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Original Research

A simple low-cost tool to predict the risk for oesophageal carcinoma: a validation study

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Abstract

Introduction: Oesophageal carcinoma (OC) is a leading cancer in Sri Lanka. Owing to late symptoms and absence of routine endoscopic screening, delayed presentation leads to severe outcomes of the patients with OC.

Objectives: To develop and validate a simple low-cost risk prediction tool to identify high-risk individuals for OC early, based on population-specific risk

Methods: A risk prediction tool including cut-off value to identify high-risk individuals, was developed based on weighted scores derived from the risk factor profile specific for Sri Lankans. Its criterion validity was assessed against histological diagnosis of OC in an unmatched case-control study conducted among 83 cases recruited from the National Cancer Institute, Maharagama (NCIM) using a non-probability sampling method, and ambulatory hospital controls (n=166) excluded of OC recruited from the Endoscopy Unit at National Hospital of Sri Lanka (NHSL). Data were collected through an interviewer-administered-questionnaire.

Results: Risk predictors in the tool included age >65 years, family history of cancer, sub-optimal consumption of fibre, antioxidants and deep-fried food, low total lifetime sports and exercise activities, high risk alcohol consumption, ever betel quid chewing, ever exposure to agrochemicals, consumption of pipe-borne water, ever exposure to radiation and ever tobacco smoking. The tool demonstrated valid predictions (92.8% sensitivity; 88.6% specificity; 80.2% positive predictive value (PPV); 96.1% negative predictive value (NPV); 8.1 positive likelihood ratio (LR); and 0.1 negative LR) to identify high-risk individuals for OC at 17.83 cut-off value.

Conclusions & Recommendations: To minimize delayed diagnosis and improve survival, this simple and low-cost risk prediction tool is recommended for identifying and prioritizing high-risk individuals for endoscopy screening for OC.

Key words: *oesophageal carcinoma, risk prediction, tool, validation, Sri Lanka*

Introduction

Oesophageal carcinoma (OC) is the eighth commonest cancer and the sixth among all cancer deaths in the world (1). It is a virulent cancer especially in developing countries, not only because of its high mortality (1) and morbidity (1-3), but also due to the economic impact (4) on individuals, households and countries, necessitating prompt attention to lessen its burden.

The prognosis of OC is related to its disease stage (5-6). 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 (7). Since OC is a fast-growing tumour with a high cell doubling time, even a brief delay of a few months in diagnosis would affect the prognosis substantially (8). Therefore, if the disease is diagnosed and treated early, the outcome is expected to be considerably better than when detected late. However, the clinical diagnosis is often delayed, as the early stages of OC are usually asymptomatic (9), as substantial circumferential involvement and penetration into the oesophageal lumen are pre-requisites for developing key symptom, dysphagia and the tumour spreading to the adjacent structures to present with pain (9). To address this issue of late diagnosis, routine upper gastro-intestinal endoscopic (UGIE) screening followed by histological confirmation is indicated for asymptomatic persons (10). It is currently practised in inherently high-risk areas in China; however, such screening is not feasible especially in low-resource countries owing to its high cost, and limited availability of trained human resources and equipment. As an alternative strategy, the delay in diagnosis could be minimized by introducing low-cost screening tools as a secondary prevention strategy to identify the high-risk individuals for developing OC, and thereby prioritize the most at-risk persons for endoscopic confirmatory diagnosis, for early detection of OC. Such prediction tools have been developed, weighted by the risk factor profiles specific to a given population (11-14). These tools may not be applicable in other countries, owing to differences in the population-specific risk factor profile.

Sri Lanka continues to report OC as one of the five leading cancers in the country (15-17). In 2019, it was the fourth commonest cancer among males and the seventh among females (17). However, endoscopy units providing UGIE services are available only in limited number of hospitals (personal communication with Director Planning, Ministry of Health), thus there are less opportunities for routine screening of OC in Sri Lanka. Even if adequate, invasiveness of the UGIE examination may play a crucial role in poor compliance of individuals to undergo screening, thus leading to delayed health seeking (7). Thereby, this study aimed at developing and validating a simple, cost-effective population-specific risk prediction tool for the purpose of identifying individuals at risk of developing OC.

Methods

Development of a risk prediction tool

A risk prediction tool was developed, based on an unmatched case control study that identified the population-specific risk factor profile of OC among Sri Lankans. Details of the study are published elsewhere (18). Using a random split sample (25 cases and 100 controls) of this study, optimal cut-off value to identify the 'high-risk' individuals for OC was derived.

Validation of the risk prediction tool

The newly developed risk prediction tool was assessed for its validity. Its judgmental validity was assessed using modified Delphi technique with a panel of experts consisting of consultant gastroenterologists, community physicians, oncologists and onco-surgeons. In addition, a hospital-based unmatched case-control study was conducted to test its criterion validity against the gold standard, viz clinical diagnosis of OC. As cases, patients newly diagnosed of OC within the last three months based on histological confirmation following UGIE examination were recruited from surgical and oncology wards and clinics of the NCIM, which is the premier tertiary referral hospital in Sri Lanka dedicated for the treatment and follow-up of cancer

patients who are referred predominantly from the state sector; and from the private sector hospitals. Those critically ill or with documented evidence of secondary carcinoma (e.g., metastasis) or any other type of cancer or relapse including OC were excluded. As controls, persons without a diagnosis of OC were recruited from the Endoscopy Unit of NHSL, which is the leading referral unit for patients referred from the state and private sector hospitals for high-risk screening (e.g., family screening for OC) and for screening of those with dyspeptic symptoms. Absence of OC was confirmed by visualizing healthy (i.e., not showing any macroscopic changes, erosions or lesions such as polyps and ulcers) oesophageal mucosa, gastro-oesophageal junction and the stomach up to distal duodenal sphincter on UGIE examination performed by two independent consultant gastroenterologists. Exclusion of OC was not based on histology, as it was not ethical to do biopsies in the absence of any lesion (e.g., structural abnormality or significant mucosal changes). Patients diagnosed of having any cancer, cirrhosis/chronic liver diseases or with dyspeptic symptoms persisting for more than six months were excluded.

The sample required was 30 cases and 138 controls, based on the equation for assessing criterion validity of a screening test (19), with 1.96 alpha error, 10% precision, 98% sensitivity and 90% specificity. For further precision however, the case number was increased to include all eligible cases encountered during a period of 12 months, while two eligible controls were recruited as controls for every case identified (1:2), based on the incidence density sampling method (i.e., controls recruited within one week of a case recruitment). Following informed written consent, all were administered a questionnaire to collect data on demographic and socio-economic characteristics, and risk predictors included in the risk prediction tool. Also, sub-optimal consumption of dietary fibre, antioxidants and high intake of deep-fried food was assessed using a locally validated food frequency questionnaire (20) and lifetime sports/exercise activities using validated Lifetime Total Physical Activity Questionnaire (LTPAQ) (21).

Data analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 22. Optimal cut-off value for identifying high-risk individuals for OC was derived using ROC analysis on the split sample. In the ROC curve, the independent variable was the total risk score of individuals (calculated by adding the weighted scores of each risk factor in the risk prediction model, where the weight is derived from the logit value (log odds) of each risk factor in the logistic regression model), while the test variable was their OC status (case or control). The shortest distance from the point that gives the maximum discrimination of the individuals with the disease and with no disease to the point on ROC curve (d^2) (22) was identified as the optimum cut-off point. This cut-off value was then applied to the validation sample, to assess the criterion validity of the risk prediction tool via validity measures (sensitivity, specificity and predictive values).

Results

Development of the risk prediction model and its optimum cut-off point

The risk prediction tool showed 0.96 (95% CI: 0.94, 0.99) area under the curve (AUC), indicating its goodness of fit. It was further improved when tobacco smoking was added to the tool (0.97; 95% CI: 0.94, 0.99). Total risk score derived from the finalised tool is as follows:

Total risk score= -11.17 + (1.37 * age >65) + (1.94 * inadequate consumption level of antioxidants) + (1.26 * inadequate consumption level of dietary fibre) + (1.79* betel quid chewing) + (1.54 * radiation exposure) + (1.63 * family history of cancer) + (2.39 * alcohol consumption risk level) + (1.77 * lifetime total sports and exercise activities level) + (1.86 * agrochemical exposure) + (1.71 * drinking water source) + (-0.12 * tobacco smoking) + (1.9 * over consumption level of deep-fried food).

According to the ROC curve (Figure 1), the optimal cut-off value for total risk scores was 17.83, which

corresponded with the shortest distance (d^2=0.0243). The AUC indicated a statistically significant good performance of the tool (p<0.0001) (23), where the ability of the risk prediction tool to correctly classify those with high risk for the disease was 97%.

Validation of the risk prediction tool

The sample included 83 cases and 166 controls, with 100% response rate. A significantly higher proportion of Sinhalese, males, aged more than 65 years with low educational level was noted among cases compared to controls (Table 1). The distribution of predictor variables in the sample are shown in Table 2. Based on the cut-off value of 17.83, the risk prediction tool showed 92.8% sensitivity; 88.6% specificity; 80.2% PPV; 96.1% NPV; 8.1 positive LR; and 0.1 negative LR.

Table 1: Demographic and socio-economic characteristics of the sample

Characteristic	Disease status, No. (%)				Significance
	Case (n=83)		Control (n=166)		
Age					χ^2=4.546
>65 years	29	34.9	37	22.3	df=1
≤65 years	54	65.1	129	77.7	**p=0.03**
Sex					χ^2=21.0
Male	55	66.3	59	35.5	df=1
Female	28	33.7	107	64.5	**p<0.001**
Marital status					χ^2=3.79
Married	68	81.9	117	70.5	df=1
Others[1]	15	18.1	49	29.5	p=0.051
Ethnicity					χ^2=5.44
Sinhalese	71	85.5	120	72.3	df=1
Non-Sinhalese[2]	12	14.5	46	27.7	**p=0.02**
Highest educational level					χ^2=14.33
<O/Level	60	72.3	78	47.0	df=1
≥O/Level	23	27.7	88	53.0	**p<0.001**
Employment status					χ^2=9.28
Ever employed	71	85.5	112	67.5	df=1
Never employed	12	14.5	54	32.5	**p=0.002**
Monthly income					χ^2=0.01
Rs. ≤20,000	39	47.0	77	46.4	df=1
Rs. >20,000	44	53.0	89	53.6	p=0.93

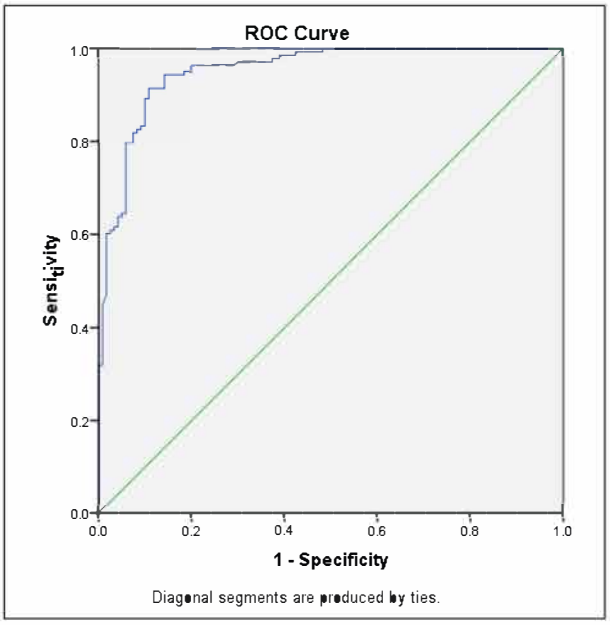
[1]Unmarried/widowed/separated categories combined

[2]Tamil/Muslim/Burgher categories combined

Table 2: Distribution of the risk predictors of oesophageal cancer in the sample

Characteristic	Disease status, No. (%)				Significance
	Case (n=83)		Control (n=166)		
Age					χ^2=4.546
>65 years	29	34.9	37	22.3	df=1
≤65 years	54	65.1	129	77.7	**p=0.03**
Family history of cancer					χ^2=8.045
Yes	19	22.9	16	9.6	df = 1
No	64	77.1	150	90.4	**p=0.005**
Sub-optimal consumption of fibre					χ^2=51.348
Yes	39	47.0	13	7.8	df = 1
No	44	53.0	153	92.2	**p<0.001**
Sub-optimal consumption of antioxidants					χ^2=44.486
Yes	55	66.3	38	22.9	df = 1
No	28	33.7	128	77.1	**p<0.001**
Over consumption of deep-fried food					χ^2=18.527
Yes	42	50.6	39	23.5	df = 1
No	41	49.4	127	76.5	**p<0.001**
'Low' total lifetime sports and exercise activities					χ^2=12.446
Yes	68	81.9	99	59.6	df = 1
No	15	18.1	67	40.4	**p<0.001**
'High risk' alcohol consumption					χ^2=58.974
Yes	43	51.8	14	8.4	df = 1
No	40	48.2	152	91.6	**p<0.001**
Ever betel quid chewing					χ^2=67.631
Yes	49	59.0	17	10.2	df = 1
No	34	41.0	149	89.8	**p<0.001**
Exposure (direct/indirect) to agrochemicals					χ^2=24.595
Yes	31	37.3	18	10.8	df = 1
No	52	62.7	148	89.2	**p<0.001**
Consumption of pipe-borne water					χ^2=12.435
Yes	49	59.0	59	35.5	df = 1
No	34	41.0	107	64.5	**p<0.001**
Ever exposure to radiation					χ^2=29.731
Yes	32	38.6	16	9.6	df = 1
No	51	61.4	150	90.4	**p<0.001**
Ever Tobacco smoking					χ^2=50.584
Yes	44	53.0	19	11.4	df = 1
No	39	47.0	147	88.6	**p<0.001**

Figure 1: ROC curve for the total risk score based on the risk prediction tool



Discussion

The National Policy for Prevention and Control of Chronic Non-communicable Diseases, Sri Lanka (2009) and National Policy and Strategic Framework on Cancer Prevention and Control (2015) identify the importance of early detection of cancer through screening of asymptomatic populations at the primary healthcare level and prompt referral of the suspicious individuals for confirmation of diagnosis and further management (24-25). Healthy lifestyle centres established island wide for this purpose however currently provide screening only for breast and cervical cancers. In this backdrop, our study demonstrates the validity of a newly developed risk prediction tool based on the population-specific risk factor profile of Sri Lanka, to identify the individuals at risk of developing OC. This tool is useful in early screening for OC and applicable as a simple, cost-effective tool in low resource settings in Sri Lanka. It is simple because all the risk predictors of the tool can be easily obtained via a brief history taken from the client, thus its application in the community does not require skilled personnel. Also, it is low cost with no requirement of expensive equipment and administered either as computer-based or paper-based. Further, having a cut-off score enables the healthcare worker to easily identify and refer the high-risk individuals for further care, while the findings could also be utilized for health education and promotion. These features highlight its suitability in other low resource settings like Sri Lanka for OC screening.

When compared with other available risk prediction tools, a similar predictive value was observed for oesophageal squamous cell carcinoma among Iranian population, with AUC of 0.87 (95% CI: 0.85, 0.89) (14); 0.84 (95% CI: 0.81, 0.87) for adenocarcinoma in Sweden (13); and AUC of 0.85 (95% CI: 0.78, 0.91) for adenocarcinoma among the Australians (12). However, the risk predictors were found to be quite different in each tool.

According to our findings, in addition to the conventional risk factors well known to predict OC risk, novel risk factors were identified, such as inadequate consumption of dietary fibre and antioxidants, over-consumption of deep-fried food, betel quid chewing, exposure to agrochemicals, pipe-borne water as the major drinking water source and exposure to radiation. Water source as well as opium use, and tea temperature have been identified as novel risk predictors in the Iranian model as well (14). These novel risk predictors are found to be quite prevalent in the developing nations compared to the developed nations (26-27), thus highlighting a higher prevalence of OC in future.

A systematic review conducted with nine studies (two cohort and seven case-control studies) had shown that the pooled odds ratio for OC and the use of aspirin/NSAIDs was 0.57 (95% CI: 0.47, 0.71), with a greater protection with frequent medication (OR: 0.54; 95% CI: 0.43, 0.67) (28). Additionally, it is shown that the use of NSAIDs have an inverse relationship with Barrette's oesophagus (OR=0.4; 95% CI: 0.19, 0.81) (29). In contrast, many health conditions related to GI system including NSAID medication, were found to be significant risk predictors of OC in the models developed in developed countries (12-13). It should be noted that inclusion of such alarming symptoms (e.g., frequency of symptoms of dysphagia and unexplained weight loss) had further improved the discrimination ability of the models. However, prolonged medication including NSAIDs, and acid-suppressants were not shown to be associated with OC among the Sri Lankans (p>0.05) (18). This could be because the community prevalence of gastro-oesophageal reflux disease for which the acid suppressants are consumed, is low in Sri Lanka (30).

Many studies show a positive relationship between obesity and OC, predominantly for adenocarcinoma (31-32). In contrast, a case-control study conducted in Sri Lanka showed potentially an inverse relationship with the risk of OC (OR=0.07; 95% CI: 0.02, 0.2) (18). Differential timings and stages of the disease at which the anthropometry measurements were taken could have resulted in the discrepancies of the results, as OC is a common disease to lose weight due to its disease process.

Chang et al. (2013) included 25 single nucleotide polymorphisms as the genetic factors in addition to non-genetic factors and interactions with alcohol drinking in their risk prediction model developed for oesophageal squamous cell carcinoma in Chinese population (11). This model showed a 5.8% increase of the AUC when compared to the model with only non-genetic factors. In contrast, Mealy (1996) had shown that the sensitivity of tumour markers such as CEA, CA 19-9, CA 125 and SCC is very low for the screening of OC and is also with less prognostic significance (33). In comparison, in the present study, risk attributable to genetic factors at the cellular level was assessed only by the family history of cancer. On one hand, owing to limited resources, technology and trained personnel required for genetic and cellular assessments, including such factors in a screening tool to be applied in low resource community-based settings is not quite practical. Also, on the other, the recent rise in the incidence is largely attributable to an increase in adenocarcinoma (16-17), and therefore these genetic factors may not reflect this risk in the Sri Lankan context.

The ideal study design would be a follow-up of high-risk individuals to observe whether they would develop OC in the future. Due to various constraints, a case-control study was conducted. Ideally, the controls for this study should be apparently healthy individuals histologically confirmed as not having OC and recruited from the community. However, in the absence of routine UGIE screening programme in Sri Lanka, it was difficult to motivate community controls to undergo invasive UGIE examination to exclude OC, thus an ambulatory hospital control group was recruited for the validation study. This limitation in recruiting a control group that may be different from the general population may have resulted in a reduction of the magnitude of the risk of certain risk factors of OC. However, this possible sharing of risk factors in the current study was considered acceptable since the internal validity should not be compromised.

Conclusions and Recommendations

The newly developed risk prediction tool for identifying high-risk individuals for OC included conventional as well as non-conventional risk factors. The tool demonstrated satisfactory validity measures (92.8% sensitivity; 88.6% specificity; 80.2% positive predictive value; 96.1% negative predictive value; 8.1 positive likelihood ratio and 0.1 negative likelihood ratio) at a cut-off value of 17.83. The tool is suitable as a simple and low-cost screening tool in community-settings to refer such persons for UGIE.

Public Health Implications

- The newly developed risk predication tool for identifying high-risk individuals for OC is based on the population-specific risk factor profile for OC, thus valid for Sri Lankans compared to other models developed elsewhere.
- It is a simple and low-cost tool solely based on the history and can be used by any healthcare provider in the community following simple training.
- This tool will identify those at higher risk of developing OC, for referral for UGIE examination, saving the limited resources, and results can also be utilized for health education and promotion purposes.

Author Declarations

Competing interests; The authors declare that they have no financial and non-financial conflicts of interest.

Ethics approval and consent to participate: Ethics clearance was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Colombo, Sri Lanka. The study was conducted in accordance with the Declaration of Helsinki. Administrative clearance was obtained from directors and specialists of the NCIM and NHSL.

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Author contributions: IAT, MN and CA made substantial contributions to the conception, drafting and critical analysis for the intellectual content of the manuscript. All authors have read and approved the manuscript.

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