MINI-REVIEW

Review of the Burden of Esophageal Cancer in Malaysia

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Abstract

Esophageal cancer is one of the top leading causes of cancer-related deaths in Malaysia. To date, neither the prevalence nor incidence of esophageal cancer nationally have been recorded. Esophageal cancer remains a major and lethal health problem even if it is not common in Malaysia. The late presentation of esophageal cancer makes it a difficult and challenging medical problem. Therefore, more governmental and non-governmental organizations of Malaysia should emphasize primary and secondary prevention strategies.

Keywords: Esophageal cancer - burden - Malaysia - primary prevention - secondary prevention

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Introduction

In Asia, esophageal cancer is the fifth most common cancer with 247, 060 cases occur in men, and eighth most common cancer with 124,507 cases occur in women in 2008 (Sankaranarayanan et al., 2014). Esophageal cancer is considered as a serious health problem concerning fatal outcome in the vast majority of cases (Li et al., 2011). It remains an important cancer in the Asia-Pacific region including Malaysia although it is often overshadowed by gastric cancer and colorectal cancer (Abdullah et al., 2010).

In Penang and Sarawak, the age-standardized rate (ASR) of esophageal cancer was relatively low of 2.5 and 2.2 per 100 000 population in males and females respectively (Curado et al., 2007). Further sub-analysis of the ASR in national cancer registry of Peninsular Malaysia 1991-1993 (Lim et al., 2003) and Singapore (Curado et al., 2007) showed a higher incidence among Chinese and Indians ethnicity.

Epidemiology of Esophageal Cancer

National Cancer Registry 2002 reported that in Malaysia, esophageal cancer ranked 17th and 19th among cancers in males and females respectively (Lim et al., 2003). This disease comprised 1.9% of all cancers in males and 0.9% of all cancers in females. In Peninsular Malaysia, there were 350 esophageal cancer cases which comprised of 221 males and 129 females. However, in 2006 and 2007, the overall cases of esophageal cancer decrease from 350 cases in 2002 to 302 cases and 206 cases in 2006 and 2007 respectively (Omar et al., 2006; Omar and Ibrahim, 2011). With regards to the contribution of ethnicity, in 2002, 123 were Malays, 125 were Chinese and 87 were Indians (Lim et al., 2003). However, in 2006, there were 103 Malays, 94 Chinese and 66 Indians (Omar et al., 2006) whereas in 2007, there were 63 Malays, 82 Chinese, and 45 Indians (Omar and Ibrahim, 2011).

Due to the limited number of prospective studies conducted in Malaysia, neither prevalence nor incidence of esophageal cancer has been recorded nationally. We describe a few studies that have been done in different Malaysia states.

In Kuala Lumpur, 143 esophageal cancer patients were admitted to University of Malaya Medical Centre over a 6-year period (January 1998 to December 2003) (Abdullah et al., 2010). Among the patients, 64.3% were males and 35.7% were female (Abdullah et al., 2010). The mean (SD) age of the patients was 63.1 (12.1) years. On the demographic data, 50.3% were Indians, 32.9% Chinese and 16.8% Malay. More squamous cell carcinoma (SCC) cases (79.0%) as compared with adenocarcinoma (AC) cases (21.0%) were observed. The stage of esophageal cancer at diagnosis was II; 18 (12.6%), III; 23 (16.1%) and IV; 102 (71.3%) (Abdullah et al., 2010).

Another study had been done in Seremban where 26 esophageal cancer patients were admitted to Hospital Tuanku Ja'afar from January 2004 to July 2008 (Tata et al., 2013). Among the patients, 71.1% were males while another 26.3% were females. The mean age (SD) of patients was 58.4 (12.1) years (Tata et al., 2013). The oldest esophageal cancer patient was 84 years old, and the youngest was 25 years old. The majority of them were Indians (44.7%), followed by Malay (26.3%) and Chinese (23.7%).

The incidence of esophageal cancer in Malaysia is slightly higher in males compared to females (Ariffin and Saleha, 2011). Both studies in Kuala Lumpur and Seremban that had been discussed above discovered the similar result where the esophageal cancer was predominant among male patients. Based on National Cancer Registry Report 2007, Indians has the highest incidence of esophageal cancer (Ariffin and Saleha, 2011).

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Again, both studies showed the similar result where the esophageal cancer was far more common in Indians than Chinese and Malays. It is interesting to note that the Malays have the lowest burden of disease (Abdullah et al., 2010). The result is in keeping with cancer statistics of the National Cancer Registry of Malaysia, where Indian men and women were found to have the highest ASR of esophageal cancer of 2.8 and 3.7 per 100 000 population respectively compared to Chinese and Malay (Ariffin and Saleha, 2011).

Interest in Helicobacter *(H.) pylori* (gram-negative bacteria that colonize the human stomach) has extended to its possible role in the etiology esophagus diseases over the past few years (McColl, 2007). It focused largely on the possibility that *H. pylori* infection may protect against the development of gastroesophageal reflux disease and its complications of Barrett's esophagus and esophageal AC (McColl, 2007). Advancements in sanitation and antibiotics have made *H. pylori* become less common and have consequently lowered the incidence stomach cancer and ulcers (American, 2008). However, as *H. pylori* have become less common, esophageal AC have increased (American, 2008). The declining rates of *H. pylori* in developed populations may be partly responsible for this elevation (American, 2008). Esophageal AC now constitutes approximately half of all esophageal cancers cases in Western Countries like the United States and United Kingdom (American, 2008). In Malaysia, more SCC cases as compared with AC cases were observed (Abdullah et al., 2010). None of the studies done in Malaysia to determine the association between *H. pylori* infection and the development of esophageal SCC. Even very few studies have examined the association between *H. pylori* infection and the development of esophageal SCC.

A study was done to investigate the association between the absence of H.pylori with a high prevalence of AC incidence among Malays in North-Eastern Peninsular Malaysia (Lee et al., 2011). In Kelantan, Malay ethnic constitutes more than 90% of a population of 1.2 million. It is among the few geographical areas in the world with a natural exceptionally low prevalence rate of *H. pylori* infection (Raj et al., 2001). The decline in *H. pylori* infection in affluent peoples has also been suggested to be one of the factors that contribute to rise in the incidence of esophageal cancer (Liu et al., 2006; DeMeester, 2009).

Lee et al., (2011) claimed if *H. pylori* infection has a protective role, populations with a naturally low prevalence of *H. pylori* infection such as the ethnic Malays of Northeastern Peninsular Malaysia should have high rates of esophageal cancer. However, Lee et al., (2011) found the low rates of the esophageal cancer, despite the fact that *H. pylori* infection is virtually absent. So, it does not support the hypothesis that the absence of *H. pylori* will likely result in a marked increase in the incidence of esophageal cancer (Lee et al., 2011).

People who had *H. pylori* strains carried a gene called cytotoxin-associated gene A (CagA), almost half were likely to get AC of the esophagus (Chow et al., 1998). However, *H. pylori* may decrease the risk of AC by reducing the acid production in the stomach and hence reducing the acid reflux to the esophagus (Chow et al., 1998). On the other hand, AC risk also can be reduced by decreasing the production of the hormone ghrelin (Chow et al., 1998). Hormone ghrelin is mostly secreted by the stomach and stimulates appetite (Wren and Bloom, 2007). A decrease in the level of ghrelin may lead to lower rates of obesity which an important risk factor for AC (Whiteman et al., 2008). CagA-positive strains of *H. pylori* have been disappearing faster than the CagA-negative ones (Perez-Perez et al., 2002). Interestingly, the inverse association between *H. pylori* and AC was seen only with CagA-positive strains (Islami and Kamangar, 2008).

A study in Taiwan found that *H. pylori* infection may protect against the development of SCC (Wu et al., 2005). An *H. pylori* infection may also increase the risk of cancers such as esophageal SCC (Craddock, 1992) by stimulating the production of nitrosamines. Mortality from esophageal cancer (predominantly SCC) was statistically significantly correlated with endogenous nitrosation ability in an ecologic study in China (Wu et al., 1993). Atrophic gastritis induced by *H. pylori* may form a milieu that favors bacterial overgrowth which, in turn, may elevated intragastric nitrosation (Houben and Stockbrugger, 1995). Thus, infection with *H. pylori*, especially CagA-positive strains, may be a risk factor for esophageal SCC. However, only one study has investigated the relationship between a CagA-positive *H. pylori* infection and the risk of esophageal SCC; a nested case–control study from China found a borderline statistically significantly increased risk for esophageal SCC associated with the presence of serum CagA antibodies (Limburg et al., 2000). Since only a few studies conducted about the association of *H. pylori* and SCC, additional studies are needed to confirm these findings.

Mortality

Diagnosis

Sophageal cancers are usually detected at advanced stages (Tata et al., 2013).The National Cancer Registry in 2007 reported about 75% of the upper gastrointestinal cancers (stomach cancer and esophageal cancer) were detected at stage III and IV (Ariffin and Saleha. 2011). Esophageal cancer generally portends a grim prognosis attributable to late presentation in most patients (HYPERLINK \l "Tettey et al., 2013). A study done by Kandasami et al., (2003) found that esophageal cancer patients have poor prognosis due to late presentation to the hospital that subsequently delay in diagnostic procedure. Patients with esophageal cancers are usually present late to hospitals due to its discernible symptoms from benign diseases (Tata et al., 2013). Almost everyone experienced coughing and hoarseness at least once in a year or once in their lifetime and most of them will self-medicate initially (Tata et al., 2013). Patients will seek either a private physician or a primary health centers that nearer to their house. Patients present late to primary care centers due to esophageal cancer symptoms are often difficult to distinguish from benign diseases. These patients go back to the primary care center for recurrent of symptoms which will be treated again with similar or different medication

until the symptoms gets more persistent or severe (Tata et al., 2013).

The diagnosis is made based on an endoscope procedure (Ariffin and Saleha, 2011). The delay of endoscope procedure can be overcome by increasing the awareness of esophageal cancers among patient through health education and mass media (Tata et al., 2013). The need for proper referral system for early endoscope for high risk patients will be useful for those medical officers in primary care centre. Getting the high risk patients for early endoscope procedure will benefit the patients and increase the quality of care in tertiary centers (Tata et al., 2013)..

Economic Impact

In 2008, there were a total of 3,955,919 disability-adjusted life-years (DALYs) attributable to esophageal cancer at a global rate of 0.58 DALYs per 1000 people annually (Di Pardo et al., 2016). The majority is due to years of life-lost (YLL) from esophageal cancer (96.8 %), rather than years lived with disability (YLD) due to it (3.2%) (Di Pardo et al., 2016). 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 (Di Pardo et al., 2016). However, no previous study about DALYs attributable to esophageal cancer in Malaysia has been conducted.

Prevention and Rehabilitation

A multidisciplinary approach should be considered to decrease the burden of esophageal cancers. From the gastroenterologists' perspective, identification and elimination of risk factors is an important first-step for primary prevention. The secondary prevention composed of the recognition of precancerous lesions (Barrett's esophagus (BE) and dysplastic squamous neoplasm) and cancer at the early stage when endoscopic treatment is possible. For tertiary prevention, the use of treatment and rehabilitation programs to improve the outcome of illness among individuals with esophageal cancer is the mainstay (Chung et al., 2015).

The risk of developing esophageal cancer can be reduced by avoiding certain factors. The most important lifestyle risk factor for esophageal cancer is tobacco and alcohol consumption. Almost 10,000 Malaysians die each year in results of smoking (Hong et al., 2013). Avoiding tobacco and consumption of alcohol is one of the ways of reducing the risk of esophageal cancer. The Malaysian government has put in a lot of efforts to reduce the number of smokers, especially youth. In 2004, the largest national anti-smoking campaign, Tak Nak (Say No), was launched by Tun Abdullah Haji Ahmad Badawi, who served as the Fifth Prime Minister of Malaysia and broadcast on all forms of media in Malaysia (Hong et al., 2013). The campaign was designed to get people to stop smoking and realize the harmful effects of smoking (Hong et al., 2013). The government introduced various strategies as part of 'Tak Nak Merokok' campaign where a new television commercial about the grisly effects of smoking were established in 2009 (Brand Consultant Asia, 2009).

An endoscopic screening acted as secondary prevention and is a diagnostic choice for esophageal cancer (Ariffin and Saleha, 2011). It might have potential benefits to control SCC of the esophagus (Norouzi et al., 2013). The most important step of screening procedure is to detect its premalignant lesions (squamous dysplasia) as well as early-stage malignant lesions (carcinoma in situ). The endoscopy procedure is considered as the method of choice for detecting these lesions and taking the biopsy for histologic confirmation (Norouzi et al., 2013). Endoscopy with iodine (Lugol's solution) staining of the esophageal mucosa, so called as chromoendoscopy, has been used to detect esophageal mucosal lesions and suggested to be considered in SCC early detection (screening) programs (Norouzi et al., 2013).

The options for treatment of esophageal cancer include surgery, radiation, chemotherapy, targeted therapy and endoscopic treatment. Traditionally, both AC and SCC have been treated by surgical resection. However, high frequencies of systemic and local tumor recurrence have urged investigations into multimodality therapies that combine surgery radiotherapy, chemotherapy and chemoradiotherapy. Preoperative therapy has also been considered for both tumor types (Baba et al., 2014).

There were 355 hospitals in Malaysia in 2010 of which 55 hospitals providing oncology services which involved 257 radiation therapies (Centre, 2012). The distribution for oncology services was more towards the urban areas, especially in the Klang Valley and the west coast of Peninsular Malaysia (Centre, 2012). The three regions with the highest oncology centres were Pulau Pinang and Selangor with nine centres and Kuala Lumpur with eight centres (Centre, 2012).

Some hospitals have traditional and complementary units that practice the traditional, complementary and alternatives medicines (TCAM) to oncology patients. TCAM has been gaining acknowledgement and recognition worldwide and has been used to treat both simple ailments and chronic diseases for many years (Nagashekhara et al., 2015). There are nine integrated public hospitals in Malaysia which are practicing TCAM (Abuduli et al., 2011). They are Kepala Batas Hospital in Pulau Pinang, Putrajaya Hospital, Sultan Ismail Hospital in Johor Bharu, Duchess of Kent in Sabah, Sultanah Nur Zahirah Hospital in Kuala Terengganu, Sarawak General Hospital, Port Dickson Hospital in Seremban, Sultanah Bahiyah Hospital in Kedah and Cameron Highlands Hospital (Abuduli et al., 2011).

Acupuncture is an ancient Chinese medical technique and the uses of acupuncture for dysphagia are well documented in Chinese medicine texts (Lu et al., 2012). Dysphagia (trouble swallowing) was the most common symptom of the esophageal cancer (Hai et al., 2007). Previous research suggests that acupuncture may reduce symptoms and side effects that are associated with primary cancer therapy, such as chemotherapy-induced nausea (Ezzo et al., 2006). Not all TCAM are free from side effects (Clarke and McLachlan, 2011). Pharmacodynamics interactions may occur when active ingredients of herbal

compounds act in an additive, synergistic or antagonistic manner with a therapeutic agent (Clarke and McLachlan, 2011). Even patients who received acupuncture may experience needle pain, bleeding and syncope although it is infrequent (Ernst and White, 2001).

Conclusion

Esophageal cancer poses a major economic burden to the individuals, families and the country although it is uncommon cases happened in Malaysia. We advise future Malaysian government officials to emphasize health-care development and services to provide effective and efficient primary and secondary prevention for esophageal cancer patients. This approach would positively impact Malaysian economic development.

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