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Oesophageal carcinoma: a neglected volcano in Sri Lanka

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“Ms X, a 37-year-old teacher and mother of two young children (three years old and five months old) found out that her nausea and vomiting were not resolved even following the delivery of her second child. In addition, she was suffering from difficulty in swallowing and generalized weakness as well, for which she was re-assured by her family, attributing these features to her lactation and the possibility of another pregnancy. With a ‘negative’ pregnancy test, she sought medical care and underwent an upper gastro-intestinal endoscopy test, which revealed a mass in the middle one third of the oesophagus. Histology confirmed this mass to be oesophageal carcinoma. She lost her life eight months following this diagnosis”.

High morbidity, mortality and financial burden due to cancer have clutched the attention of policy makers throughout the globe, particularly in low- and middle-income countries, which account for 77% of the global disability-adjusted life years (DALYs); 78% of years of life lost (YLLs); and 71% of the cancer deaths (1-3).

In Sri Lanka, cancer poses a great impact on the economy of individuals, households as well as the country, with the care being predominantly provided by the state and increasingly being financed out-of-pocket by family (4). Oral cavity, breast, cervix and oesophageal cancer are reported to be the commonest cancer types in Sri Lanka (5), of which the latter continues to be the third commonest cancer among males and fifth commonest among females (6). It is shown that the incidence of oesophageal carcinoma in Sri Lanka has been gradually, yet steadily increasing in the recent past. This increase is most likely to be due to a change in the histological trend from squamous cell carcinoma to adenocarcinoma which follows a more aggressive disease progression, further fuelling the burden due to oesophageal carcinoma (5, 7). It is important to note that oesophageal carcinoma lacks a

specific prevention programme, unlike in the case of oral, breast and cervical cancers. Considering these facts, oesophageal carcinoma is presumably a volcano that has been neglected in the country, and awaits its eruption to cause severe damage. This catastrophe can be prevented by prompt action taken through primary, secondary and tertiary prevention modalities against oesophageal carcinoma in Sri Lanka.

Primary prevention: identifying population-specific risk factors

The underlying causes of oesophageal carcinoma are multi-factorial. As with any other chronic non-communicable disease, the conventional risk factors are related to non-modifiable demographic (e.g. older age, male sex, genetic predisposition) (8-9) and socio-economic status (e.g. low socio-economic status) (10-11); clinical conditions such as gastro-oesophageal reflux disease (12) and Barrett’s oesophagus (13); medication such as non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin (14); and lifestyle factors such as physical inactivity (15), tobacco, alcohol, and low intake of fruits and vegetables (16-17). In addition to these, several other risk factors have been newly

identified in the recent past, which are related to specific elements in the diet (e.g. diet deficient in vitamins A, B, C and E, selenium and beta carotene) (18-19); food preparation methods (e.g. chillies and spicy food) (18, 20); consumption of food/drinks at high temperatures (21); drinking water sources (22); chewing betel leaf with tobacco (23) and arecanut (24); and exposure to ionizing radiation (25). However, evidence on these risk factors is largely from the developed countries and may not be directly applicable to the risk profile in developing countries including Sri Lanka. Furthermore, there may be other risk factors unique to developing countries, owing to practices related to agriculture-based settings and occupations (e.g. indiscriminate use of agrochemicals and other occupational hazards).

Currently, there is minimal research evidence on the risk factors of oesophageal carcinoma in Sri Lanka, which could assist health care planners to provide targeted primary prevention for oesophageal carcinoma. In bridging this knowledge gap, a hospital-based unmatched case-control study was conducted among 49 incident cases of oesophageal carcinoma and 196 ambulatory controls powered enough to detect the smallest reported risk for oesophageal carcinoma (odds ratio of 2.5 for consumption of alcohol) (26). The cases were newly diagnosed oesophageal carcinoma patients recruited from the National Cancer Institute Maharagama. Controls were those without oesophageal carcinoma confirmed by negative findings of upper

gastro-intestinal endoscopy (UGIE) examination (apparently healthy oesophageal mucosa, gastro-oesophageal junction and the stomach up to the distal duodenal sphincter with no macroscopic changes, erosions or lesions) (27). They were recruited from the Endoscopy Unit of the National Hospital of Sri Lanka. Several exclusion criteria were considered to avoid early disease, pre-malignant stages and shared risk factors of other cancers. In both cases and controls, several potential risk factors were assessed using valid and reliable tools.

After controlling for confounders and interactions using logistic regression (LR) analysis, population-specific risk profile for oesophageal carcinoma was identified. This risk profile included: age more than 65 years; family history of cancer; sub-optimal consumption of fibre in the diet; sub-optimal consumption of antioxidants in the diet; over-consumption of deep fried food; 'low' total lifetime sports and exercise activities; 'high risk' alcohol consumption; ever betel quid chewing; exposure to agrochemicals; consumption of pipe-borne water as the major source of water; and ever exposure to radiation (Table 1). Most of these risk factors are highly prevalent among Sri Lankan populations and therefore, it is essential that public health professionals pay more attention to empower the general public on lifestyle and environmental modifications relevant to oesophageal carcinoma.

Table 1. Risk factor profile of oesophageal carcinoma

Independent variable	Odds ratio	95% CI	
		Lower	Upper
Age more than 65 years	3.99	1.12	14.25
Family history of cancer	5.04	1.34	19.00
Sub-optimal consumption of fibre	3.58	1.10	12.32
Sub-optimal consumption of antioxidants	7.01	2.18	22.54
Sub-optimal consumption of deep fried food	6.68	1.98	22.59
'Low' level of total lifetime sports and exercise activities	5.83	1.48	23.03
'High risk' alcohol consumption	11.71	2.78	49.43
Ever betel quid chewing	6.11	1.90	20.00
Exposure (direct/indirect) to agrochemicals	6.57	1.42	30.30
Pipe-borne water as the major drinking source	5.62	1.67	18.88
Ever exposure to radiation	4.64	1.38	15.53

Secondary prevention: risk prediction tool for early diagnosis

As with other cancers, the prognosis of oesophageal carcinoma depends largely on its stage of disease (28). It is shown that the five-year survival rates for stages I, II and III are 50-80%; 30-40%; and 10-15%, while stage IV has a median survival of less than one year (11). Since it is a fast growing tumour with a potentially high cell doubling time, even a delay of a few months in diagnosis would affect the prognosis substantially (29). As such, every effort should be taken to diagnose the disease as early as possible, so that the outcome could be considerably better than when detected late. However, clinical symptoms of oesophageal carcinoma are well-known to appear late. Substantial circumferential involvement and considerable penetration into the oesophageal lumen act as pre-requisites for dysphagia and the tumour spreading to adjacent structures to present with pain (30).

Limiting the number of individuals in advanced disease stages is achieved by means of early diagnosis and early initiation of relevant treatment. This could be accomplished by a well-organized screening program for oesophageal carcinoma, which is a secondary prevention strategy to address the issue of late diagnosis. The recommended screening is routine UGIE followed by histological confirmation (31). However, this is routinely practiced in the world only in inherently high-risk areas of China, owing to its high cost and the limited availability of trained human resources and equipment. For example, in Sri Lanka, endoscopy units are available in only 61 hospitals with only 12 consultant gastroenterologists and 144 consultant surgeons providing services on UGIE examination (S Wimalaratne, personal communication, 17 June 2016). In addition, invasiveness of the UGIE examination plays a crucial role in poor compliance of individuals to undergo screening. As a solution, a simple, low-cost, non-invasive, easily administrable screening tool (i.e. a risk prediction model) could be introduced as a primary screening strategy to identify the most at-risk persons for oesophageal carcinoma among the general population, so that only those identified could be subsequently offered UGIE as a secondary screening strategy for endoscopic confirmatory diagnosis, thus, preventing the delays in diagnosis of the disease. Such screening tools will address the existing gaps in secondary prevention of oesophageal carcinoma especially in low-resource settings.

Risk prediction models that are already in use in the world for screening for oesophageal carcinoma, have been developed based on non-modifiable and modifiable risk factors specific for geographical regions, and include a variety of predictors in relation to genetic variants (25 single nucleotide polymorphisms), socio-economic factors (age, sex, level of education), lifestyles (smoking and alcohol), anthropometry, and clinical features (gastro-oesophageal reflux, use of acid suppressant medications and NSAID) (32-33). As these models have their own restrictions to be used in other settings, it is mandatory that countries develop their own population-specific risk prediction tools to identify those at risk of developing oesophageal carcinoma.

In an attempt to develop a simple risk prediction tool to identify those at increased risk of oesophageal carcinoma, a hospital-based unmatched case-control study was conducted among Sri Lankans, utilizing the newly developed population-specific risk factor profile. For this purpose, 30 cases and 138 controls were recruited to achieve 98% expected sensitivity and 90% expected specificity. Recruitment and sampling of subjects was similar to the previously described case-control study (27). When developing the risk prediction model, all the risk factors significant in the previous study as well as those not significant but clinically important according to previous studies were considered.

The best model that was derived using receiver operating characteristic (ROC) curve, described 0.97 (95% CI=0.94-0.99) area under the curve. This risk prediction model is shown in Table 2. The risk score for identifying those at risk of oesophageal carcinoma from those without was 34.5 at 96.7% sensitivity and 84.1% specificity, indicating good predictive ability of the risk prediction tool. This risk prediction model was further tested for judgmental validity by a panel of experts using modified Delphi technique. It demonstrated high reliability (Spearman correlation coefficient=0.81) as well during split-half cross-validation.

Tertiary prevention: improving the quality of life

The primary focus of any cancer treatment is to improve the quality of life (QoL) either by curing the disease or by ameliorating the worst symptoms as long as possible. Improving the QoL in oncology patients

Table 2. Risk prediction model for assessing the risk of oesophageal cancer

Predictor variable	Categories	Weighted score ¹
Age of the individual	> 65 years	4 ²
Lifetime sports and exercise activities	Low level	6 ²
Alcohol consumption	High risk	12 ²
Consumption of dietary Fibre	Sub-optimal	4 ²
Consumption of antioxidants	Sub-optimal	7 ²
Consumption of deep fried food	Over-consumption	7 ²
Family history of cancer	Yes	5 ²
Ever betel quid chewing	Yes	6 ²
Ever exposure to radiation	Yes	5 ²
Exposure (direct/indirect) to agrochemicals	Yes	7 ²
Drinking water source	Pipe-borne	6 ²
Ever tobacco smoking	Yes	11 ³
Total score		80

¹ Weighted score based on the odds ratio obtained for each variable

² Based on the adjusted odds ratio of the population-specific risk factor profile for oesophageal carcinoma

³ Based on the odds ratio of the bivariate analysis

has become an important therapeutic goal, with most treatment decisions being heavily influenced by their effect on patients' QoL (34). Oesophageal carcinoma is well-known for poor prognosis, with its five-year survival rate being as low as 5-10% (35). However, the advancements in treatment modalities in the last few decades have drastically improved the survival of these patients (36), but how this improvement has affected their QoL remains inconclusive (37).

The national policy for cancer prevention and control in Sri Lanka aims at a comprehensive programme (38), which includes the provision of palliative care services for cancer survivors through universal health coverage. Though many initiatives have been undertaken, further improvement of these services has been hampered due to the lack of evidence on the improvement in QoL following treatment which would otherwise enable targeted palliative care services as a tertiary preventive strategy. To provide this much-needed evidence, a prospective cohort study was conducted at the National Cancer Institute Maharama among 51 newly diagnosed patients of

oesophageal carcinoma who had not yet undergone the initial treatment (surgery, chemotherapy and/or radiotherapy). The majority were males (70.6%), over 60 years of age (53%), employed (60.8%) and of low social status (social classes IV and V) (64.7%). Their QoL was assessed and compared before (baseline) and one month after the completion of initial treatment (follow-up irrespective of the treatment plan), using three questionnaires validated for Sri Lanka (EORTC QLQ-C30 core-questionnaire, EORTC QLQ-OES18 modules specific for oesophageal carcinoma and questionnaire on family support (39-41). One month was considered long enough to avoid the temporary effect of side effects during treatment phase on their QoL. The QoL dimensions that showed a significant change (improvement or deterioration) following the initial treatment are given in Table 3. Worsening aspects in the QoL following initial treatment were physical, emotional, social and role functioning as well as the general symptoms, financial difficulties and reduction of family support. Dysphagia seemed to improve significantly following the initial treatment in contrast to dry mouth.

Table 3. The dimensions in QoL that showed a significant change after initial treatment

Scale	Baseline score		Follow up score		Mean difference ⁴	95% CI
	Mean (N=51)	SD	Mean (N=41) ³	SD		
Physical functioning ¹	53.1	28.8	34.3	24.5	-20.8	-30.0, -11.6
Role functioning ¹	42.2	34.5	21.5	26.2	-22.8	-34.7, -10.8
Emotional functioning ¹	53.4	26.4	42.1	31.2	-14.0	-24.4, -3.7
Social functioning ¹	57.2	23.2	37.4	26.8	-23.2	-31.9, -14.4
Family support ¹	82.6	20.4	80.5	14.4	-6.5	-10.6, -2.44
Fatigue ²	52.1	28.9	71.3	28.8	20.9	9.8, 31.9
Dysphagia ²	54.0	27.0	37.1	29.0	-13.6	-22.9, -4.2
Dry mouth ²	39.2	34.5	58.5	37.1	20.3	7.9, 32.7
Nausea & vomiting ²	40.2	34.4	54.1	37.6	13.0	0.7, 25.3
Pain ²	45.4	32.7	71.5	28.7	27.6	15.8, 39.5
Insomnia ²	33.3	32.0	43.9	35.3	13.8	2.3, 25.3
Loss of appetite ²	42.5	34.0	54.5	37.8	13.0	0.4, 25.7
Constipation ²	30.1	35.4	47.9	41.5	16.3	5.5, 27.1
Financial difficulties ²	50.9	31.5	77.2	21.6	30.9	20.5, 41.3

¹ Scores range from 0-100, with higher scores indicating a higher level of functioning/family support

² Scores range from 0-100, with higher scores indicating a higher degree of symptoms/financial difficulties

³ Ten patients died during the follow up period

⁴ A negative mean difference indicates deterioration of functioning, family support and improvement of symptoms while a positive mean difference indicates worsening of symptoms and financial difficulties

Evidence for improved health services

It is justifiable to consider oesophageal carcinoma as a neglected volcano in Sri Lanka, based on the evidence derived on the risk factors and quality of life of patients with oesophageal carcinoma.

The national policies and strategic frameworks on non-communicable diseases and cancer prevention and control identify the importance of targeted primary preventive measures to prevent cancer as well as early detection at primary healthcare level through screening of asymptomatic populations and prompt referral of the suspicious ones for confirmation of diagnosis and further management (38, 42). In line, knowledge on the conventional as well as newly identified risk factors for oesophageal carcinoma enables the health policy

makers to prioritize evidence-based primary prevention activities in the country, and thereby utilize the limited resources to a maximum to reduce the future burden of this disease. Also, the burden caused by advanced disease condition can be controlled by adopting the simple low cost risk prediction tool that would enable the identification of those at risk of developing oesophageal carcinoma, who could then be referred for the UGIE assessment.

The national policy on cancer further elaborates on providing disease-specific and patient-centred palliative care. Evidence on different aspects of QoL of patients with oesophageal carcinoma that may change over time should shape the management aspects of these patients towards tertiary prevention strategies.

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