics and male life-style risk factors are likely to be important contributors.[29,35]

The fraction of cases attributed to EBV also varied significantly depending on the type of malignancy. Whilst more than 95% of NPC cases were attributed to EBV, for GC, this fraction was less than 10%. In spite of this low attributed fraction, GC was still the leading cause of EBV-attributed cancer burden, accounting for 43% of all incident cases and nearly 50% of all deaths in 2017. This burden is due to the fact that GC is amongst the top 6 most frequently diagnosed cancer globally, and the most common cancer in some East Asian countries.[1] Although the absolute number of EBV-attributed GC incident cases has increased from 78,000 in 1990 to over 113,000 in 2017, the age-standardized incidence rate has actually declined globally. GC peaks in late adulthood (above 65 years) and the absolute increase in incidence of GC could be explained by the increase in life expectancy and change in population age structure. East Asia also had by far the highest incidence of NPC. In fact, approximately 50% of the global number of EBV-attributed cases of GC and NPC occurred in East Asia. The reasons for the high prevalence of these two malignancies in this region is not clear. It is believed that a combination of genetic and environmental risk factors are involved. Early infection with EBV and/or *Helicobacter pylori*, both of which are common in the region are important risk factors, as is diet, high salt intake, smoking, and life style factors.[29,35] A change in exposure to these risk factors has been reported to reduce the incidence rates, as shown in studies on descendants of migrants from high to low incidence regions.[29]

In contrast to NPC and GC, the epidemiology of BL and HL is very different. Burkitt lymphoma is a childhood malignancy most prevalent in Eastern and Western Sub-Saharan Africa. Males are more predominantly affected.[16–21] Three risk factors have been shown to be involved in the development of BL; EBV infection, malaria, and genetic translocation involving the *c-myc* oncogene.[9] However, the level of contribution of each of these risk factors and how they interact to promote the development of BL is unknown. As for HL, this study shows that around 40% of all cases worldwide are EBV-attributed and this fraction varies not only by gender and age, but also by geographical region.[22] These variations suggest that other risk factors, in addition to EBV are involved in the pathogenesis of HL. Studies have demonstrated that infectious mononucleosis, a self-limiting lymphoproliferative condition caused by primary EBV infection, is associated with a significantly increased risk of developing HL.[9]

Limitations

The analysis presented in this report is to our knowledge the most comprehensive and up-to-date assessment of the magnitude and distribution EBV-attributed malignancies. However, the accuracy of the results rely on a number predictions and assumptions. First, our estimates of the burden of EBV-attributed BL, HL, NPC and GC were calculated based on the GBD 2017 estimates on incidence, mortality and DALYs of these malignancies. The GBD study, albeit the most comprehensive and most refined, nevertheless has its own drawbacks and limitations.[1,33] Second, GBD groups BL as part of the larger category of non-Hodgkin lymphomas (NHL). In this study, when calculating the incidence, mortality and DALYs for BL, we assumed that these measures were proportionally the same for all the lymphomas in the NHL group. In reality this is not quite true.[36] In future GDB studies, we aim to include BL as a separate entity, which will provide more accurate estimates. Third, although age, gender and regional variations in EBV-attributable fractions of these malignancies were taken into consideration, we assumed that the EBV-attributable fraction was the same for incidence, mortality and DALYs. Fourth, it is currently unclear if EBV-attributed malignancies have a better or worse prognosis. Thus, in this study we assumed that the mortality and DALYs was the same for EBV-associated and non-associated cancers. Similarly, it was assumed that the mortality from EBV-attributed malignancies was the same in both males and females. In spite of these limitations, this is the only study of its kind to provide a detailed picture of incidence, mortality and DALYs of EBV-attributed malignancies by age, sex, geographical region and SDI.

Conclusion

Our study shows that EBV-attributed malignancies account for a sizable fraction of the global burden of cancer. Increasing global population and life expectancy will further increase this burden. It is possible to prevent or at least significantly reduce this burden if an effective vaccine was available.[37] Future efforts should be aimed at accelerating and expanding vaccine developments.[38]

Contributors

GK conceptualized the study and prepared the first draft.

LAA and GK did the analysis and prepared the figures and tables.

GK, LAA, CF, and MN contributed to data interpretation and drafting of the manuscript.

All coauthors approved the final draft of the manuscript.

Conflict of interest

The authors have nothing to disclose.

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References

1 Fitzmaurice C, Abate D, Abbasi N et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol*. 2019. doi:10.1001/jamaoncol.2019.2996.

2 Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006;118(12):3030–3044.

3 de Martel C, Ferlay J, Franceschi S et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *The Lancet Oncology*. 2012;13(6):607–615.

4 Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *The Lancet Global Health*. 2016;4(9):e609–e616.

5 Pagano JS, Blaser M, Buendia M-A et al. Infectious agents and cancer: criteria for a causal relation. *Semin Cancer Biol*. 2004;14(6):453–471.

6 Young LS, Yap LF, Murray PG. Epstein-Barr virus: more than 50 years old and still providing surprises. *Nat Rev Cancer*. 2017;(12):789–802.

7 Fleisher G, Henle W, Henle G, Lennette ET, Biggar RJ. Primary infection with Epstein-Barr virus in infants in the United States: clinical and serologic observations. *J Infect Dis*. 1979;139(5):553–558.

8 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(2):173–179.

9 Longnecker R, Kieff E, Cohen JI. In: *Epstein-Barr virus. In: Knipe DM, Howley PM, eds. Fields Virology.* Lippincott Williams & Wilkins: Philadelphia, PA, 2013, pp 1898–1959.

10 Cohen JI. Epstein-Barr virus infection. *N Engl J Med*. 2000;343(7):481–492.

11 Rigaud S, Fondanèche M-C, Lambert N et al. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. *Nature*. 2006;444(7115):110–114.

12 Münz C, Moormann A. Immune escape by Epstein Barr virus associated malignancies. *Semin Cancer Biol*. 2008;18(6):381–387.

13 Carbone A, Gloghini A, Dotti G. EBV-Associated Lymphoproliferative Disorders: Classification and Treatment. *The Oncologist*. 2008;13(5):577–585.

14 Coffey AJ, Brooksbank RA, Brandau O et al. Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. *Nat Genet*. 1998;20(2):129–135.

15 Khan G, Hashim MJ. Global burden of deaths from Epstein-Barr virus attributable malignancies 1990-2010. *Infect Agents Cancer*. 2014;9(1):38.

16 Philip T. Burkitt's lymphoma in Europe. *IARC Sci Publ*. 1985;60:107–118.

17 Hsu JL, Glaser SL. Epstein-barr virus-associated malignancies: epidemiologic patterns and etiologic implications. *Crit Rev Oncol Hematol*. 2000;34(1):27–53.

18 Stefan DC, Lutchman R. Burkitt lymphoma: epidemiological features and survival in a South African centre. *Infectious Agents and Cancer*. 2014;9(1):19.

19 Queiroga EM, Gualco G, Weiss LM et al. Burkitt lymphoma in Brazil is characterized by geographically distinct clinicopathologic features. *Am J Clin Pathol*. 2008;130(6):946–956.

20 Boerma EG, van Imhoff GW, Appel IM, Veeger NJGM, Kluin PM, Kluin-Nelemans JC. Gender and age-related differences in Burkitt lymphoma--epidemiological and clinical data from The Netherlands. *Eur J Cancer*. 2004;40(18):2781–2787.

21 Magrath IT. African Burkitt's lymphoma. History, biology, clinical features, and treatment. *Am J Pediatr Hematol Oncol*. 1991;13(2):222–246.

22 Glaser SL, Lin RJ, Stewart SL et al. Epstein-Barr virus-associated Hodgkin's disease: epidemiologic characteristics in international data. *Int J Cancer*. 1997;70(4):375–382.

23 Jarrett RF, Armstrong AA, Alexander E. Epidemiology of EBV and Hodgkin's lymphoma. *Ann Oncol*. 1996;7(suppl 4):S5–S10.

24 Murray PG, Billingham LJ, Hassan HT et al. Effect of Epstein-Barr virus infection on response to chemotherapy and survival in Hodgkin's disease. *Blood*. 1999;94(2):442–447.

25 Stark GL, Wood KM, Jack F et al. Hodgkin's disease in the elderly: a population-based study. *Br J Haematol*. 2002;119(2):432–440.

26 Herling M, Rassidakis GZ, Medeiros LJ et al. Expression of Epstein-Barr virus latent membrane protein-1 in Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma: associations with presenting features, serum interleukin 10 levels, and clinical outcome. *Clin Cancer Res*. 2003;9(6):2114–2120.

27 Jarrett RF, Stark GL, White J et al. Impact of tumor Epstein-Barr virus status on presenting features and outcome in age-defined subgroups of patients with classic Hodgkin lymphoma: a population-based study. *Blood*. 2005;106(7):2444–2451.

28 Glaser SL, Gulley ML, Clarke CA et al. Racial/ethnic variation in EBV-positive classical Hodgkin lymphoma in California populations. *Int J Cancer*. 2008;123(7):1499–1507.

29 Chang ET, Adami H-O. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2006;15(10):1765–1777.

30 Murphy G, Pfeiffer R, Camargo MC, Rabkin CS. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. *Gastroenterology*. 2009;137(3):824–833.

31 Lee J-H, Kim S-H, Han S-H, An J-S, Lee E-S, Kim Y-S. Clinicopathological and molecular characteristics of Epstein-Barr virus-associated gastric carcinoma: a meta-analysis. *J Gastroenterol Hepatol*. 2009;24(3):354–365.

32 Dicker D, Nyguyen D, Abate KH, Abay SM, Abbasi N. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1684–1735.

33 Roth G A, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736–1788.

34 Spina M, Tirelli U, Zagonel V et al. Burkitt's lymphoma in adults with and without human immunodeficiency virus infection: a single-institution clinicopathologic study of 75 patients. *Cancer*. 1998;82(4):766–774.

35 Joossens JV, Hill MJ, Elliott P et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol*. 1996;25(3):494–504.

36 Al-Naeeb AB, Ajithkumar T, Behan S, Hodson DJ. Non-Hodgkin lymphoma. *BMJ*. 2018;362:k3204.

37 Cohen JI, Fauci AS, Varmus H, Nabel GJ. Epstein-Barr Virus: An Important Vaccine Target for Cancer Prevention. *Sci Transl Med*. 2011;3(107):107fs7.

38 Boyle M. A vaccine to kiss EBV goodbye. *Science Translational Medicine*. 2019;11(489):eaax1729.

FIGURES

Figure 1.
Global burden of (A) incident (B) deaths (C) DALYs for EBV-attributed malignancies in 2017 by world regions.

Figure 2.
Global burden of incident (A), deaths (B) and DALYs (C) for EBV-attributed malignancies by gender from 1990-2017.

Figure 3.
Global burden of incident and deaths of EBV-attributed (A) Burkitt lymphoma (B) Hodgkin lymphoma (C) Nasopharyngeal carcinoma (D) Gastric carcinoma in 2017 by SDI world regions.

Table 1. Characteristics and prevalence of EBV-attributable cases of BL, HL, NPC and GC

Malignancy	Comment on age, gender, regional variations	Prevalence of EBV in cases (%)	Cellular origin of malignant cells	Pattern of EBV gene expression in malignant cells	Ref.
Burkitt's Lymphoma (BL)					
• Endemic regions (M:F ratio 3:1)	Sub-Saharan Africa have highest risk	95%	B-cells	Type I latency (EBERs, EBNA1)	16–21
• Intermediate regions (M:F ratio 3:1)	North Africa & Middle East, Latin America, have intermediate risk	50%			
• Non-endemic regions (M:F ratio 3:1)	All other regions have low risk	20%			
Hodgkin disease (HL)					
• Children <14yrs	Age group 0-14 yrs have highest risk	62%	B-cells	Type II latency (EBERs, EBNA1, LMP1)	22–28
• Adults 15-54yrs	Age group 15-54 yrs lowest risk	30%			
• Adults >55yrs	Age group 55+ yrs have medium/high risk	55%			
Nasopharyngeal carcinoma (NPC)					
• High/intermediate incident regions	East Asia, South Asia, South East Asia, North Africa & Middle East	100%	Epithelial cells	Type II latency (EBERs, EBNA1, LMP1)	2,3,29
• Low incident regions	All other regions	80%			
Gastric carcinoma (GC)					
• Males	Males have higher risk	11%	Epithelial cells	Type II latency (EBERs, EBNA1, LMP1)	30,31
• Females	Females have lower risk	6%			

Based on published studies, we estimated the proportion of BL, HL, NPC and GC that are attributable to EBV, taking into consideration any established variations that have been reported in different age, sex and ethnic groups. The cellular origin of each malignancy and the pattern of EBV gene expression is also indicated. EBERs: Epstein-Barr encoded RNA; EBNA: Epstein-Barr nuclear antigen; LMP: Latent membrane protein.

Table 2. Global burden of incidence and deaths of EBV-attributed malignancies in 2017

Type of malignancy	All Cases						EBV-attributed Cases						% incidence of EBV-attributed cases (both)	
	Males		*Females*		*Both*		*Males*		*Females*		*Both*			
	Incidence	*Death*	*Incidence*	*Death*	*Incidence*	*Death*	*Incidence*	*Death*	*Incidence*	*Death*	*Incidence*	*Death*	*Incidence*	*Death*
BL	9,318	5,085	1,967	1,029	11,285	6,114	5,302	3,151	1,017	585	6,318	3,736	67.8	73·5
HL	60,751	20,720	40,381	11,840	101,133	32,560	24,806	9,281	15,303	5,083	40,109	14,364	39.7	44·1
NPC	81,249	50,993	28,531	18,557	109,781	69,550	78,127	48,883	27,427	17,846	105,554	66,729	96.1	95·9
GC	799,309	546,441	421,353	318,548	1,220,662	864,989	87,924	60,108	25,281	19,113	113,205	79,221	9.3	9·2
Total	**950,627**	**623,239**	**492,232**	**349,974**	**1,442,861**	**973,213**	**196,159**	**121,423**	**69,028**	**42,627**	**265,186**	**164,050**	**18.4**	**16·9**

BL: Burkitt lymphoma; HL: Hodgkin lymphoma; NPC: Nasopharyngeal carcinoma; GC: Gastric carcinoma

Figure 1.

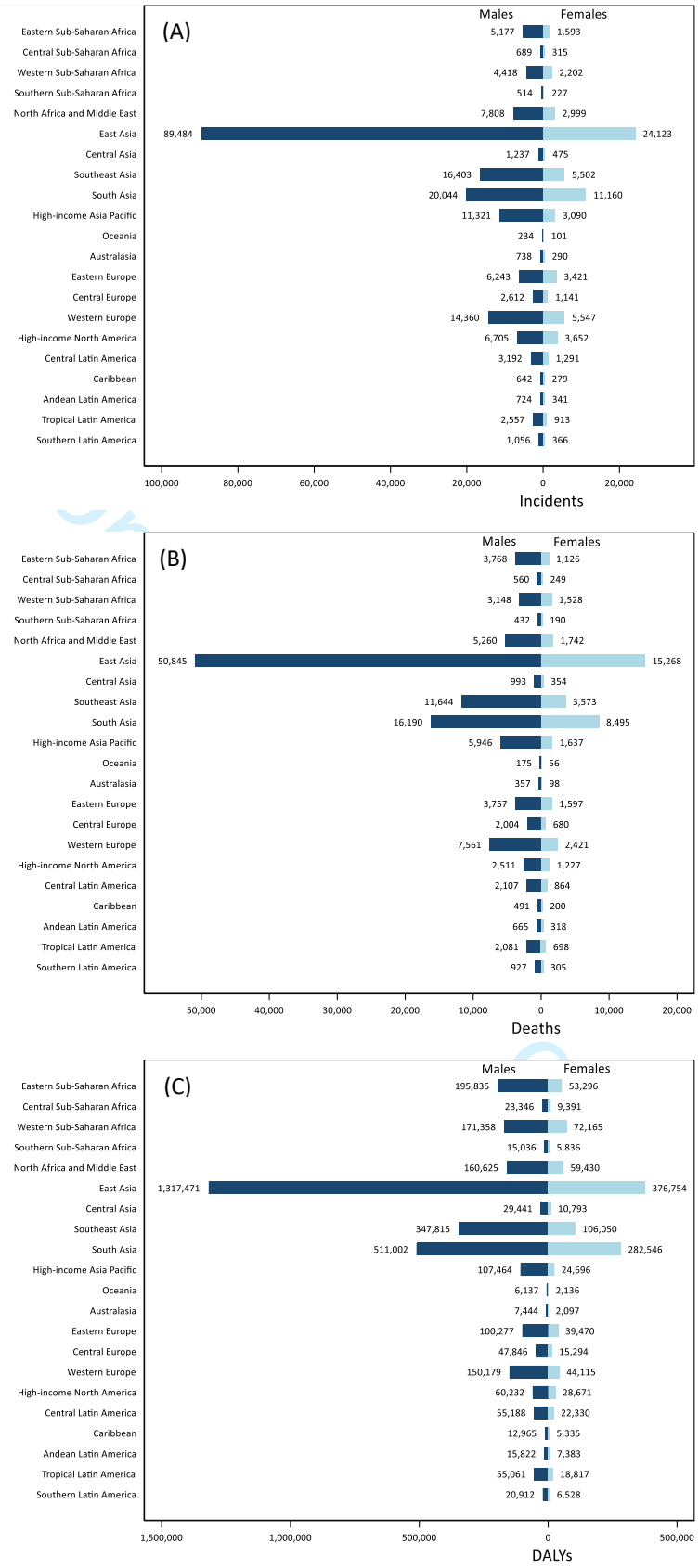

(A)
Males
Females
Eastern Sub-Saharan Africa 5,177 1,593
Central Sub-Saharan Africa 689 315
Western Sub-Saharan Africa 4,418 2,202
Southern Sub-Saharan Africa 514 227
North Africa and Middle East 7,808 2,999
East Asia 89,484 24,123
Central Asia 1,237 475
Southeast Asia 16,403 5,502
South Asia 20,044 11,160
High-income Asia Pacific 11,321 3,090
Oceania 234 101
Australasia 738 290
Eastern Europe 6,243 3,421
Central Europe 2,612 1,141
Western Europe 14,360 5,547
High-income North America 6,705 3,652
Central Latin America 3,192 1,291
Caribbean 642 279
Andean Latin America 724 341
Tropical Latin America 2,557 913
Southern Latin America 1,056 366
100,000 80,000 60,000 40,000 20,000 0 20,000
Incidents
(B)
Males
Females
Eastern Sub-Saharan Africa 3,768 1,126
Central Sub-Saharan Africa 560 249
Western Sub-Saharan Africa 3,148 1,528
Southern Sub-Saharan Africa 432 190
North Africa and Middle East 5,260 1,742
East Asia 50,845 15,268
Central Asia 993 354
Southeast Asia 11,644 3,573
South Asia 16,190 8,495
High-income Asia Pacific 5,946 1,637
Oceania 175 56
Australasia 357 98
Eastern Europe 3,757 1,597
Central Europe 2,004 680
Western Europe 7,561 2,421
High-income North America 2,511 1,227
Central Latin America 2,107 864
Caribbean 491 200
Andean Latin America 665 318
Tropical Latin America 2,081 698
Southern Latin America 927 305
50,000 40,000 30,000 20,000 10,000 0 10,000 20,000
Deaths
(C)
Males
Females
Eastern Sub-Saharan Africa 195,835 53,296
Central Sub-Saharan Africa 23,346 9,391
Western Sub-Saharan Africa 171,358 72,165
Southern Sub-Saharan Africa 15,036 5,836
North Africa and Middle East 160,625 59,430
East Asia 1,317,471 376,754
Central Asia 29,441 10,793
Southeast Asia 347,815 106,050
South Asia 511,002 282,546
High-income Asia Pacific 107,464 24,696
Oceania 6,137 2,136
Australasia 7,444 2,097
Eastern Europe 100,277 39,470
Central Europe 47,846 15,294
Western Europe 150,179 44,115
High-income North America 60,232 28,671
Central Latin America 55,188 22,330
Caribbean 12,965 5,335
Andean Latin America 15,822 7,383
Tropical Latin America 55,061 18,817
Southern Latin America 20,912 6,528
1,500,000 1,000,000 500,000 0 500,000
DALYs

Figure 2.

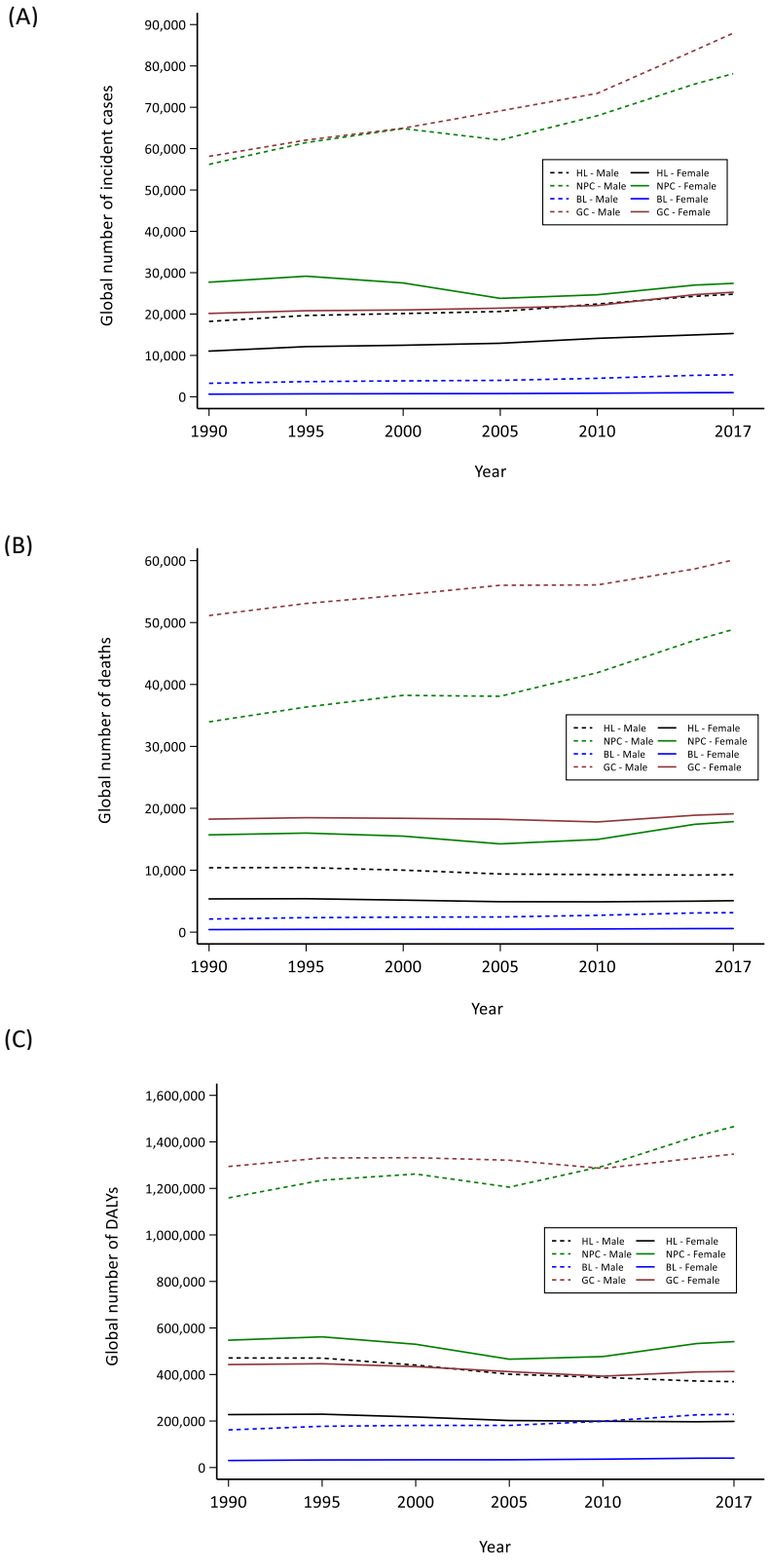
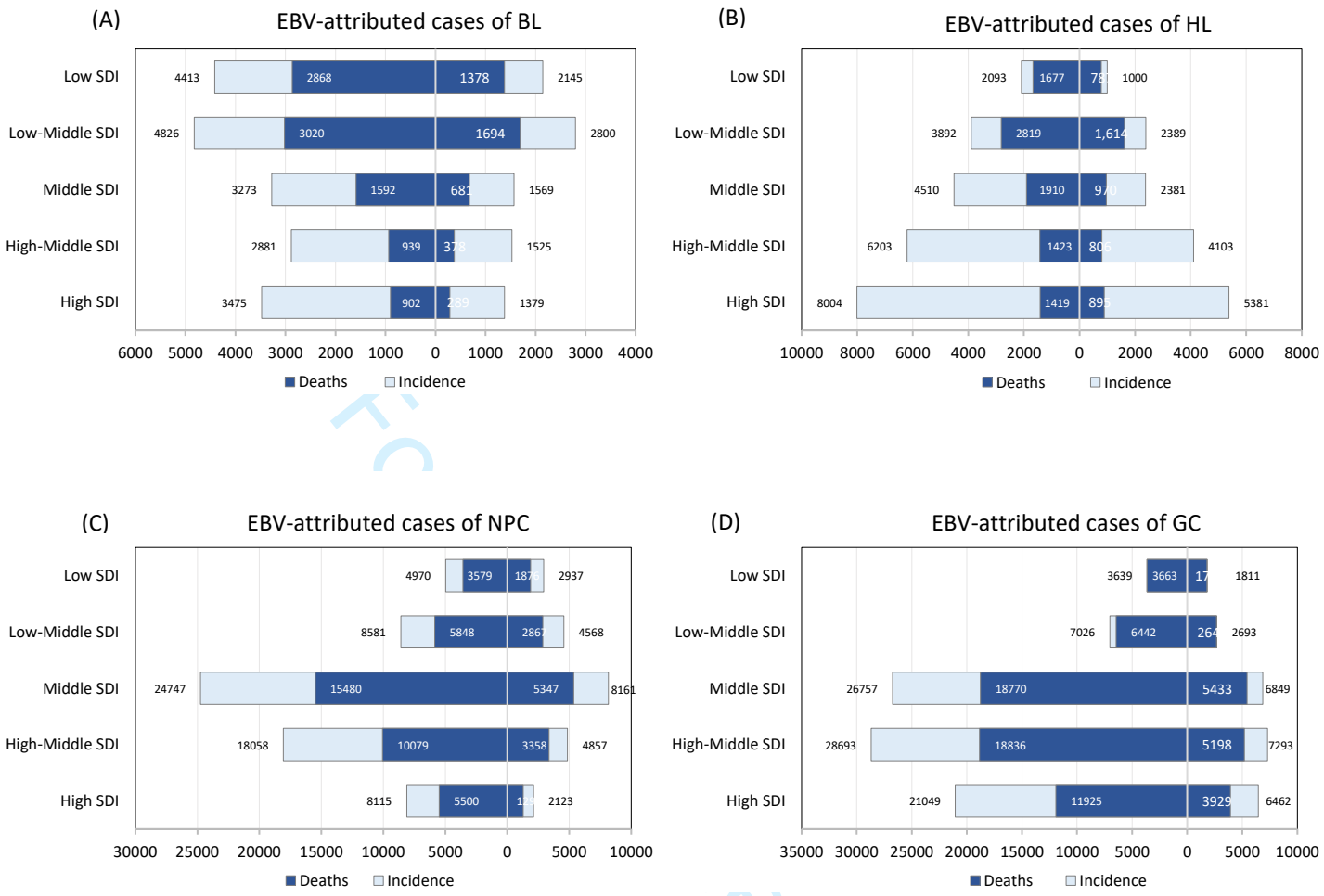

(A)
Global number of incident cases
90,000
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
1990
1995
2000
2005
2010
2017
Year
HL - Male
HL - Female
NPC - Male
NPC - Female
BL - Male
BL - Female
GC - Male
GC - Female
(B)
Global number of deaths
60,000
50,000
40,000
30,000
20,000
10,000
0
1990
1995
2000
2005
2010
2017
Year
HL - Male
HL - Female
NPC - Male
NPC - Female
BL - Male
BL - Female
GC - Male
GC - Female
(C)
Global number of DALYs
1,600,000
1,400,000
1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
1990
1995
2000
2005
2010
2017
Year
HL - Male
HL - Female
NPC - Male
NPC - Female
BL - Male
BL - Female
GC - Male
GC - Female

Figure 3.



Supplement 1

Global and regional incidence, mortality and disability-adjusted life-years for Epstein-Barr virus-attributable malignancies, 1990-2017

Gulfaraz Khan, PhD[1*], Christina Fitzmaurice, MD[2], Mohsen Naghavi, PhD[2,] Luai A. Ahmed, PhD[3]

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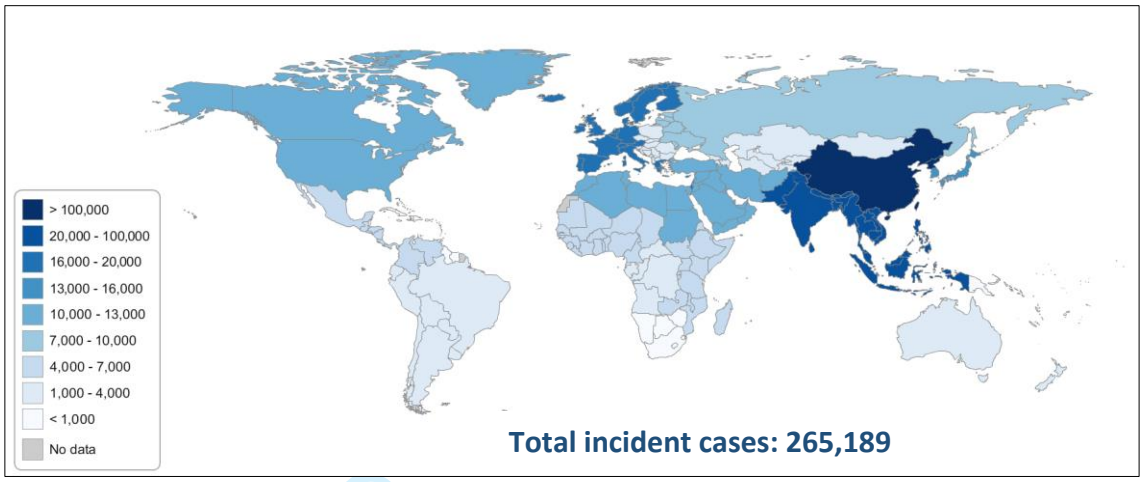
* Corresponding author

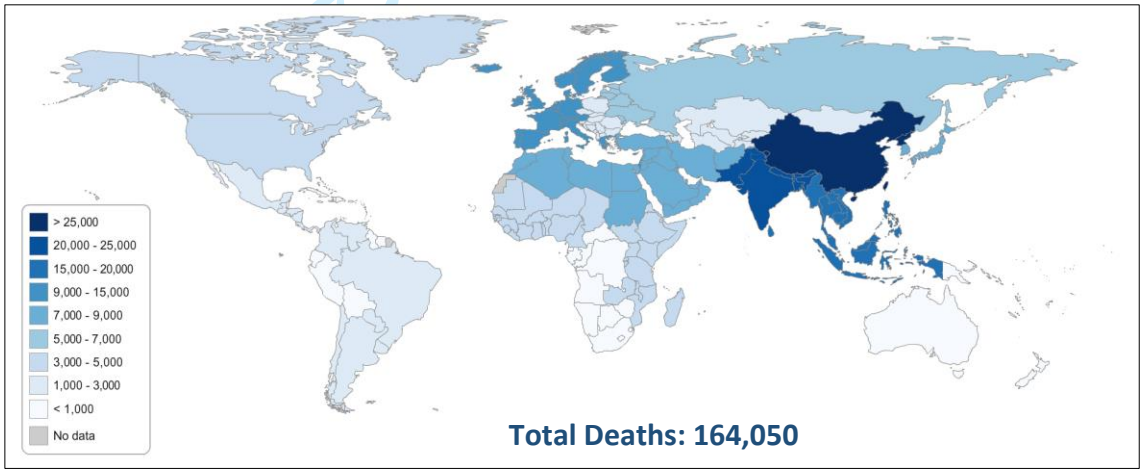
Contents

eFigure 1. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributable malignancies in 2017 by location

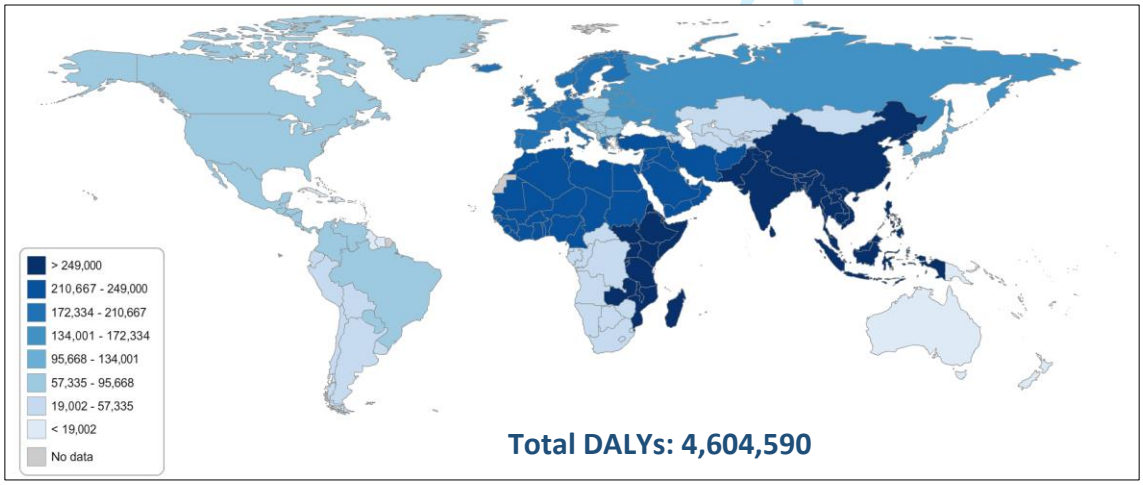
(A)



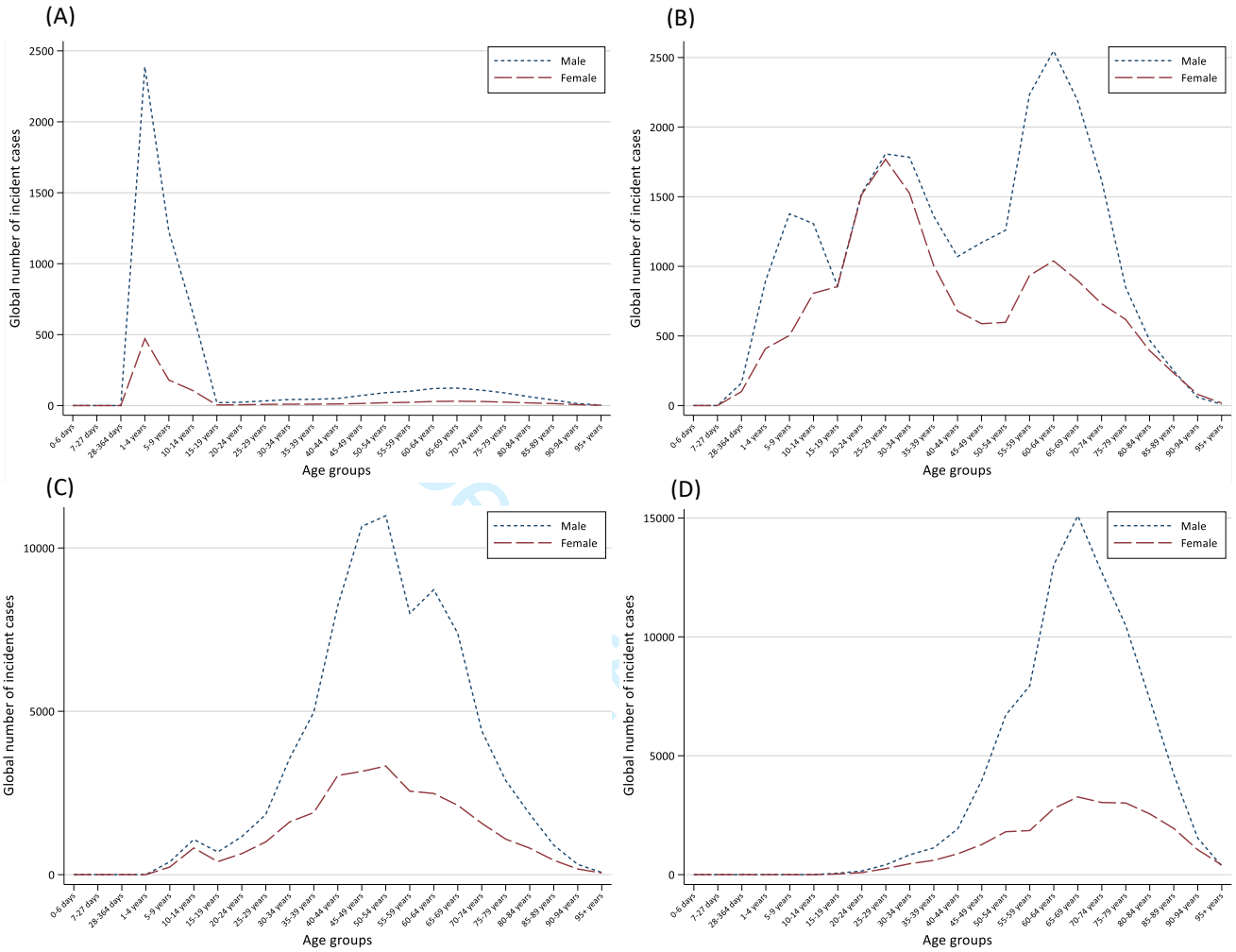
(B)



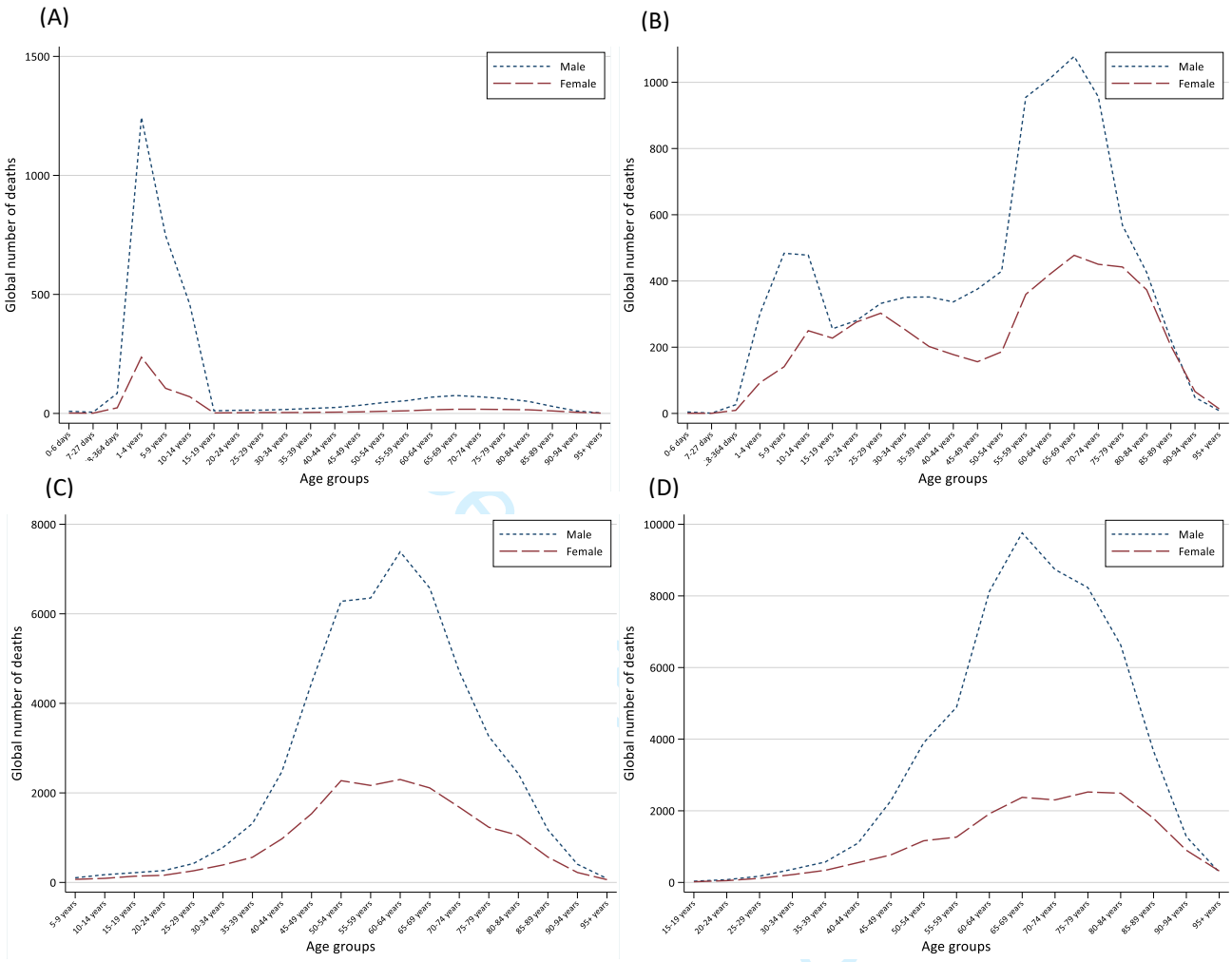
(C)



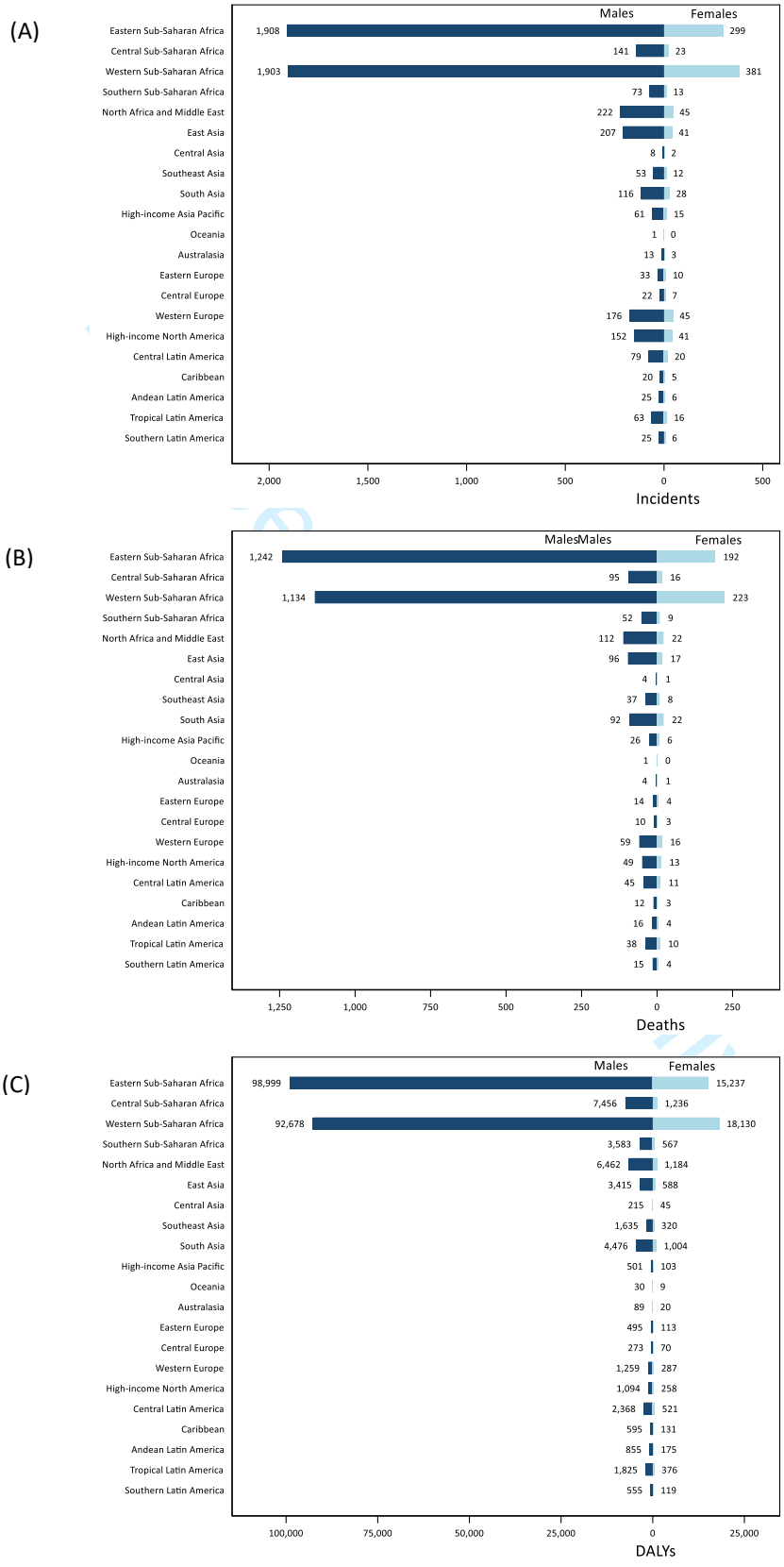
eFigure 2. Global burden of incidence of EBV-attributed (A) Burkitt lymphoma (B) Hodgkin lymphoma (C) nasopharyngeal carcinoma (D) gastric carcinoma in 2017 by gender and age



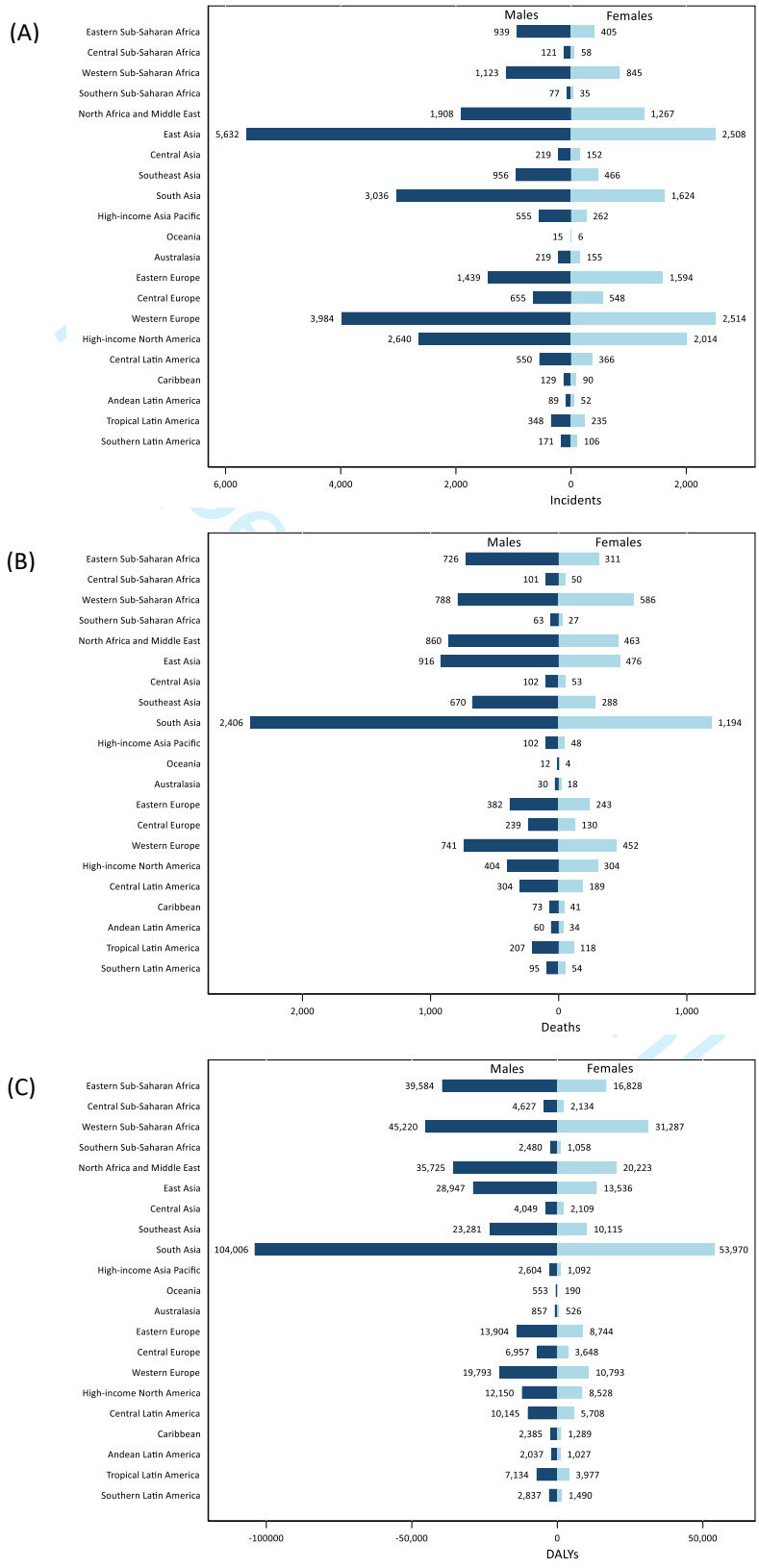
eFigure 3. Global burden of mortality from EBV-attributed (A) Burkitt lymphoma (B) Hodgkin lymphoma (C) nasopharyngeal carcinoma (D) gastric carcinoma in 2017 by gender and age



eFigure 4. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributed Burkitt lymphoma cases in 2017 by world regions

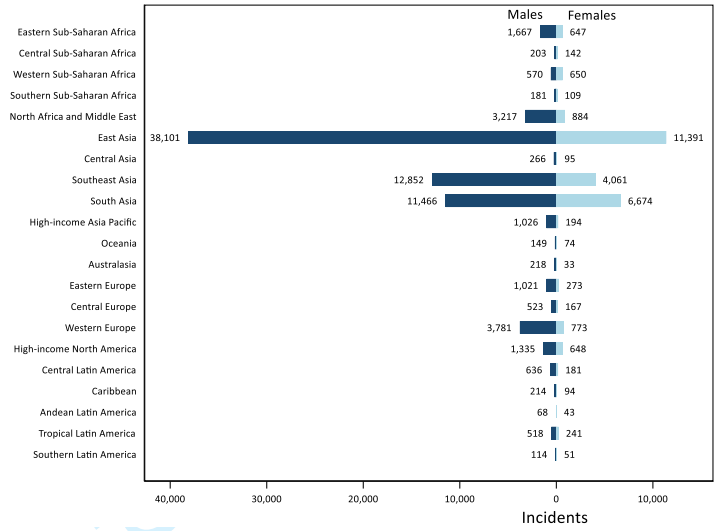


eFigure 5. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributed Hodgkin lymphoma cases in 2017 by world regions

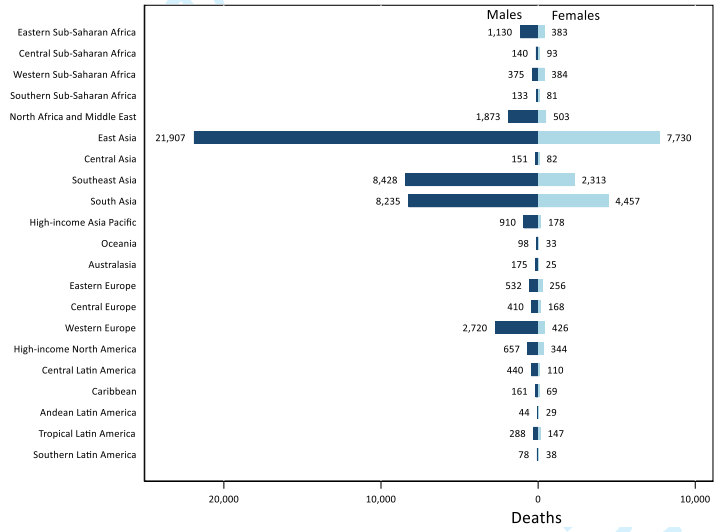


eFigure 6. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributed nasopharyngeal carcinoma cases in 2017 by world regions

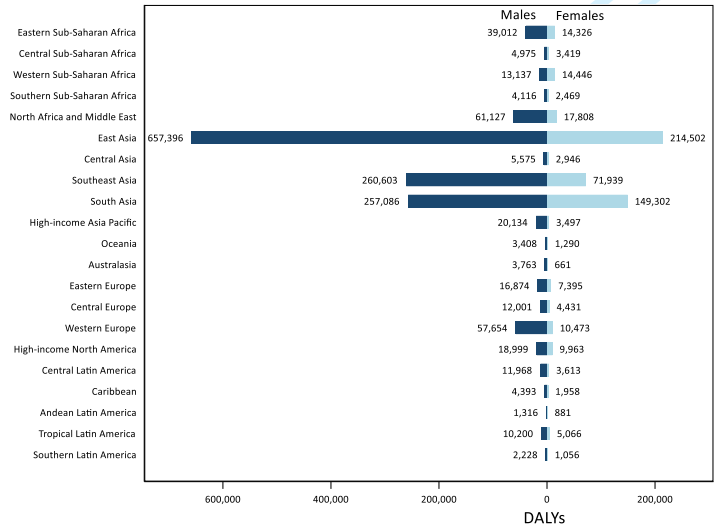
(A)



(B)

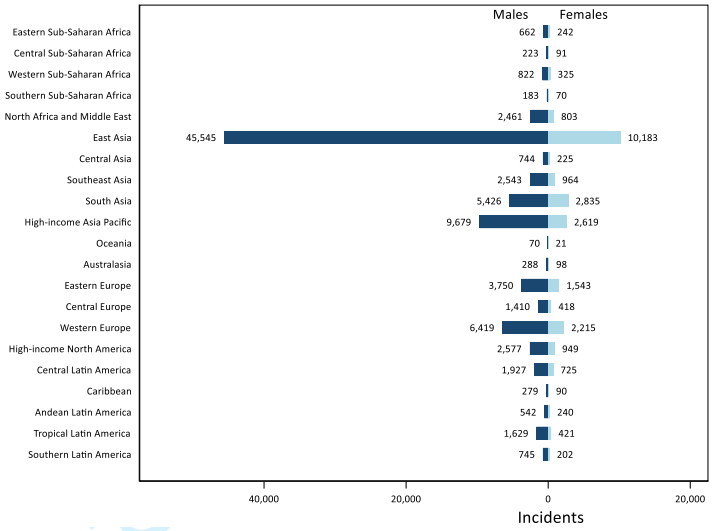


(C)

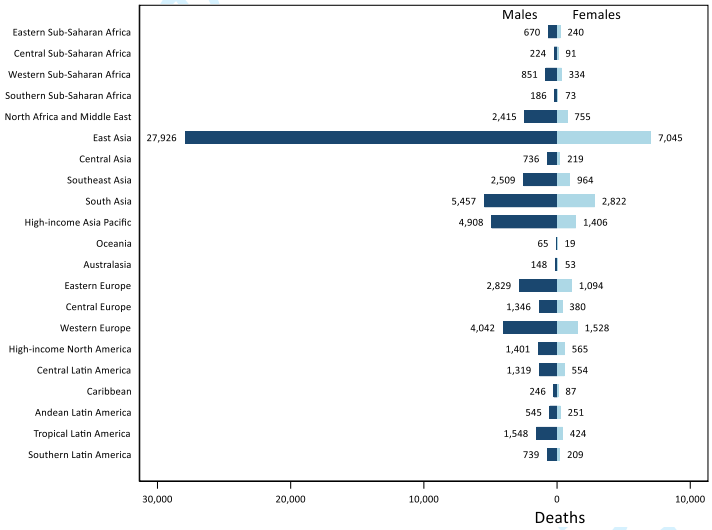


eFigure 7. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributed gastric cancer cases in 2017 by world regions

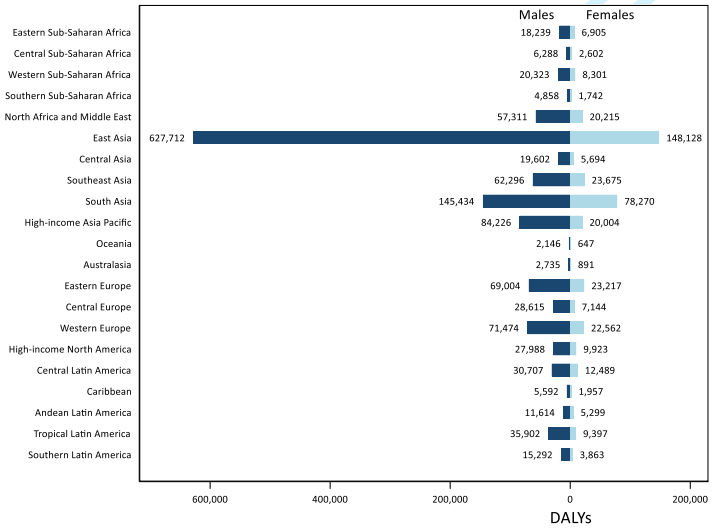
(A)



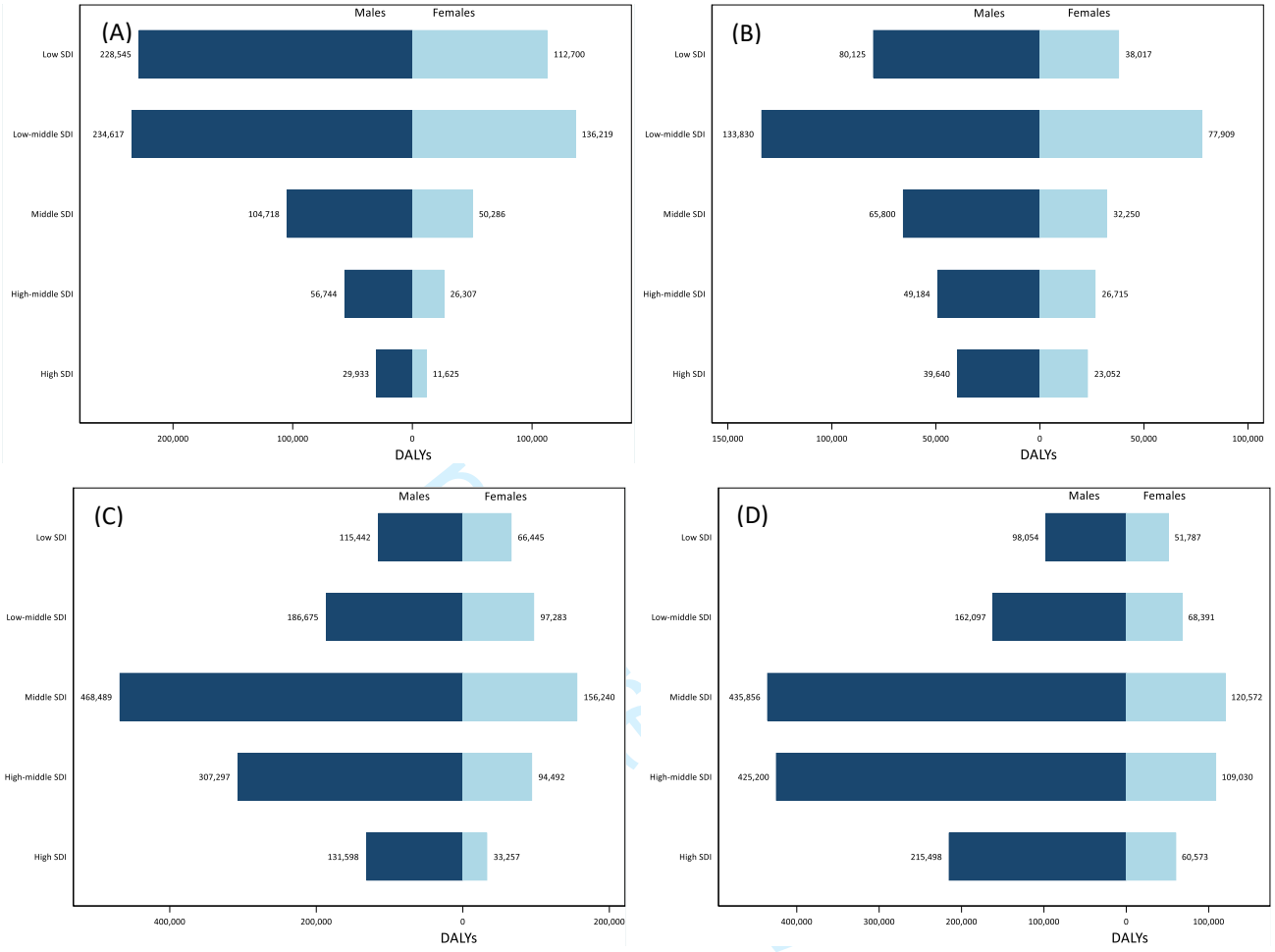
(C)



(B)



eFigure 8. Global burden of DALYs for EBV-attributed (A) Burkitt lymphoma (B) Hodgkin lymphoma (C) Nasopharyngeal carcinoma (D) Gastric carcinoma in 2017 by SDI world regions



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Global and regional incidence, mortality and disability-adjusted life-years for Epstein-Barr virus-attributable malignancies, 1990-2017

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Global and regional incidence, mortality and disability-adjusted life-years for Epstein-Barr virus-attributable malignancies, 1990-2017

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ABSTRACT

Objective To determine the global and regional burden of EBV-attributed malignancies.

Design An international comparative study based on the Global Burden of Disease (GBD) Study estimates.

Setting Global population by age, sex, region, demographic index and time.

Methods and outcome measures The burden of EBV-attributed Burkitt lymphoma (BL), Hodgkin lymphoma (HL), nasopharyngeal carcinoma (NPC) and gastric carcinoma (GC) was estimated in a 2-step process. In the first step, the fraction of each malignancy attributable to EBV was estimated based on published studies; this was then applied to the GBD estimates to determine the global and regional incidence, mortality and disability-adjusted life-years (DALYs) for each malignancy by age, sex, geographical region and social demographic index (SDI) from 1990-2017.

Results The combined global incidence of BL, HL, NPC and GC in 2017 was 1.442 million cases, with over 973,000 deaths. An estimated 265,000 (18%) incident cases and 164,000 (17%) deaths were due to the EBV-attributed fraction. This is an increase of 36% in incidence and 19% in mortality from 1990. In 2017, EBV-attributed malignancies caused 4.604 million DALYs, of which 82% was due to NPC and GC alone. The incidence of both of these malignancies was higher in high- and middle-high SDI regions and peaked in adults aged between 50-70 years. All four malignancies were more common in males and the highest burden was observed in East Asia.

Conclusions This study provides comprehensive estimates of the burden of EBV-attributed BL, HL, NPC and GC. The overall burden of EBV related malignancies is likely to be higher since EBV is etiologically linked to several other malignancies not included in this analysis. Increasing global population and life expectancy is expected to further raise this burden in the future. The urgency for developing an effective vaccine to prevent these malignancies cannot be overstated.

Strengths and limitations of this study

- This study examined the burden of EBV-attributed malignancies using the most up-to-date and reliable data from the GBD Study.
- This is the first study of its kind to quantitate the global and regional incidence, mortality and DALYs of EBV-attributed malignancies by age, sex, geographical region and SDI from 1990-2017.
- Although EBV is linked to a number of malignancies, this study assessed only four EBV-associated malignancies.
- The GBD estimates, albeit the most comprehensive and most refined, have their own drawbacks and limitations.

INTRODUCTION

Cancer is one of the leading causes of death worldwide. The latest estimates indicate that in 2017, there were nearly 17 million new cases and over 9 million deaths worldwide.[1] Alarmingly, the overall burden due to cancer is on the rise, primarily due to population growth and increasing life expectancy.[1] Cancer is a complex and multi-factorial disease and strategies to reduce its burden will require not only basic research, but also a global action plan targeting early detection, control and prevention. One fundamental aspect of prevention is to understand the causes of cancers. It is now well-established that infectious agents, either on their own or in combination with genetic and environmental factors, play a role in the pathogenesis of approximately 15-20% of all human malignancies.[2–4] Most of these malignancies are linked to only a handful of infectious agents.[4,5] One such agent is Epstein-Barr virus (EBV).

EBV is a very common virus asymptomatically infecting over 90% of the population.[6] In most cases, the infection is acquired early in childhood, often before the age of 5 years.[7] Once infected, the virus persists in B-cells for life.[8] Depending on the pattern of EBV gene expression in the infected cells, four latency programs, referred to as latency 0 to 3, have been recognized. Different latency programs are associated with different pathologies.[9] Moreover, the fact that EBV is very common in the general population, and yet only a very small fraction of infected individuals develop EBV-associated pathologies, indicates that other risk factors such immune deficiencies, genetic predisposition and environmental factors are also essential in the development of these pathologies.[10–12] Thus, to establish a causal link, it is necessary to directly demonstrate the virus in the affected tissues. With the advancement in technology and detection methods, the virus has now been unequivocally demonstrated in the tumour cells of several different malignancies.[9] EBV is now firmly linked to the development of Burkitt's lymphoma (BL), nasopharyngeal carcinoma (NPC), Hodgkin lymphoma (HL) and gastric carcinomas (GC).[9] Additionally, EBV is also clearly implicated in the pathogenesis of several other malignancies, including lymphomas arising in immunocompromised individuals, such as allograft recipients, AIDS patients and individuals with congenital immunodeficiencies.[13,14]

Although EBV was the first virus identified to be etiologically associated with human malignancies, no effective anti-viral drug or approved vaccine is available for its elimination or prevention. An accurate estimate of the burden of EBV-attributed disorders is unknown. The purpose of this study was to partially fill this gap by providing estimates of EBV-attributed BL, HL, NPC and GC, using the Global Burden of Disease (GBD 2017) estimates.

METHODS

Patient and public involvement

This study was based on an open-access database available from the website of the Institute of Health Metrics and Evaluation, University of Washington. The database has no identifiable information on the patients. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Definition and prevalence of EBV-attributable cases of BL, HL, NPC, GC

For the purpose of this study, we define EBV-attributable cancers as those in which viral nucleic acid, and/or viral proteins can be demonstrated directly in the malignant cells (Table 1). This has consistently and unequivocally been confirmed for BL, HL, NPC and GC by numerous studies (Table 1). However, not all of the cases of these malignancies are EBV-attributable. Moreover, the EBV-attributable fraction appears to vary with age, gender and geographical region. Taking these variables into account, we first estimated the fraction of EBV-attributable malignancies based on published studies as described in our previous study.[15] Table 1 summarizes the outcome of this analysis.

Table 1. Characteristics and prevalence of EBV-attributable cases of BL, HL, NPC and GC

Malignancy	Comment on age, gender, regional variations	Prevalence of EBV in cases (%)	Cellular origin of malignant cells	Pattern of EBV gene expression in malignant cells	Ref.
Burkitt's Lymphoma (BL)					
• Endemic regions (M:F ratio 3:1)	Sub-Saharan Africa have highest risk	95%	B-cells	Type I latency (EBERs, EBNA1)	16–21
• Intermediate regions (M:F ratio 3:1)	North Africa & Middle East, Latin America, have intermediate risk	50%			
• Non-endemic regions (M:F ratio 3:1)	All other regions have low risk	20%			
Hodgkin disease (HL)					
• Children <14yrs	Age group 0-14 yrs have highest risk	62%	B-cells	Type II latency (EBERs, EBNA1, LMP1)	22–28
• Adults 15-54yrs	Age group 15-54 yrs lowest risk	30%			
• Adults >55yrs	Age group 55+ yrs have medium/high risk	55%			
Nasopharyngeal carcinoma (NPC)					
• High/intermediate incident regions	East Asia, South Asia, South East Asia, North Africa & Middle East	100%	Epithelial cells	Type II latency (EBERs, EBNA1, LMP1)	2,3,29
• Low incident regions	All other regions	80%			
Gastric carcinoma (GC)					
• Males	Males have higher risk	11%	Epithelial cells	Type II latency (EBERs, EBNA1, LMP1)	30,31
• Females	Females have lower risk	6%			

Based on published studies, we estimated the proportion of BL, HL, NPC and GC that are attributable to EBV, taking into consideration any established variations that have been reported in different age, sex and ethnic groups. The cellular origin of each malignancy and the pattern of EBV gene expression is also indicated. EBERs: Epstein-Barr encoded RNA; EBNA: Epstein-Barr nuclear antigen; LMP: Latent membrane protein.

Estimation of the incidence, mortality and DALYs for BL, HL, NPC, GC

Estimates of incidence, mortality and DALYs for HL, NPC and GC were obtained from the GBD 2017 study. GBD methods are described extensively elsewhere.[1,32,33] Briefly, estimates are based on multiple data sources, including vital registration systems, cancer registries and verbal autopsy data.[1,32,33] A range of statistical models were used to derive the final estimates. Since each GBD study re-estimates the entire data sets annually, the results presented here are the most refined and up-to-date.

Data sets of age and sex-specific estimates of incidence, mortality and DALYs for 21 global regions from 1990-2017 were directly available from the GBD results database for HL, NPC and GC (http://ghdx.healthdata.org/gbd-results-tool, downloaded on 24th of March 2019). For BL, no direct estimates were available. The GBD study includes BL under the broader category of non-Hodgkin lymphomas (NHL). Based on previous studies,[2,15] we estimated the percentage of BL cases within the NHL category in the age group 0-14 years 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 percentage of BL in HIV-negative adults was conservatively estimated to be 2% of all NHL cases.[34] BL is approximately 3-4 times more common in males compared to females.[16,20,21] In this study we used male:female ratio of 3:1 in calculating the prevalence of BL. Thus, for BL, we first estimated the incidence, mortality and DALYs by age, sex and geographical region, before calculating the fractions attributable to EBV.

Estimation of the incidence, mortality and DALYs of EBV-attributed fraction of BL, HL, NPC, GC

The EBV-attributable proportion of BL, HL, NPC and GC estimated from published studies (Table 1) was applied to the GBD 2017 estimates. For example, for BL in East Sub-Saharan Africa, GBD 2017 estimates show 1526 incident cases of NHL in the age group 1-4 years. In this region, 90.5% of NHL cases have been estimated to be BL in this age group,[2] with a male predominance of 3:1.[16,17,20] Based on this, 1526 × 0.905 × 0.75 gives an estimate of the incidence of BL in males in the 1-4 year age group in East Sub-Saharan Africa in 2017 to be 1036. Since 95% of BL cases in this age group and in this region are EBV associated, [2,3] the incidence of EBV-attributed BL cases was estimated to be 984 cases (1036 x 0.95). Using this approach, we calculated the incidence, mortality and DALYs for each of the four EBV-associated malignancy in males and females in 23 different age groups and 21 different geographical regions from 1990-2017.

Estimation of the burden of EBV-attributed fraction of BL, HL, NPC, GC by socio-demographic index

To assess the influence of demographic development on the burden of EBV-attributable malignancies, we used each country's socio-demographic index (SDI) to estimate EBV-attributed fraction of BL, HL, NPC and GC. SDI is a summary measure of the lag distributed income (LDI) per capita, educational attainment and fertility rate and it is regarded as a good indicator of a country's socio-demographic development.[1] We assessed the burden of EBV-attributed malignancies by five SDI categories: low, low-middle, middle, middle-high and high.[1]

RESULTS

Global burden of EBV-attributed malignancies

In 2017, there were 1.442 million incident cases and 973,000 deaths from BL, HL, NPC and GC, contributing to 22.958 million DALYs (Table 2). The overall global burden of EBV-attributed fraction of these four malignancies contributed to over 265,000 (18%) of the incident cases, 164,000 (17%) of deaths and 4.6 million (20%) of DALYs (Tables 2 and Supplementary Figure 1). The individual contribution of each of these four malignancies to the overall burden of EBV-attributed fractions varied considerably. NPC and GC together accounted for over 218,000 (82%) incident cases, 146,000 (89%) deaths and 3.8 million (82%) DALYs (Tables 2). Over the period of 27 years (1990-2017), the burden of mortality from these EBV-attributed malignancies increased by 19%.

Table 2. Global burden of incidence and deaths of EBV-attributed malignancies in 2017

Type of malignancy	All Cases						EBV-attributed Cases						% incidence of EBV-attributed cases (both)	
	Males		*Females*		*Both*		*Males*		*Females*		*Both*			
	Incidence	*Death*	*Incidence*	*Death*	*Incidence*	*Death*	*Incidence*	*Death*	*Incidence*	*Death*	*Incidence*	*Death*	*Incidence*	*Death*
BL	9,318	5,085	1,967	1,029	11,285	6,114	5,302	3,151	1,017	585	6,318	3,736	67.8	73·5
HL	60,751	20,720	40,381	11,840	101,133	32,560	24,806	9,281	15,303	5,083	40,109	14,364	39.7	44·1
NPC	81,249	50,993	28,531	18,557	109,781	69,550	78,127	48,883	27,427	17,846	105,554	66,729	96.1	95·9
GC	799,309	546,441	421,353	318,548	1,220,662	864,989	87,924	60,108	25,281	19,113	113,205	79,221	9.3	9·2
Total	**950,627**	**623,239**	**492,232**	**349,974**	**1,442,861**	**973,213**	**196,159**	**121,423**	**69,028**	**42,627**	**265,186**	**164,050**	**18.4**	**16·9**

BL: Burkitt lymphoma; HL: Hodgkin lymphoma; NPC: Nasopharyngeal carcinoma; GC: Gastric carcinoma

EBV-attributed malignancies by sex and age

The incidence and mortality of all four malignancies (BL, HL, NPC and GC) was higher in males than in females in all world regions. The EBV-attributed fraction of these malignancies was also higher in males compared to females (Figure 1). The combined incidence of EBV-attributed BL, HL, NPC and GC in 2017 was 196,000 in males and 69,000 in females (2.8:1.0) (Tables 2). Incidence and mortality of EBV-attributed malignancies also varied with age (Supplementary Figures 2-3). Burkitt lymphoma was primarily seen in children, peaking in the 5-10 year age group (Supplementary Figure 2A). By contrast, NPC and GC occurred in adults, peaking in the 45-60 (Supplementary Figure 2C) and 65-80 (Supplementary Figure 2D) age group, respectively. The distribution of EBV-attributable incidence of HL revealed more than one age group to be affected (Supplementary Figure 2B). For men, incidence peaked in three age groups, 5-15, 25-40 and 55-70 years. Interestingly, for women, only two peaks were noted; a large peak in the 25-40 year age group and a smaller peak in the 55-70 year group.

EBV-attributed malignancies by region and time

There was considerable regional variation in the burden of EBV-attributed BL, HL, NPC and GC (Supplementary Figures 4-6). This ranged from less than 1000 incident cases in Southern Sub-Saharan Africa to more than 100,000 cases in East Asia (Supplementary Figure 1). In fact, 43% of all global incident cases of these four malignancies and 40% of all deaths were in East Asia (Figure 1). This high burden is primarily due to the high incidence of NPC and GC in East Asia (Supplementary Figure 6-7), particularly in China (Supplementary Figure 1).

The combined incidence of the four EBV-attributed malignancies has increased from 195,000 in 1990 to 265,000 in 2017. This increase is particularly evident for males (Figure 2A). For females, the increase has been either moderate, or in the case of NPC, actually decreased slightly (277,000 in 1990 to 274,000 in 2017). In terms of the burden of deaths, absolute numbers declined only for HL (Figure 2B). Since the global population has increased over the same timeframe, the rate of death per 100,000 for HL has decreased significantly from 0.67 in 1990 to 0.43 in 2017.

EBV-attributed malignancies by socio-demographic index

Since a country's socio-economic development is an important driver of the burden of disease, we assessed the impact of SDI on the burden of EBV-attributed malignancies. Countries were grouped into five categories, low, low-middle, middle, middle-high and high SDI. As expected, there was considerable heterogeneity in both incidence and mortality by SDI status (Figure 3). For EBV-attributed BL, low and low-middle SDI regions had the highest burden of incidence and deaths, whilst for EBV-attributed HL, incidence appeared to directly correlate with the SDI index; the highest burden was observed in the high SDI region (Figure 3B). The burden of deaths from EBV-attributed HL on the other hand, did not follow the pattern seen for incident cases. The burden of deaths was greater in low and low-middle SDI regions, possibly reflecting less resources for treating HL in these regions compared to the affluent high SDI countries (Figure 3B). The burden of DALYs for EBV-attributed cases also varied by SDI; low and low-middle countries had the highest burden for BL and HL, but for NPC and GC, the highest burden was observed in middle and middle-high countries (Supplementary Figure 8).

DISCUSSION

Improvements in life expectancy and population growth has led to an increase in the global burden of cancer, which now ranks second after cardiovascular diseases.[1] To address this growing global health problem, a multi-pronged approach is needed. It is essential not only to find better therapies for cancer, but importantly, to prevent cancer from occurring in the first place. Thus, understanding the causes and risk factors involved in the development of cancer is of central importance. In this first of a kind study, we provide detailed estimates of the global and regional incidence, mortality and DALYs of EBV-attributed malignancies by age, sex, geographical region and SDI from 1990-2017.

Our analysis revealed that in 2017, BL, HL, NPC and GC accounted for 1.44 million incident cases and almost 1 million deaths. Of these, just over 265,000 incident cases and 164,000 deaths were attributed to EBV infection. This is an increase of 19% and 36% respectively from 1990. Since the global prevalence and pattern of EBV infection has not changed, the drivers of the increase in burden of EBV-attributed cancers appear to be due to an increase in the life expectancy, population growth and changing age structure.[1] The contribution of these drivers varies with socio-economic development. Whist, population growth is a major driver of the increased burden in low SDI regions, increased life expectancy appears to be more important in middle-high and high SDI regions.[1] As previously reported, all four malignancies were more common in males.[1] The reasons for the male preponderance is not known, but genetics and male life-style risk factors are likely to be important contributors.[29,35]

The fraction of cases attributed to EBV also varied significantly depending on the type of malignancy. Whilst more than 95% of NPC cases were attributed to EBV, for GC, this fraction was less than 10%. In spite of this low attributed fraction, GC was still the leading cause of EBV-attributed cancer burden, accounting for 43% of all incident cases and nearly 50% of all deaths in 2017. This burden is due to the fact that GC is amongst the top 6 most frequently diagnosed cancer globally, and the most common cancer in some East Asian countries.[1] Although the absolute number of EBV-attributed GC incident cases has increased from 78,000 in 1990 to over 113,000 in 2017, the age-standardized incidence rate has actually declined globally. GC peaks in late adulthood (above 65 years) and the absolute increase in incidence of GC could be explained by the increase in life expectancy and change in population age structure. East Asia also had by far the highest incidence of NPC. In fact, approximately 50% of the global number of EBV-attributed cases of GC and NPC occurred in East Asia. The reasons for the high prevalence of these two malignancies in this region is not clear. It is believed that a combination of genetic and environmental risk factors are involved. Early infection with EBV and/or *Helicobacter pylori*, both of which are common in the region are important risk factors, as is diet, high salt intake, smoking, and life style factors.[29,35] A change in exposure to these risk factors has been reported to reduce the incidence rates, as shown in studies on descendants of migrants from high to low incidence regions.[29]

In contrast to NPC and GC, the epidemiology of BL and HL is very different. Burkitt lymphoma is a childhood malignancy most prevalent in Eastern and Western Sub-Saharan Africa. Males are more predominantly affected.[16–21] Three risk factors have been shown to be involved in the development of BL; EBV infection, malaria, and genetic translocation involving the *c-myc* oncogene.[9] However, the level of contribution of each of these risk factors and how they interact to promote the development of BL is unknown. As for HL, this study shows that around 40% of all cases worldwide are EBV-attributed and this fraction varies not only by gender and age, but also by geographical region.[22] These variations suggest that other risk factors, in addition to EBV are involved in the pathogenesis of HL. Studies have demonstrated that infectious mononucleosis, a self-limiting lymphoproliferative condition caused by primary EBV infection, is associated with a significantly increased risk of developing HL.[9]

Limitations

The analysis presented in this report is to our knowledge the most comprehensive and up-to-date assessment of the magnitude and distribution EBV-attributed malignancies. However, the accuracy of the results rely on a number predictions and assumptions. First, our estimates of the burden of EBV-attributed BL, HL, NPC and GC were calculated based on the GBD 2017 estimates on incidence, mortality and DALYs of these malignancies. The GBD study, albeit the most comprehensive and most refined, nevertheless has its own drawbacks and limitations.[1,33] Second, GBD groups BL as part of the larger category of non-Hodgkin lymphomas (NHL). In this study, when calculating the incidence, mortality and DALYs for BL, we assumed that these measures were proportionally the same for all the lymphomas in the NHL group. In reality this is not quite true.[36] In future GDB studies, we aim to include BL as a separate entity, which will provide more accurate estimates. Third, although age, gender and regional variations in EBV-attributable fractions of these malignancies were taken into consideration, we assumed that the EBV-attributable fraction was the same for incidence, mortality and DALYs. Fourth, it is currently unclear if EBV-attributed malignancies have a better or worse prognosis. Thus, in this study we assumed that the mortality and DALYs was the same for EBV-associated and non-associated cancers. Similarly, it was assumed that the mortality from EBV-attributed malignancies was the same in both males and females. In spite of these limitations, this is the only study of its kind to provide a detailed picture of incidence, mortality and DALYs of EBV-attributed malignancies by age, sex, geographical region and SDI.

Conclusion

Our study shows that EBV-attributed malignancies account for a sizable fraction of the global burden of cancer. Increasing global population and life expectancy will further increase this burden. It is possible to prevent or at least significantly reduce this burden if an effective vaccine was available.[37] Future efforts should be aimed at accelerating and expanding vaccine developments.[38]

Contributors

GK conceptualized the study and prepared the first draft.

LAA and GK did the analysis and prepared the figures and tables.

GK, LAA, CF, and MN contributed to data interpretation and drafting of the manuscript.

All coauthors approved the final draft of the manuscript.

Conflict of interest

The authors have nothing to disclose.

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Patient consent for publication

Not required.

Data availability statement

Data are publicly available from the Global Burden of Disease Study (http://ghdx.healthdata.org/gbd-results-tool).

References

1 Fitzmaurice C, Abate D, Abbasi N et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol*. 2019. doi:10.1001/jamaoncol.2019.2996.

2 Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006;118(12):3030–3044.

3 de Martel C, Ferlay J, Franceschi S et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *The Lancet Oncology*. 2012;13(6):607–615.

4 Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *The Lancet Global Health*. 2016;4(9):e609–e616.

5 Pagano JS, Blaser M, Buendia M-A et al. Infectious agents and cancer: criteria for a causal relation. *Semin Cancer Biol*. 2004;14(6):453–471.

6 Young LS, Yap LF, Murray PG. Epstein-Barr virus: more than 50 years old and still providing surprises. *Nat Rev Cancer*. 2017;(12):789–802.

7 Fleisher G, Henle W, Henle G, Lennette ET, Biggar RJ. Primary infection with Epstein-Barr virus in infants in the United States: clinical and serologic observations. *J Infect Dis*. 1979;139(5):553–558.

8 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(2):173–179.

9 Longnecker R, Kieff E, Cohen JI. In: *Epstein-Barr virus. In: Knipe DM, Howley PM, eds. Fields Virology.* Lippincott Williams & Wilkins: Philadelphia, PA, 2013, pp 1898–1959.

10 Cohen JI. Epstein-Barr virus infection. *N Engl J Med*. 2000;343(7):481–492.

11 Rigaud S, Fondanèche M-C, Lambert N et al. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. *Nature*. 2006;444(7115):110–114.

12 Münz C, Moormann A. Immune escape by Epstein Barr virus associated malignancies. *Semin Cancer Biol*. 2008;18(6):381–387.

13 Carbone A, Gloghini A, Dotti G. EBV-Associated Lymphoproliferative Disorders: Classification and Treatment. *The Oncologist*. 2008;13(5):577–585.

14 Coffey AJ, Brooksbank RA, Brandau O et al. Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. *Nat Genet*. 1998;20(2):129–135.

15 Khan G, Hashim MJ. Global burden of deaths from Epstein-Barr virus attributable malignancies 1990-2010. *Infect Agents Cancer*. 2014;9(1):38.

16 Philip T. Burkitt's lymphoma in Europe. *IARC Sci Publ*. 1985;60:107–118.

17 Hsu JL, Glaser SL. Epstein-barr virus-associated malignancies: epidemiologic patterns and etiologic implications. *Crit Rev Oncol Hematol*. 2000;34(1):27–53.

18 Stefan DC, Lutchman R. Burkitt lymphoma: epidemiological features and survival in a South African centre. *Infectious Agents and Cancer*. 2014;9(1):19.

19 Queiroga EM, Gualco G, Weiss LM et al. Burkitt lymphoma in Brazil is characterized by geographically distinct clinicopathologic features. *Am J Clin Pathol*. 2008;130(6):946–956.

20 Boerma EG, van Imhoff GW, Appel IM, Veeger NJGM, Kluin PM, Kluin-Nelemans JC. Gender and age-related differences in Burkitt lymphoma--epidemiological and clinical data from The Netherlands. *Eur J Cancer*. 2004;40(18):2781–2787.

21 Magrath IT. African Burkitt's lymphoma. History, biology, clinical features, and treatment. *Am J Pediatr Hematol Oncol*. 1991;13(2):222–246.

22 Glaser SL, Lin RJ, Stewart SL et al. Epstein-Barr virus-associated Hodgkin's disease: epidemiologic characteristics in international data. *Int J Cancer*. 1997;70(4):375–382.

23 Jarrett RF, Armstrong AA, Alexander E. Epidemiology of EBV and Hodgkin's lymphoma. *Ann Oncol*. 1996;7(suppl 4):S5–S10.

24 Murray PG, Billingham LJ, Hassan HT et al. Effect of Epstein-Barr virus infection on response to chemotherapy and survival in Hodgkin's disease. *Blood*. 1999;94(2):442–447.

25 Stark GL, Wood KM, Jack F et al. Hodgkin's disease in the elderly: a population-based study. *Br J Haematol*. 2002;119(2):432–440.

26 Herling M, Rassidakis GZ, Medeiros LJ et al. Expression of Epstein-Barr virus latent membrane protein-1 in Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma: associations with presenting features, serum interleukin 10 levels, and clinical outcome. *Clin Cancer Res*. 2003;9(6):2114–2120.

27 Jarrett RF, Stark GL, White J et al. Impact of tumor Epstein-Barr virus status on presenting features and outcome in age-defined subgroups of patients with classic Hodgkin lymphoma: a population-based study. *Blood*. 2005;106(7):2444–2451.

28 Glaser SL, Gulley ML, Clarke CA et al. Racial/ethnic variation in EBV-positive classical Hodgkin lymphoma in California populations. *Int J Cancer*. 2008;123(7):1499–1507.

29 Chang ET, Adami H-O. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2006;15(10):1765–1777.

30 Murphy G, Pfeiffer R, Camargo MC, Rabkin CS. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. *Gastroenterology*. 2009;137(3):824–833.

31 Lee J-H, Kim S-H, Han S-H, An J-S, Lee E-S, Kim Y-S. Clinicopathological and molecular characteristics of Epstein-Barr virus-associated gastric carcinoma: a meta-analysis. *J Gastroenterol Hepatol*. 2009;24(3):354–365.

32 Dicker D, Nyguyen D, Abate KH, Abay SM, Abbasi N. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1684–1735.

33 Roth G A, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736–1788.

34 Spina M, Tirelli U, Zagonel V et al. Burkitt's lymphoma in adults with and without human immunodeficiency virus infection: a single-institution clinicopathologic study of 75 patients. *Cancer*. 1998;82(4):766–774.

35 Joossens JV, Hill MJ, Elliott P et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol*. 1996;25(3):494–504.

36 Al-Naeeb AB, Ajithkumar T, Behan S, Hodson DJ. Non-Hodgkin lymphoma. *BMJ*. 2018;362:k3204.

37 Cohen JI, Fauci AS, Varmus H, Nabel GJ. Epstein-Barr Virus: An Important Vaccine Target for Cancer Prevention. *Sci Transl Med*. 2011;3(107):107fs7.

38 Boyle M. A vaccine to kiss EBV goodbye. *Science Translational Medicine*. 2019;11(489):eaax1729.

FIGURES

Figure 1.
Global burden of (A) incident (B) deaths (C) DALYs for EBV-attributed malignancies in 2017 by world regions.

Figure 2.
Global burden of incident (A), deaths (B) and DALYs (C) for EBV-attributed malignancies by gender from 1990-2017.

Figure 3.
Global burden of incident and deaths of EBV-attributed (A) Burkitt lymphoma (B) Hodgkin lymphoma (C) Nasopharyngeal carcinoma (D) Gastric carcinoma in 2017 by SDI world regions.

Figure 1.

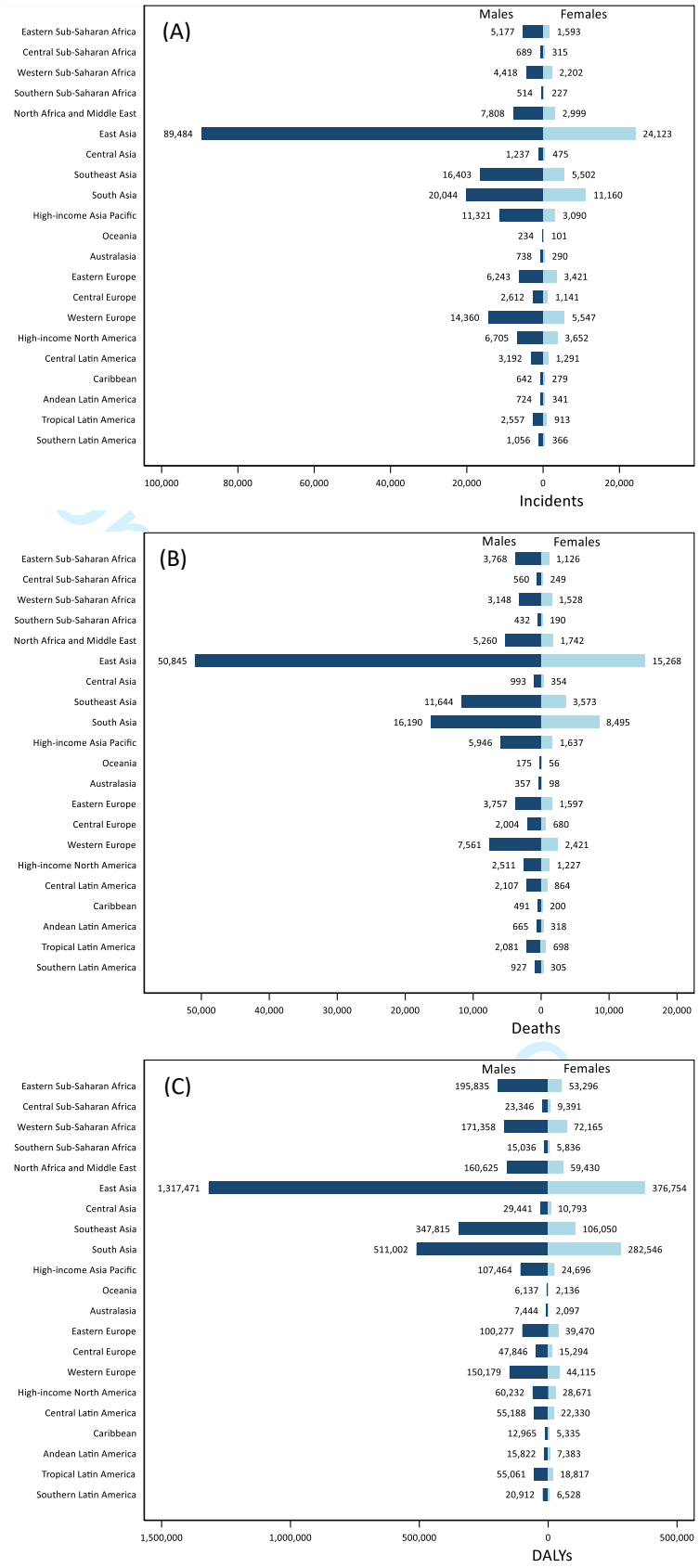

(A)
Males
Females
Eastern Sub-Saharan Africa 5,177 1,593
Central Sub-Saharan Africa 689 315
Western Sub-Saharan Africa 4,418 2,202
Southern Sub-Saharan Africa 514 227
North Africa and Middle East 7,808 2,999
East Asia 89,484 24,123
Central Asia 1,237 475
Southeast Asia 16,403 5,502
South Asia 20,044 11,160
High-income Asia Pacific 11,321 3,090
Oceania 234 101
Australasia 738 290
Eastern Europe 6,243 3,421
Central Europe 2,612 1,141
Western Europe 14,360 5,547
High-income North America 6,705 3,652
Central Latin America 3,192 1,291
Caribbean 642 279
Andean Latin America 724 341
Tropical Latin America 2,557 913
Southern Latin America 1,056 366
100,000 80,000 60,000 40,000 20,000 0 20,000
Incidents
(B)
Males
Females
Eastern Sub-Saharan Africa 3,768 1,126
Central Sub-Saharan Africa 560 249
Western Sub-Saharan Africa 3,148 1,528
Southern Sub-Saharan Africa 432 190
North Africa and Middle East 5,260 1,742
East Asia 50,845 15,268
Central Asia 993 354
Southeast Asia 11,644 3,573
South Asia 16,190 8,495
High-income Asia Pacific 5,946 1,637
Oceania 175 56
Australasia 357 98
Eastern Europe 3,757 1,597
Central Europe 2,004 680
Western Europe 7,561 2,421
High-income North America 2,511 1,227
Central Latin America 2,107 864
Caribbean 491 200
Andean Latin America 665 318
Tropical Latin America 2,081 698
Southern Latin America 927 305
50,000 40,000 30,000 20,000 10,000 0 10,000 20,000
Deaths
(C)
Males
Females
Eastern Sub-Saharan Africa 195,835 53,296
Central Sub-Saharan Africa 23,346 9,391
Western Sub-Saharan Africa 171,358 72,165
Southern Sub-Saharan Africa 15,036 5,836
North Africa and Middle East 160,625 59,430
East Asia 1,317,471 376,754
Central Asia 29,441 10,793
Southeast Asia 347,815 106,050
South Asia 511,002 282,546
High-income Asia Pacific 107,464 24,696
Oceania 6,137 2,136
Australasia 7,444 2,097
Eastern Europe 100,277 39,470
Central Europe 47,846 15,294
Western Europe 150,179 44,115
High-income North America 60,232 28,671
Central Latin America 55,188 22,330
Caribbean 12,965 5,335
Andean Latin America 15,822 7,383
Tropical Latin America 55,061 18,817
Southern Latin America 20,912 6,528
1,500,000 1,000,000 500,000 0 500,000
DALYs

Figure 2.

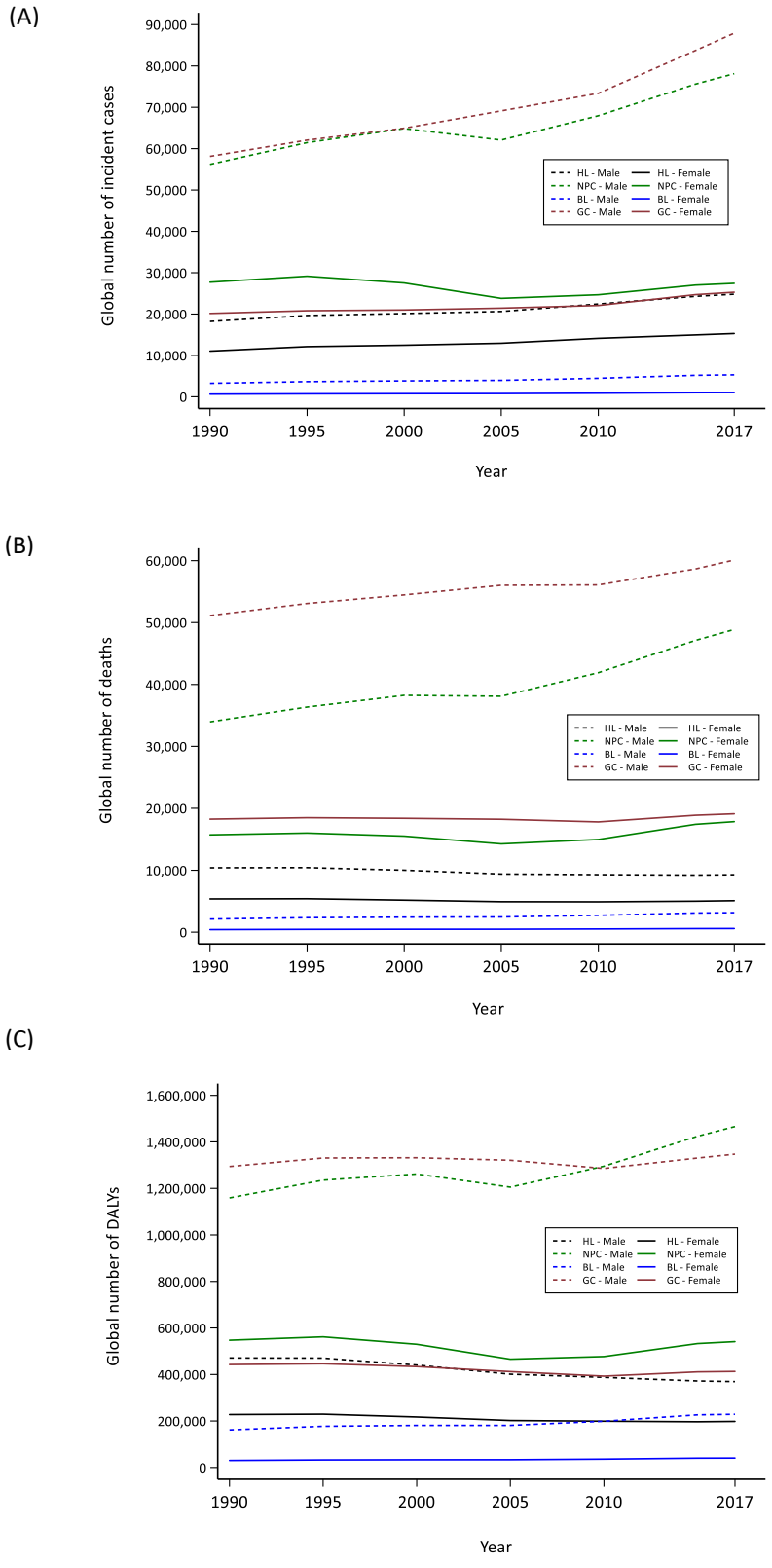
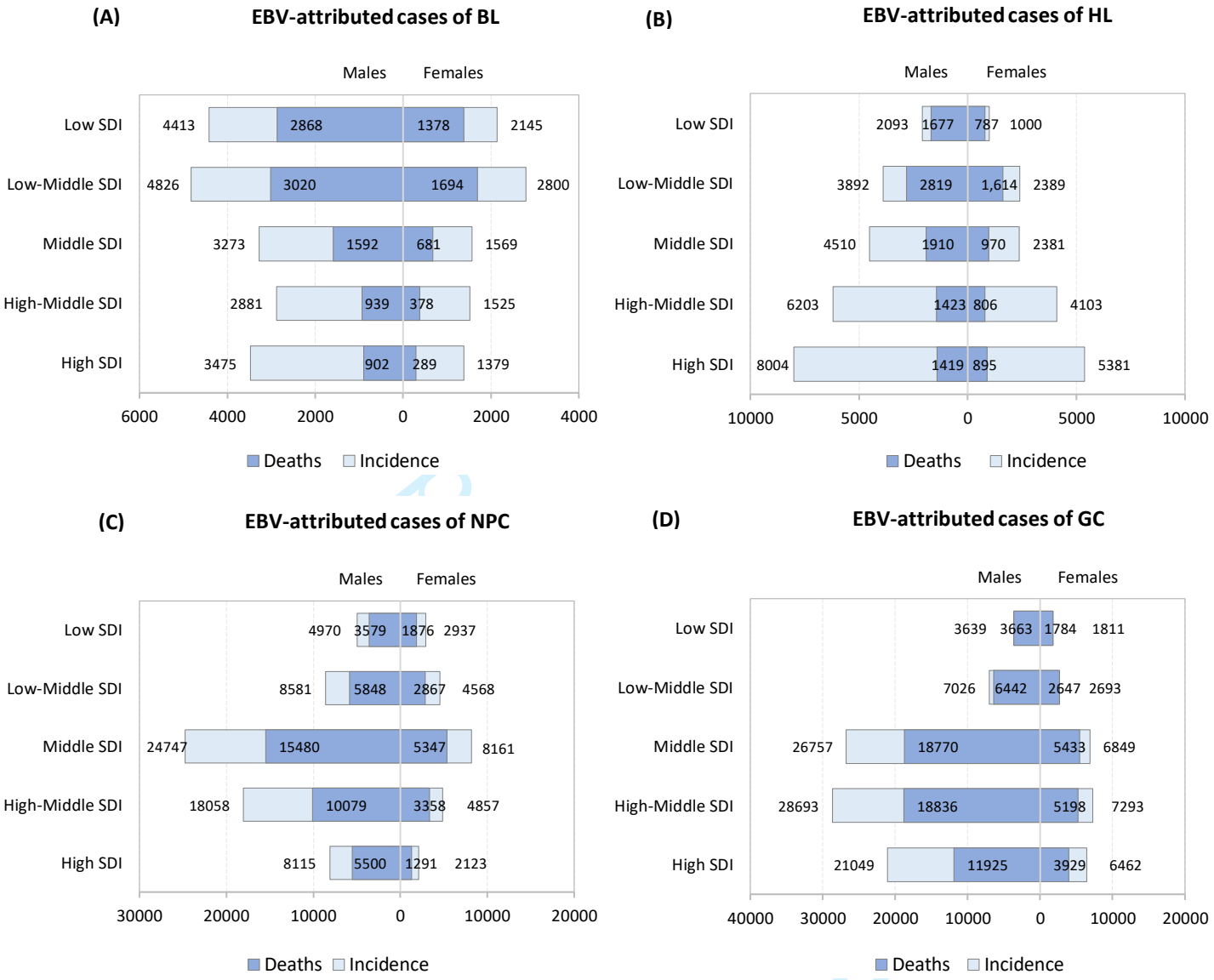

(A)
Global number of incident cases
90,000
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
1990
1995
2000
2005
2010
2017
Year
HL - Male
HL - Female
NPC - Male
NPC - Female
BL - Male
BL - Female
GC - Male
GC - Female
(B)
Global number of deaths
60,000
50,000
40,000
30,000
20,000
10,000
0
1990
1995
2000
2005
2010
2017
Year
HL - Male
HL - Female
NPC - Male
NPC - Female
BL - Male
BL - Female
GC - Male
GC - Female
(C)
Global number of DALYs
1,600,000
1,400,000
1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
1990
1995
2000
2005
2010
2017
Year
HL - Male
HL - Female
NPC - Male
NPC - Female
BL - Male
BL - Female
GC - Male
GC - Female

Figure 3.



Supplement 1

Global and regional incidence, mortality and disability-adjusted life-years for Epstein-Barr virus-attributable malignancies, 1990-2017

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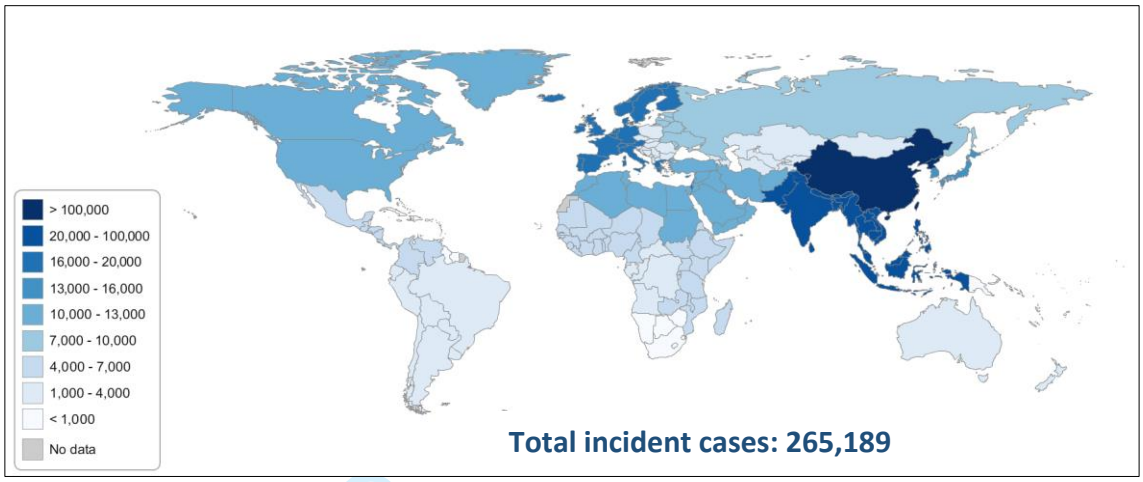
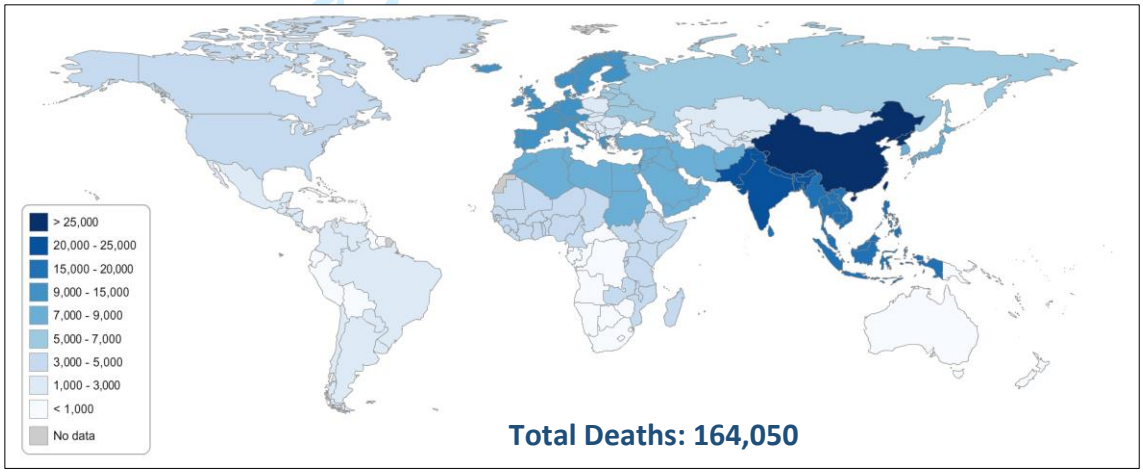
Contents

eFigure 1. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributable malignancies in 2017 by location

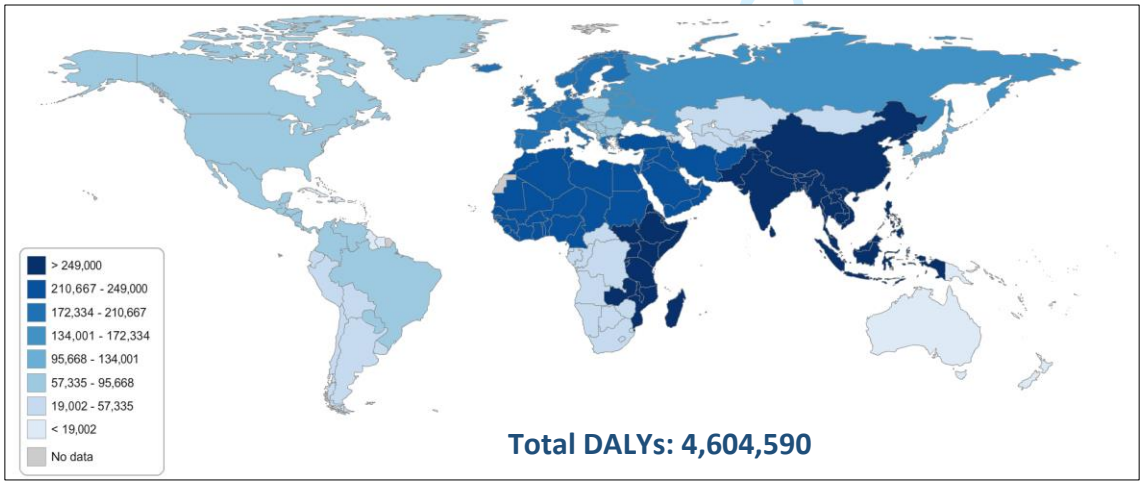
(A)



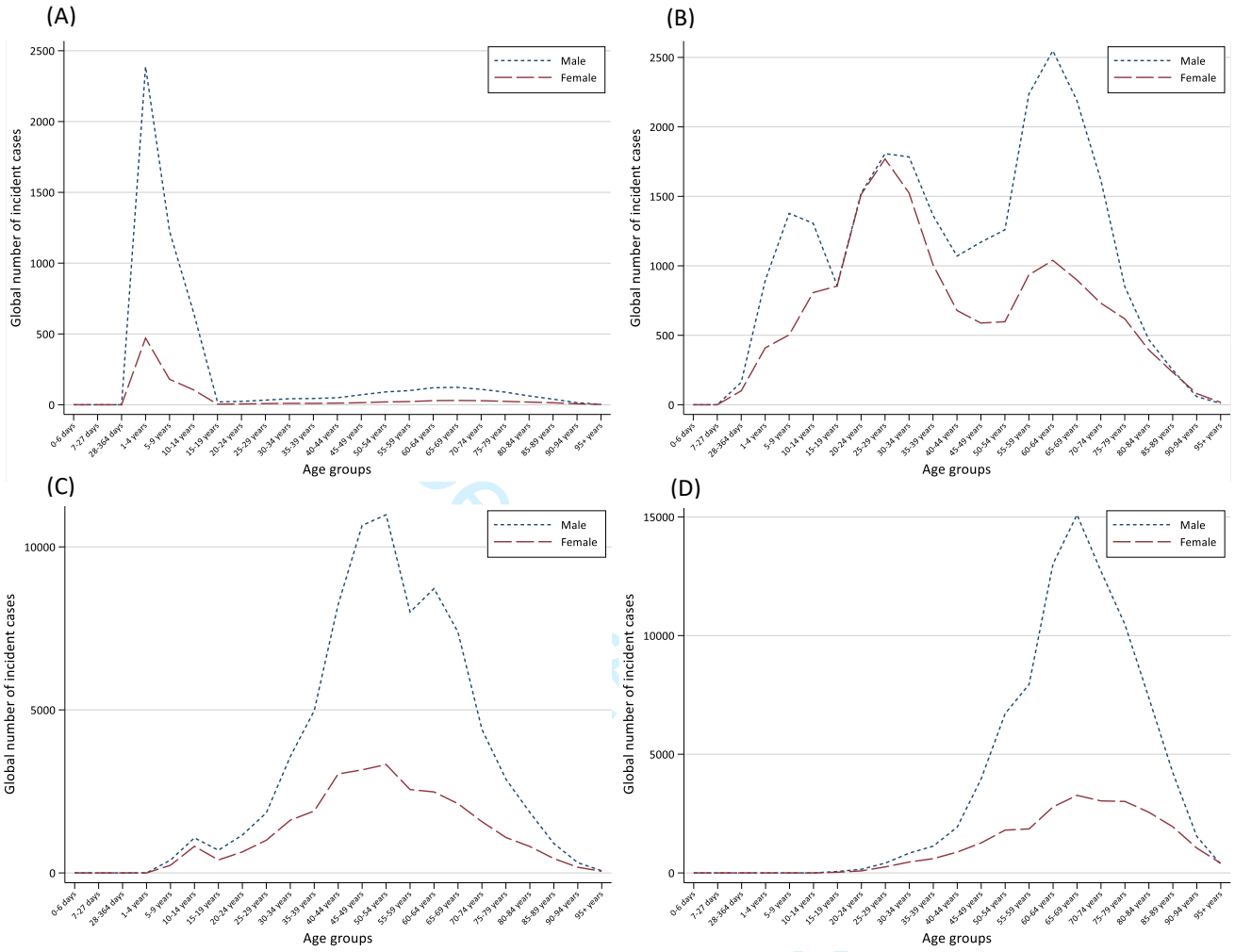
(B)



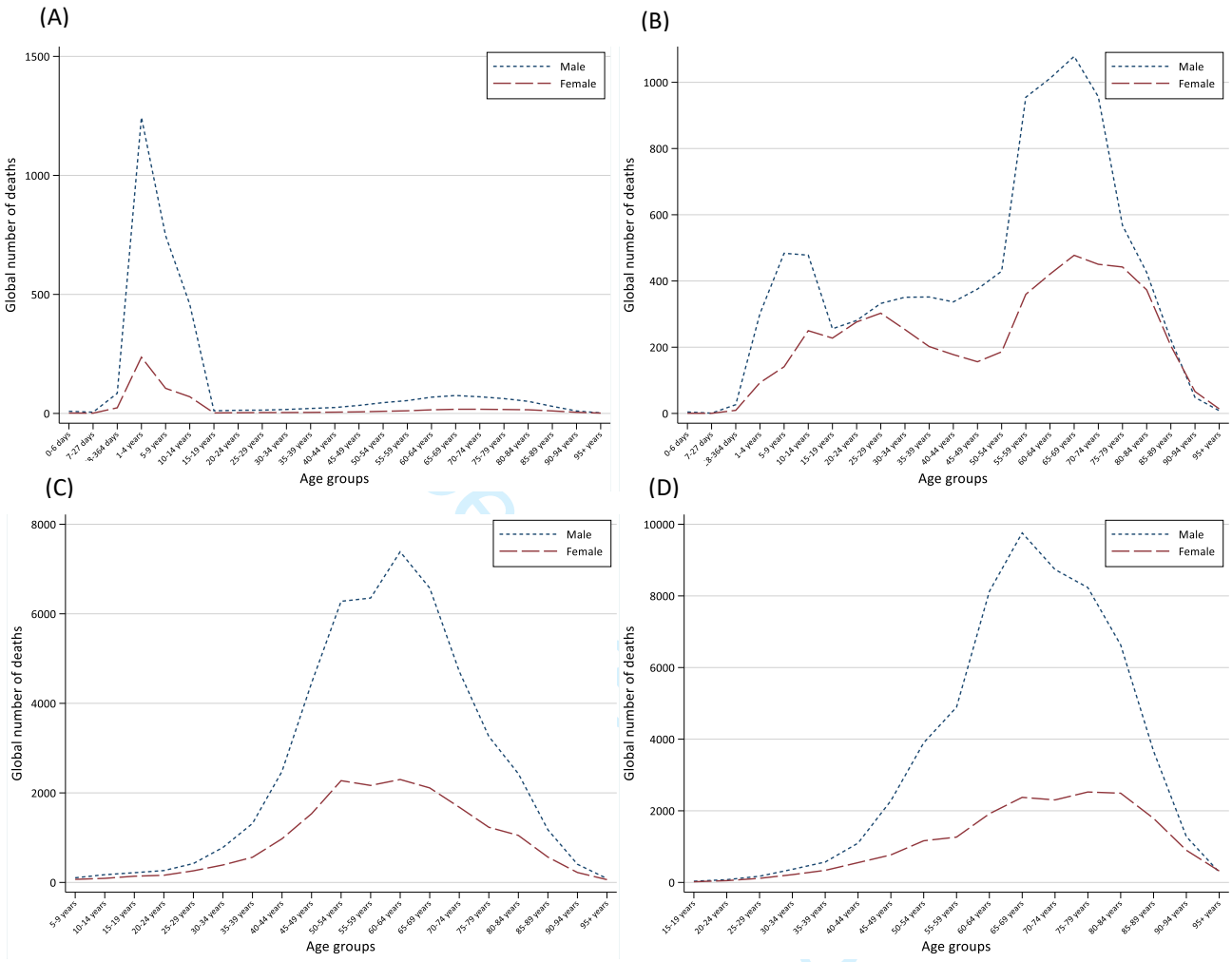
(C)



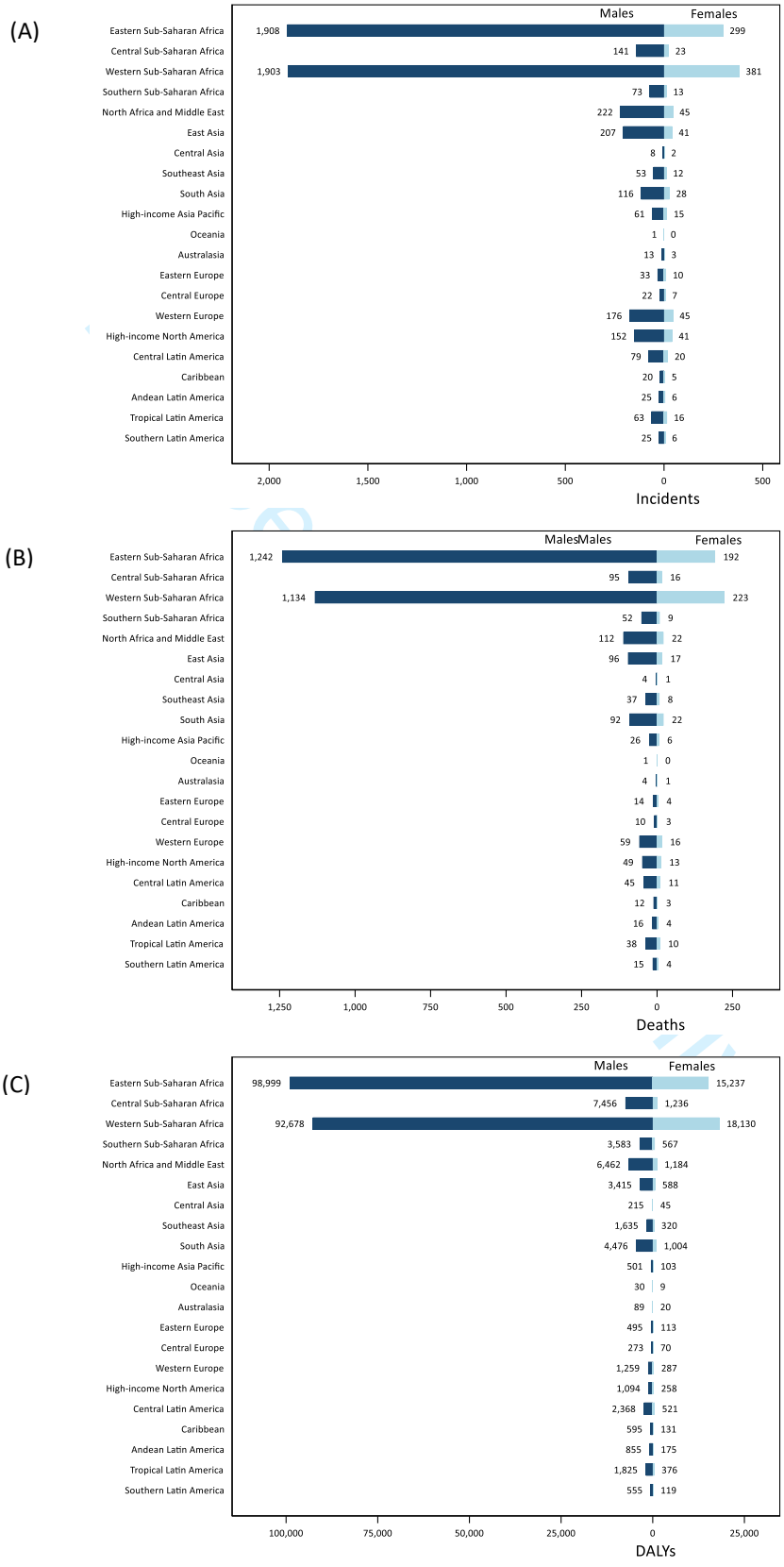
eFigure 2. Global burden of incidence of EBV-attributed (A) Burkitt lymphoma (B) Hodgkin lymphoma (C) nasopharyngeal carcinoma (D) gastric carcinoma in 2017 by gender and age



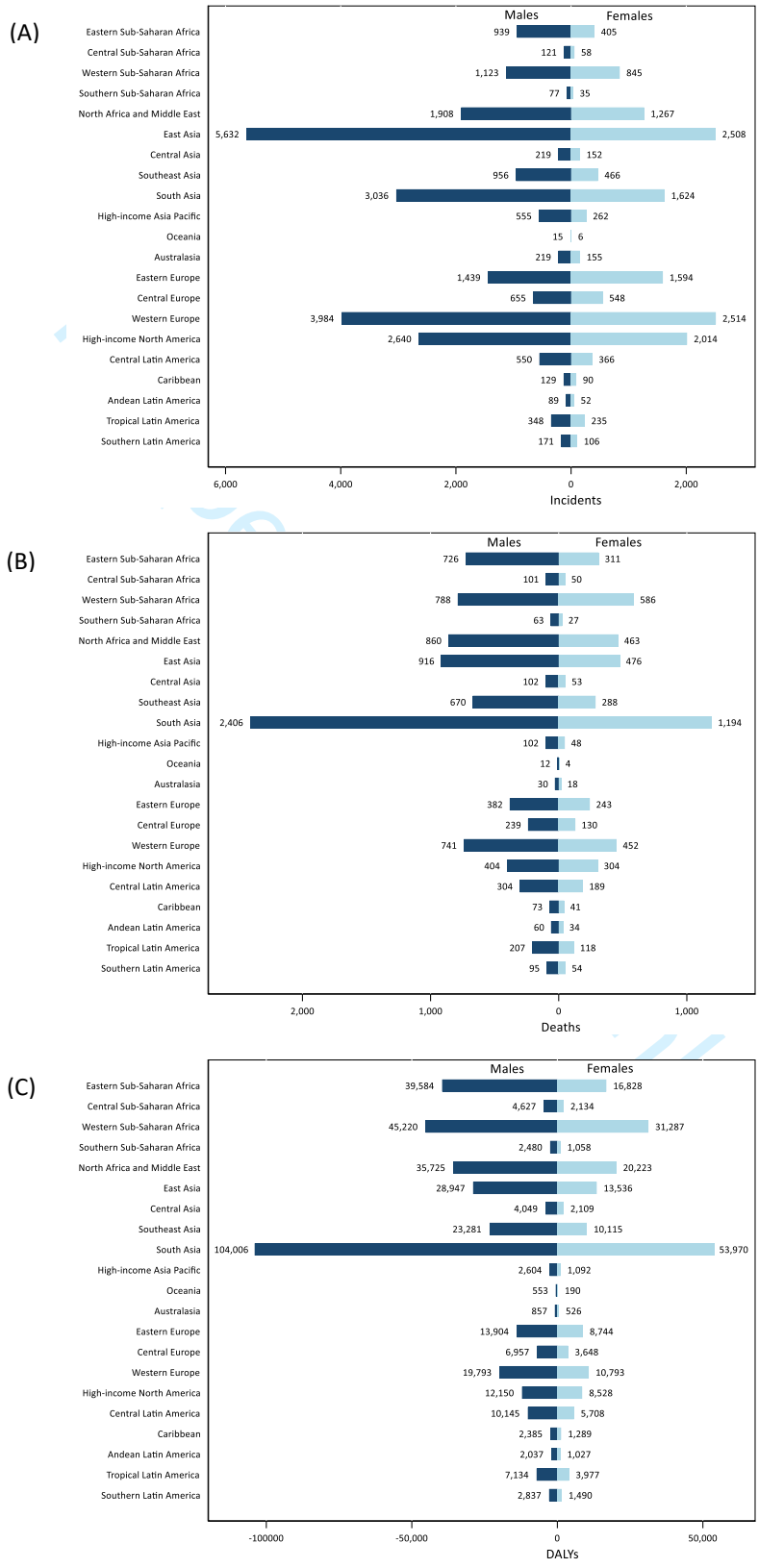
eFigure 3. Global burden of mortality from EBV-attributed (A) Burkitt lymphoma (B) Hodgkin lymphoma (C) nasopharyngeal carcinoma (D) gastric carcinoma in 2017 by gender and age



eFigure 4. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributed Burkitt lymphoma cases in 2017 by world regions

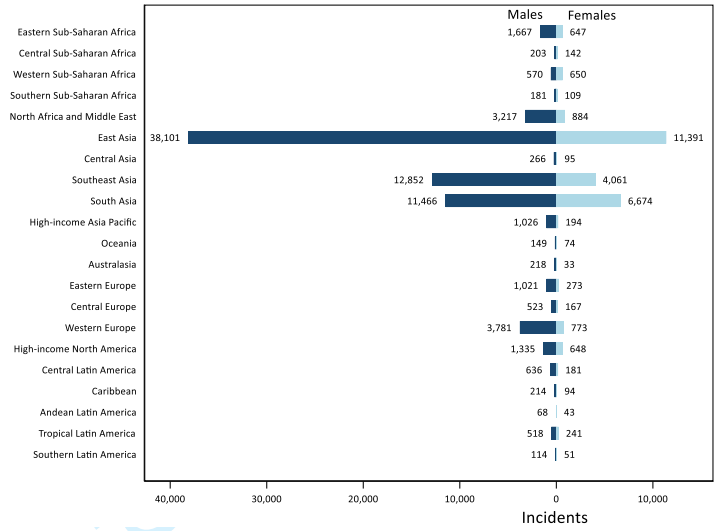


eFigure 5. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributed Hodgkin lymphoma cases in 2017 by world regions

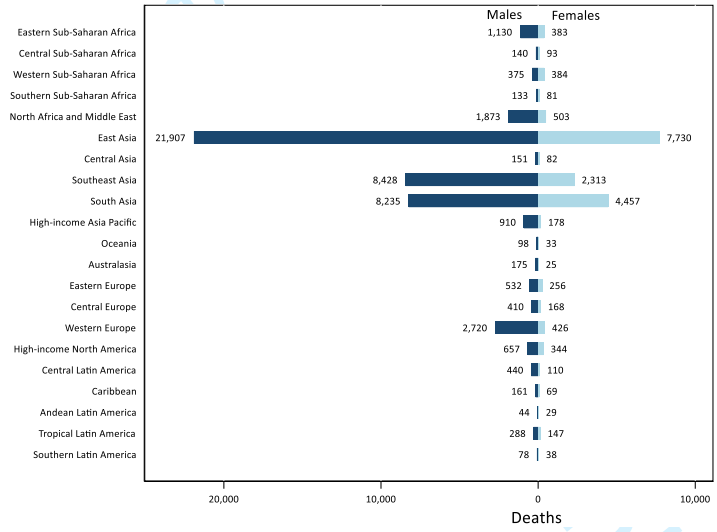


eFigure 6. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributed nasopharyngeal carcinoma cases in 2017 by world regions

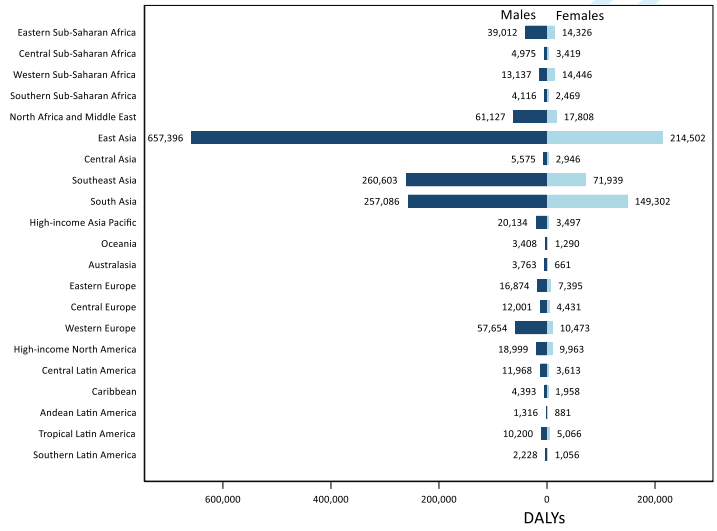
(A)



(B)

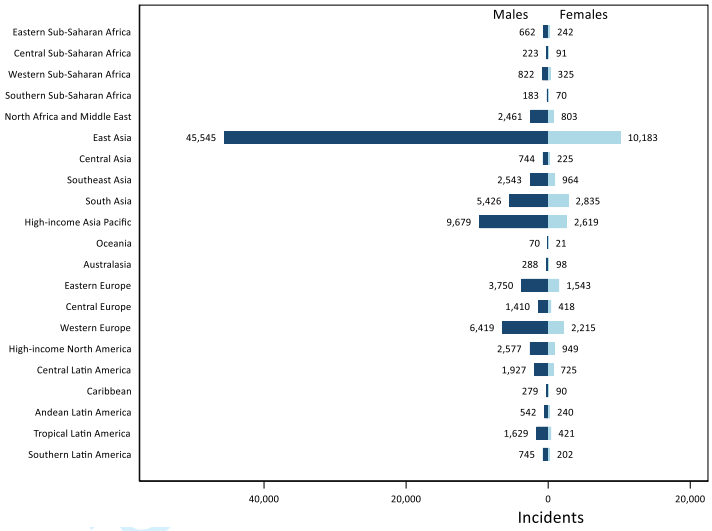


(C)

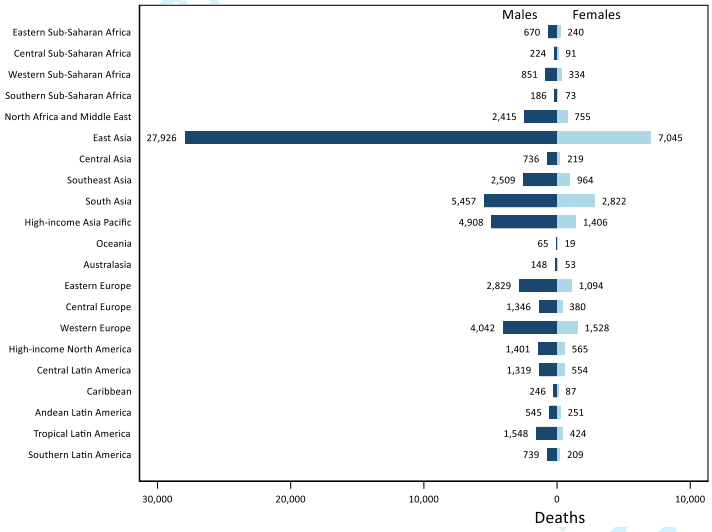


eFigure 7. Global burden of (A) incidence (B) deaths (C) DALYs for EBV-attributed gastric cancer cases in 2017 by world regions

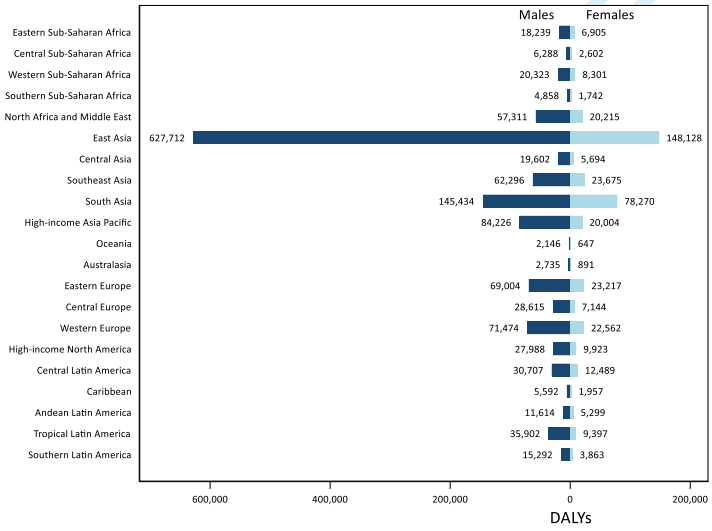
(A)



(C)



(B)



eFigure 8. Global burden of DALYs for EBV-attributed (A) Burkitt lymphoma (B) Hodgkin lymphoma (C) Nasopharyngeal carcinoma (D) Gastric carcinoma in 2017 by SDI world regions