PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Global and regional incidence, mortality and disability-adjusted life-years for Epstein-Barr virus-attributable malignancies, 1990-2017
AUTHORS	Khan, G; Fitzmaurice, C; Naghavi, Moshen; Ahmed, Luai

VERSION 1 – REVIEW

REVIEWER	Zhijun Dai The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China
REVIEW RETURNED	22-Feb-2020

GENERAL COMMENTS	This study provides comprehensive estimates of the burden of EBV-attributed BL, HL, NPC and GC. It provided some interesting results. But I consider some following questions. 1. The author stated that the fraction of each malignancy attributable to EBV was estimated based on published studies. Obviously, EBV etiologically linked several other malignancies not included in this analysis. Please add more specific description to explain the reason or selection criteria. 2. “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.” How can population growth explain the decline? 3. The author described that for BL, no direct estimates were available. The GBD study includes BL under the broader category of non-Hodgkin lymphomas (NHL). All the data of BL were calculated. However, there are three clinical forms of Burkitt lymphoma: regional, sporadic and HIV-associated. How about other three cancers? In the methods part, the EBV-related incidence were calculated according to Table 1. As for death, the EBV-related incidence were also calculated according to Table 1? That seems unreasonable. Therefore, the reliability of the calculation method needs to be further clarified and verified. 4. The data of death and DALYs risks attributed to cancers were available, maybe this article could give you some suggestions, please refer to it. (PMID：31864424, Global burden of breast cancer and attributable risk factors in 195 countries and territories, from 1990 to 2017: results from the Global Burden of Disease Study 2017) 5. In Fig.3, The white numbers overlap with the light blue ones, making the Numbers hard to see. Please change all the white numbers into black. 6. The discussion should be improved. The author should discuss around the novel results.

REVIEWER	Erle Robertson University of Pennsylvania
REVIEW RETURNED	14-Mar-2020

GENERAL COMMENTS	The manuscript by Gulfaraz Khan and colleagues describes the global and regional burden of EBV-attributable malignancies based on the study of the Global Burden of Disease (GBD) project from 1990 to 2017. This paper is an update of the previous publication (Khan G, Hashim MJ. Global burden of deaths from Epstein-Barr virus attributable malignancies 1990-2010. Infect Agent Cancer. 2014) from the same group. It is important to clearly identify the strategy used for identification of the numbers of EBV and actual cases of these different cancers, the "Prevalence of EBV in cases (%)" in Table 1 and 2, which will validate the accuracy of the numbers included in these tables. How does these data compare to those from Globocan 2018 and should there be a comparison if different? The conclusions are also largely relying on predictions and assumptions. Although there are many limitations in this study as mentioned in the manuscript ("Limitations" section), the authors have provided a comprehensive picture of the burden of the most prominent EBV-associated malignancies (BL, HL, NPC, and GC) through estimating the incidence, mortality, and DALYs, and further determining these features for each malignancy by age, sex, geographical region and social demographic index (SDI) from 1990 to 2017. These interesting investigations demonstrate the important role of EBV in the global and regional cancer burden.

VERSION 1 – AUTHOR RESPONSE

Comment by reviewer	Response by authors
Reviewer 1 (Dr Zhijun Dai) Reviewer comments: Reviewer #1 (Remarks to the Author): This study provides comprehensive estimates of the burden of EBV-attributed BL, HL, NPC and GC. It provided some interesting results. But I consider some following questions.	Thank you for reviewing our manuscript and for your positive and constructive feedback.
1. The author stated that the fraction of each malignancy attributable to EBV was estimated based on published studies. Obviously, EBV etiologically linked several other malignancies not included in this analysis. Please add more specific description to explain the reason or selection criteria.	The details of the selection were described in our initial study (Khan & Hashim, 2014) which has been listed and referred to in the current study. Additionally, for further clarification, please see the highlighted sections (introduction, paragraph 2; methods, section 1, paragraph 2).
2. "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	Global population has increased during the 27 year period from 1990 to 2017. However, the absolute number of deaths from HL during this period has declined. Since we are expressing the rate of death from HL per

decreased significantly from 0.67 in 1990 to 0.43 in 2017." How can population growth explain the decline?	100,000, the rate has decrease from 0.67/100,000 in 1990 to 0.43/100,000 in 2017.
3. The author described that for BL, no direct estimates were available. The GBD study includes BL under the broader category of non-Hodgkin lymphomas (NHL). All the data of BL were calculated. However, there are three clinical forms of Burkitt lymphoma: regional, sporadic and HIV-associated. How about other three cancers? In the methods part, the EBV-related incidence were calculated according to Table 1. As for death, the EBV-related incidence were also calculated according to Table 1? That seems unreasonable. Therefore, the reliability of the calculation method needs to be further clarified and verified.	Table 1 describes **EBV-attributable** cases (i.e. proportion of cases attributed to be linked to EBV based on published literature, taking into account any variables such as age, gender, regional variations). Table 2 describes **EBV-attributed** cases (i.e. our estimates, calculated by imputed the attributable proportions into the GBD data sets). For BL, no direct estimates of BL incidence, mortality or DALYs were available from GBD data sets for us to use. We therefore had to perform an additional step to first estimate these figures from the larger category of NHL. Since, BL incidence varies by age, gender and region, we had to take these variables into consideration (as outlined in Table 1). For the 3 other malignancies i.e. GC, NPC, HL, estimates of incidence, mortality and DALYs were directly available from the GBD data set. These estimates were directly used to determine the proportion of cases that were **EBV attributable** (table 1). The attributable fractions were then imputed to the GBD data set to estimate the **EBV attributed** fractions. For further clarification, we have now also revised the manuscript and inserted the words "EBV-attributable" or EBV-attributed" as appropriated.
4. The data of death and DALYs risks attributed to cancers were available, maybe this article could give you some suggestions, please refer to it. (PMID：31864424, Global burden of breast cancer and attributable risk factors in 195 countries and territories, from 1990 to 2017: results from the Global Burden of Disease Study 2017) 5. In Fig.3, The white numbers overlap with the light blue ones, making the Numbers hard to see. Please change all the white numbers into black.	Yes we have seen this article. Our study estimates deaths and DALYs due to EBV-attributed cancers. As suggested, numbers in Figure 3 have now been changed to black text.
5. The discussion should be improved. The author should discuss around the novel results.	We have added a little more to the discussion to highlight the novelty of our study. However, we believe we have extensively discussed our results and further elaboration will only dilute and complicate the message being communicated.
Reviewer 2 (Dr Erle Robertson)	

The manuscript by Gulfaraz Khan and colleagues describes the global and regional burden of EBV-attributable malignancies based on the study of the Global Burden of Disease (GBD) project from 1990 to 2017. This paper is an update of the previous publication (Khan G, Hashim MJ. Global burden of deaths from Epstein-Barr virus attributable malignancies 1990-2010. Infect Agent Cancer. 2014) from the same group.	Thank you for your positive comments.
1. It is important to clearly identify the strategy used for identification of the numbers of EBV and actual cases of these different cancers, the "Prevalence of EBV in cases (%)" in Table 1 and 2, which will validate the accuracy of the numbers included in these tables. How does these data compare to those from Globocan 2018 and should there be a comparison if different? The conclusions are also largely relying on predictions and assumptions.	Thank you for this comment. As mentioned in the abstract and the methods section, we estimated the burden of EBV attributed BL, HL, GC, NPC by a two-step process. (1) In the first step, the fraction of each malignancy attributable to EBV was estimated based on published studies, which have been cited in the Table1. In estimating the attributable fraction, variables such as age, sex, geographical region was taken into account. This is mentioned in the methods section. Moreover, further details of our approach is provided in our initial study (Khan & Hashim 2014), which we have cited. (2) In the second step, the EBV-attributable fractions were then applied to the GBD estimates to determine the global and regional incidence, mortality and DALYs for each malignancy by age, sex, geographical region and SDI from 1990-2017. The details of how GBD estimates are collected and calculated has been extensively described in the GDB publications. We have cited some of the references most relevant to this study. Although we used GBD data set for estimating EBV-attributed cases, the GLOBOCAN estimates are very similar. GBD estimated a total 16.8 million incident cases in 2017, whilst GLOBOCAN estimated this to be 17.0 million in 2018. This comparison has been mentioned in our previous study (Fitzmaurice C et al, JAMA Oncol. 2019) (ref 1 in a reference list).
2. Although there are many limitations in this study as mentioned in the manuscript ("Limitations" section), the authors have provided a comprehensive picture of the burden of the most prominent EBV-associated malignancies (BL, HL, NPC, and GC) through estimating the incidence, mortality, and DALYs, and further	Thank you for your positive comments. We too feel that these findings are very exciting and highlight the importance of EBV as a risk factor in the aetiology of several malignancies. Developing an effective vaccine against EBV could prevent these malignancies.

determining these features for each malignancy by age, sex, geographical region and social demographic index (SDI) from 1990 to 2017. These interesting investigations demonstrate the important role of EBV in the global and regional cancer burden.	

VERSION 2 – REVIEW

REVIEWER	Zhijun Dai Department of Breast Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China
REVIEW RETURNED	06-Jun-2020

GENERAL COMMENTS	The manuscript has been improved a lot.