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ORIGINAL SCIENTIFIC REPORT

The Global Burden of Esophageal Cancer: A Disability-Adjusted Life-Year Approach

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Abstract

Introduction Esophageal cancer is the eighth most common cancer worldwide and the sixth leading cause of cancer-related deaths. As a significant cause of morbidity and mortality, its burden on society has yet to be fully characterized. The aim of this study is to examine its global burden through estimation of the disability-adjusted life years (DALYs) attributable to it.

Methods Global incidence and mortality estimates for esophageal cancer were obtained from the International Agency for Research on Cancer GLOBOCAN 2008 database. DALYs were calculated, using methodology established by the World Health Organization.

Results In 2008, 3,955,919 DALYs were attributed to esophageal cancer, at a global rate of 0.58 DALYs per 1000 people annually. Years of life lost (YLL) accounted for 96.8 % of DALYs, while years lived with disability (YLD) accounted for 3.2 %. 83.8 % of the global DALYs occurred in less-developed countries, with most accrued in Eastern Asia, comprising 50.9 % of the total. The highest rate of DALY accrual was in Southern Africa, at 1.62 DALYs per 1000 people annually.

Conclusions A substantial number of years of life were lost or affected by esophageal cancer worldwide in 2008, with the burden resting disproportionately on less-developed countries. Geographically, the greatest burden is in Eastern Asia. The vast majority of DALYs were due to YLL, rather than YLD, indicating the need to focus resources on disease prevention and early detection. Our findings provide an additional basis upon which to formulate global priorities for interventions that affect DALY reduction in esophageal cancer.

Introduction

Esophageal cancer is the eighth most common cancer worldwide, the sixth leading cause of cancer-related deaths, and the fifth leading cause of cancer-related deaths among men [1]. Its epidemiology varies widely, particularly in incidence rates, among geographic regions [1–4]. The global incidence of the two histological subtypes of esophageal cancer, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), also varies considerably due to differences in lifestyle, genetic predisposition, and effects of multiple environmental factors [5–12].

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This malignancy places a considerable burden on society that is reflected in both economic and humanitarian costs [13]. Consequences, including premature death, disability due to the disease, and treatment itself, are all stressors on a nation's gross domestic product [13–17]. The full extent of these costs is reflected in the sum of time lost due to premature death, and time lost due to the disability resulting from diagnosis and treatment. To date, these variables have not been fully characterized on a national or global scale. Consequently, the specific aim of this study is to provide a better examination of the global burden of esophageal cancer through analysis of the disability-adjusted life years (DALYs) [18–24] attributable to it.

Materials and methods

Data extraction

Calculation of DALYs required global estimates of esophageal cancer incidence and mortality. Data for the year 2008 were obtained for the 184 countries and territories represented in the International Agency for Research on Cancer (IARC) GLOBOCAN 2008 database [25]. Population data were obtained from the United Nations Population Division [26], except the data for Chinese Taipei, which were obtained from the United States Census Bureau International Data Base [27]. Per capita health expenditure for 2008 was obtained from the World Health Organization (WHO) [28].

Geographical regions and definitions of "more developed" and "less developed" were derived from the GLOBOCAN 2008 database [25]. According to this classification, the "more developed" countries included the United States, Canada, all of Europe (including the Russian Federation), Japan, Australia, and New Zealand; the remaining countries are considered "less developed."

DALYs

DALYs describe the total time lost due to a health condition, including from premature death and disability. This metric was developed for the WHO Global Burden of Disease (GBD) 1990 study and has since become a standard measure of disease burden [13, 17–19]. DALYs allow comparison of disease burden on a global scale and are valuable for analyzing who is most affected by a disease and for prioritization of intervention-based resource allocation. DALYs incorporate both the years of life lost (YLL) due to premature death and the years lived with disability (YLD) from a condition. YLLs are the product of mortal cases and standard life expectancy at age of death. This was determined by referencing the model life-table West Level 26 [18, 21, 22], which gives a global life expectancy at birth of 80 years for males and 82.5 years for females. YLDs are the product of incident cases, average length of case until remission or death, and disability weight attributable to that condition. Disability weight serves to describe the level of disability produced by a given condition, scaled from 0 to 1, with 0 representing perfect health and 1 representing death. As both describe morbidity and mortality, DALYs are a combined indicator of disease burden [20]. DALYs were calculated by using the methodology and parameters utilized by the WHO GBD study, including the use of the adjustments of discounting (devaluing future health outcomes to convert them into present-day values, under the assumption that present health is more valuable than future health), and age weighting (differentially weighting life lived at different ages in an attempt to balance consumption early in life against productivity later in life). Standard convention is to represent DALYs in the form DALYs [r, K], with r representing the discounting rate and K denoting the presence or absence of age weighting ($K = 1$ or $K = 0$, respectively). This study reports DALYs calculated with discounting and age weighting (DALYs [0.03, 1]), reflecting GBD methodology unless otherwise noted. A complete description of the methodology for calculating DALYs is detailed in supplementary material accompanying this manuscript and was also previously described by others [18, 21–24].

The GLOBOCAN 2008 data partitioned incidence and mortality into ten age groups: 0–14, 15–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and 75 +. Because YLL calculation requires average age at death, and YLD calculation requires average age at onset, the midpoints of these age ranges were used. Disability weight was estimated, using those described in the GBD and clinical staging data for the United States. The GBD gives a disability weight of 0.20 to esophageal cancer diagnosis/therapy and control, 0.75 to any cancer with pre-terminal metastasis, and 0.81 to terminal cancer [17]. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database [29] was queried to determine the relative frequencies of esophageal cancer diagnosed at clinical stage I–II (considered diagnosis/therapy and control), stage III (considered pre-terminal metastasis given node-positive localized metastasis), and stage IV (considered terminal cancer) [30, 31]. A weighted average of these frequencies gave a disability weight of 0.544.

The parameter in the YLD equation representing length of disability was interpreted as the median survival under the assumption that all years of life lived after diagnosis are lived with some level of disability. Median survival was estimated, based on US esophageal cancer survival data represented in the SEER database. The database was queried for esophageal cancer cases, excluding those

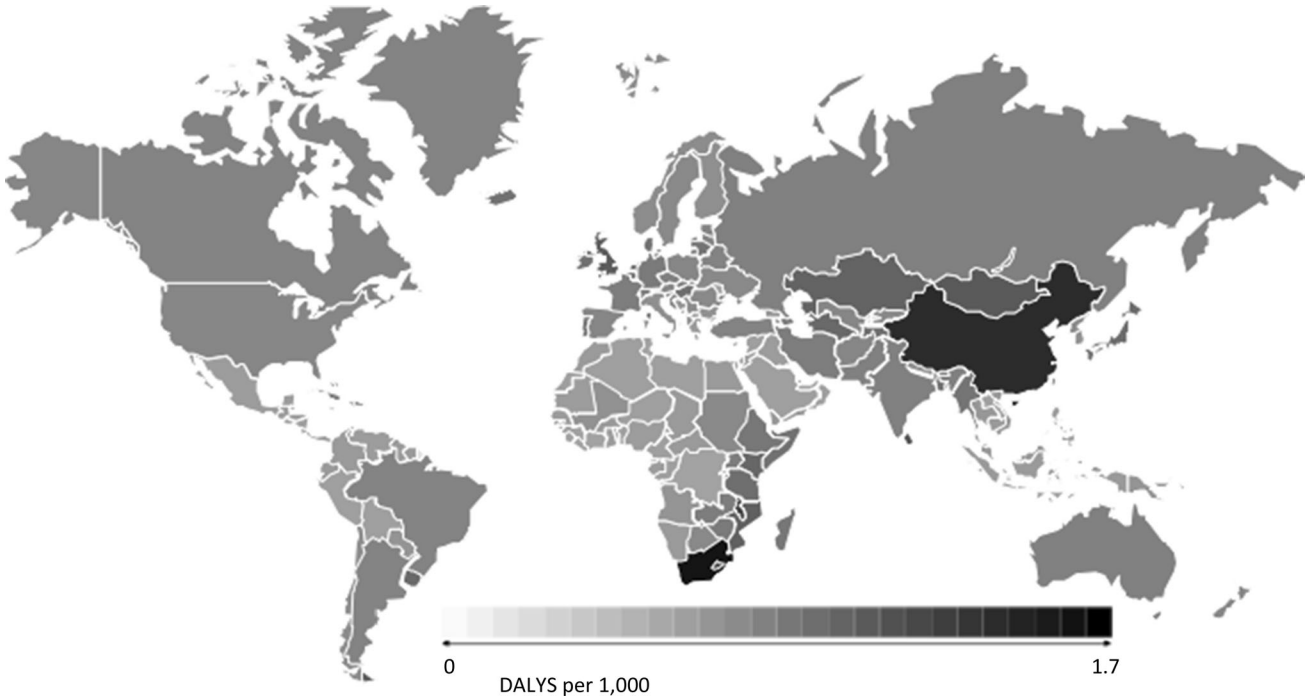

Fig. 1 Global esophageal cancer disability-adjusted life years (DALYs) per 1000 population, 2008

diagnosed on autopsy or death certificate to reflect survival following clinical diagnosis of esophageal cancer, giving a median survival of nine months for all cases combined.

A sensitivity analysis was performed to assess the impact of disability weighting, life expectancy (survival), age weighting, and discounting for the parameters used in DALY calculation. Sensitivity calculations were performed for both a 50 % increase and a decrease in our study values for disability weight and life expectancy. DALYs were also assessed without discounting and age weighting and compared to our study assumptions for these parameters.

Results

Incidence and mortality

In 2008, it is estimated that there were 481,514 global incident cases of esophageal cancer (67.7 % were male) and 406,437 deaths (67.9 % were male). The global age-standardized incidence rate based on the world population [ASIR (W)] was 7.0 per 100,000 annually, and the global age-standardized mortality rate [ASMR (W)] was 5.8 per 100,000. China alone accounts for 53.8 % of the incident cases and 51.9 % of the deaths.

There is nearly a 50-fold global variation in esophageal cancer incidence rates. The ASIR (W) among men in the South African Republic is 23.6 per 100,000, and several countries with more than 100 cases annually have ASIR (W) rates of less than 0.5 per 100,000. The South African Republic has the highest incidence and mortality rates for men (ASIR (W) = 23.6 per 100,000 and ASMR (W) = 22.6 per 100,000). Mongolia shows the highest incidence and mortality rates for women [ASIR (W) = 16.1 per 100,000 and ASMR (W) = 19.9 per 100,000].

DALYs

In 2008, there were a total of 3,955,919 DALYs attributable to esophageal cancer at a global rate of 0.58 DALYs per 1000 people annually. The majority is due to YLL from esophageal cancer (96.8 %), rather than YLD due to it (3.2 %). Regionally, Eastern Asia shows the greatest burden in terms of highest total DALYs. This area accumulated 2,013,248 DALYs or 50.9 % of the global total. China alone contributes 1,885,642 DALYs or 47.7 % of the global total. A comprehensive table of incidence, deaths, YLLs, YLDs, and DALYs for all countries is available in the online supplementary material accompanying this report. The geographic variation in DALY rates is shown in Fig. 1. Southern Africa shows the highest DALY rate (1.62 per 1000 people annually).

Table 1 DALYs incorporating age weighting and discounting [0.03, 1] and DALYs per 1000 population for countries with >10 % higher DALY rates among women, 2008

Country	Men		Women		% difference in rate
	DALYs	DALYs per 1000	DALYs	DALYs per 1000	
United Arab Emirates	115	0.037	137	0.091	145
Burkina Faso	612	0.078	1193	0.151	94
Saudi Arabia	722	0.051	915	0.079	54
Bhutan	236	0.643	316	0.958	49
Mali	1255	0.195	1516	0.230	18
Uzbekistan	4485	0.328	5307	0.384	17
Pakistan	39923	0.429	43043	0.491	14

Men contribute 67.9 % of the global DALYs for esophageal cancer, and women contribute 32.1 %, though several countries had higher rates among women. Among countries with greater than ten reported cases of esophageal cancer, several reported DALY rates over 10 % higher for women than men (Table 1). In one country, the United Arab Emirates, women accrued 145 % more DALYs than men.

The majority of DALYs are distributed to less-developed countries, as previously defined [1]. Less-developed countries (79.6 % of the world population) account for 3,314,806 DALYs (83.8 % of the global total). More-developed countries (20.4 % of the world population) account for 641,113 DALYs (16.2 % of the global total). The DALY rate per 1000 people annually is also higher in less-developed countries (0.61) than in more-developed countries (0.46). Specific data for the five highest DALY countries in each development category are shown in Table 2. In addition, more DALYs were reported from countries with lower per capita health expenditure (Fig. 2).

The sensitivity analysis is shown in Table 3. Analysis of the disability weight parameter showed that the value used had little effect on the total number of DALYs. Increasing disability weight by 50 % to 0.82 increased total DALYs by only 2.9 %, and decreasing disability weight by 50 % to 0.27 decreased total DALYs by only 1.2 %. Analysis of the value used for median survival showed that this also had a small effect on the total number of DALYs. Increasing median survival by 50 % from nine to 13.5 months increased total DALYs only 1.5 %, and decreasing median survival by 50 % from nine to 4.5 months decreased total DALYs only 1.6 %. DALYs were also calculated without the adjustments of discounting or age weighting (i.e., DALYs [0,0]). This showed a large increase in total DALYs by 93.8 %.

Table 2 Annual DALYs reported for the top five less-developed and more-developed countries, 2008

Country	Total DALYs	DALYs per 1000
Less developed		
China	1,885,642	1.40
India	531,101	0.44
Bangladesh	100,641	0.62
Pakistan	82,966	0.46
Brazil	81,717	0.42
More developed		
United States of America	122,063	0.39
Japan	87,456	0.69
Russian Federation	61,000	0.43
United Kingdom	54,030	0.88
Germany	43,279	0.53

Discussion

In this study, we have reported the estimated global incidence, mortality, and DALYs attributable to esophageal cancer. Our findings demonstrate a substantial number of

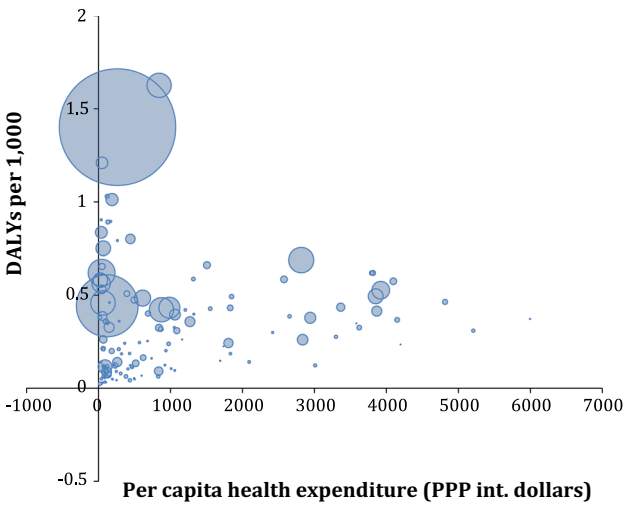

Fig. 2 DALY rate versus per capita health expenditure for 180 countries and territories, 2008. Circle area is proportional to the total number of DALYs

Table 3 Sensitivity analysis of parameters used in DALY calculation

	YLL	YLL % change	YLD	YLD % change	DALY	DALY % change
Disability weight						
0.816 (×1.5)	3,830,301	–	238,937	+90.2 %	4,069,238	+2.9 %
0.544	*3,830,301*	–	*125,617*	–	*3,955,919*	–
0.272 (×0.5)	3,830,301	–	78,767	−37.3 %	3,909,068	−1.2 %
Life expectancy						
13.5 months (×1.5)	3,830,301	–	186,588	+48.5 %	4,016,890	+1.5 %
9 months	*3,830,301*	–	*125,617*	–	*3,955,919*	–
4.5 months (×0.5)	3,830,301	–	63,429	−49.5 %	3,893,730	−1.6 %
Age weighting and discounting						
DALYs [0.03,1]	*3,830,301*	–	*125,617*	–	*3,955,919*	–
DALYs [0,0]	7,512,068	+96.1 %	154,927	+23 %	7,666,995	+93.8

Italics represent parameters used in this study. Percent changes reflect differences in results with adjusted parameters

global YLL or affected by esophageal cancer in 2008 alone. In addition, we have better defined patterns in the geographic and socioeconomic distribution of esophageal cancer burden across the world.

A striking finding, from the GLOBOCAN 2008 data, is the tremendous global variation in the ASIR (W) for esophageal cancer. Unlike many cancers showing higher incidence in developed countries with increased detection rates, esophageal cancer shows higher incidence in less-developed countries. The geographic variation in its incidence has long been noted, and many of the countries with the highest incidences are within the so-called "esophageal cancer belt," [32] extending from the Caspian Sea through northern China. A dramatic variation in incidence from five to nine-fold has also been reported within small geographical partitions of single countries [3, 4]. A very large portion of the burden of esophageal cancer, as measured by the number of DALYs accrued, falls on Eastern Asia, particularly China. The South African Republic shows the highest rate of DALYs per capita. There, esophageal cancer represented the second-leading cause of cancer-related deaths in 2008.

Although the GLOBOCAN database does not include information on histological subtypes of esophageal cancer, EAC and ESCC do demonstrate previously described geographic variations. ESCC is more prevalent in developing countries and is the main subtype in the Asia-Pacific region [33]. Rates of EAC tend to be much higher in developed countries, particularly the United States. Here, the incidence of EAC has been increasing over the past several decades [6, 34, 35]. ESCC and EAC show very different risk factor profiles. ESCC is associated with tobacco use and alcohol consumption, as well as ingestion of *N*-nitroso compounds, mycotoxins, opium, and very hot food and beverages. Additional risk factors include poor oral hygiene, poor nutrition, and low body mass index [2, 9, 36–42]. The majority of these factors are associated with low socioeconomic status [41]. It has also been suggested that human papilloma virus may be partially responsible for elevated ESCC rates in high-risk areas [43]. In contrast, EAC risk is correlated with tobacco consumption and increasing BMI (10, 36). Oddly, *Helicobacter pylori* (*H. pylori*) infection seems to be protective against EAC and decreased prevalence of infection in developed countries may contribute to the increased rates of EAC [37]. When viewed from a molecular level, there is also global variation in the prevalence of predisposing genetic polymorphisms [5, 44].

Taken together, the incidence of esophageal cancer has an associated profile of complex and intertwined risk factors, many of which are tied to socioeconomic status [45]. Consequently, the wide variation in its global burden is likely due to the predominant constellations of risk factors present in different areas and potential variation of etiologies among geographic regions. To substantiate this, the increased DALY rates seen in less-developed countries are in keeping with the preponderance of factors associated with living in a lower socioeconomic status.

Globally, we have found that esophageal cancer affects men more than women. We have, however, defined several areas of the world where DALY rates are higher among women. It is largely unknown why these exceptions exist, but such a consistent difference in incidence rates, with only a few dramatic exceptions, seems, suggesting the presence of an undefined cultural or environmental exposure.

While our results define the differential geographic burden of esophageal cancer, they also describe where intervention may be most beneficial. In some areas, improved screening and surveillance may be warranted and effective [46]. As environmental risk factors are likely an important part of esophageal cancer's etiology, it may be particularly suited to population-based interventions in

order to address modifiable risk factors. For example, in regions where extremely hot tea is suspected to be responsible for high esophageal cancer incidence, allowing tea to cool longer could curb high incidence rates [10, 47]; where carcinogens are a suspected culprit, chemoprevention may be a feasible strategy [48].

Our results also highlight the need to translate improvements in esophageal cancer care and outcomes seen in more-developed countries to less-developed countries. Reducing incidence in Eastern Asia alone would have a tremendous impact on its global burden. For example, if the DALY rate in Eastern Asia were reduced to the current global rate (already buoyed by Eastern Asia's high rate), the total number of global DALYs would be reduced by 28 % of its current value.

There are a number of limitations to this study. Primary among them is the use of GLOBOCAN 2008 data used to calculate DALYs. While the IARC's Cancer Incidence in Five Continents (CI5) series has stricter guidelines for cancer registry inclusion, many less-developed countries are underrepresented in CI5. Rather than limiting data, GLOBOCAN corrects datasets for incompleteness and underreporting. Our use of the GLOBOCAN data supports our goal to provide the best characterization of the global burden of esophageal cancer and, while the data contain estimates, we believe they are the most comprehensive available. GLOBOCAN's methods of estimating cancer incidence and mortality in countries with incomplete or absent reporting are previously described [1] and rely on extrapolating from available regional and national cancer registries. In doing so, GLOBOCAN represents a dataset with internal validity in which countries can be compared to each other to allow worldwide analysis to be performed. Because of the adjustment process, it is unlikely that the differences in incidence and mortality among countries are due to under- or over-reporting. More correctly, they represent the varied epidemiology of esophageal cancer. An additional potential limitation of this study is our use of US data to derive a global median survival after diagnosis. We expect that this parameter would show global variability because stage at diagnosis, histological subtype, and treatment modalities differ globally. These data, however, are not universally available, and furthermore, sensitivity analysis showed minimal effect of this parameter on total DALYs, as described. This reflects the reality that the majority of the global burden of esophageal cancer is in YLLs, rather than YLDs. As new data from GLOBOCAN emerge [49], these patterns may continue to evolve, but it is unlikely that there will be substantial changes without fundamental efforts in limiting environmental exposures, increased public health efforts, more screening, cultural change, better understanding of cancer genetics, and better treatment. Similarly, as populations increase, esophageal cancer incidence and mortality are surely increasing, but it is unlikely that substantial change in the distribution of disease burden is occurring.

We hope to encourage further discussion and investigation into peculiar and widely variable epidemiology of esophageal cancer. This study should serve as a foundation for additional investigations of how lifestyle modification and medical and surgical intervention can reduce the global burden of esophageal cancer. Our study also highlights the need to transition improvements in esophageal cancer prevention, detection, and care from well-developed countries to less-developed countries and helps solidify global priorities for the prevention and treatment of esophageal cancer.

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Compliance with ethical standards

Conflicts of interest One of the authors of this manuscript is the Editor in Chief of the World Journal of Surgery. To avoid privileged treatment of this manuscript during peer review, Dr Hunter's name was not included as an author during the review process. His contributions were only revealed after this manuscript was finally accepted, nearly 18 months after initial submission and many revisions.

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