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Preventing colorectal cancer in Sri Lanka: step forward

Yasara Samarakoon

Directorate of Non-Communicable Diseases, Ministry of Health and Indigenous Medical Services, Sri Lanka

Correspondence: yasara.samarakoon@gmail.com https://orcid.org/0000-0001-6146-9767

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Introduction

Cancers, which origin from the caecum, ascending colon, transverse colon, descending colon, sigmoid colon, recto-sigmoid junction and rectum are included as colorectal cancer and has been recognized as a major cause of mortality and morbidity throughout the world (1).

Global burden of colorectal cancer

Globally, colorectal cancer is ranked as the third most common cancer in men (age standardized rate (ASR) of 23.6/ 100,000 population) and the second in women (ASR of 12.8/ 100,000 population). As shown in Figure 1, it is the fourth common cancer among both sexes worldwide (2).

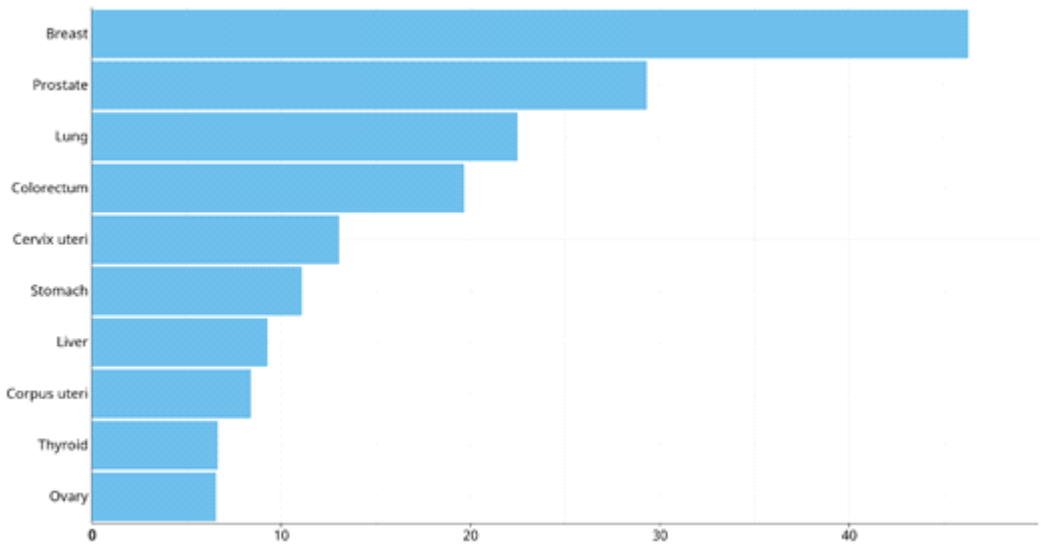

Figure 1. Estimated age standardised incidence rates of cancer in 2018, worldwide among both sexes, all ages

Source: GLOBOCAN 2018, International Agency for Research on Cancer, WHO

When considering mortality, globally, colorectal cancer was the second leading cause of cancer deaths in 2018 among both sexes (2).

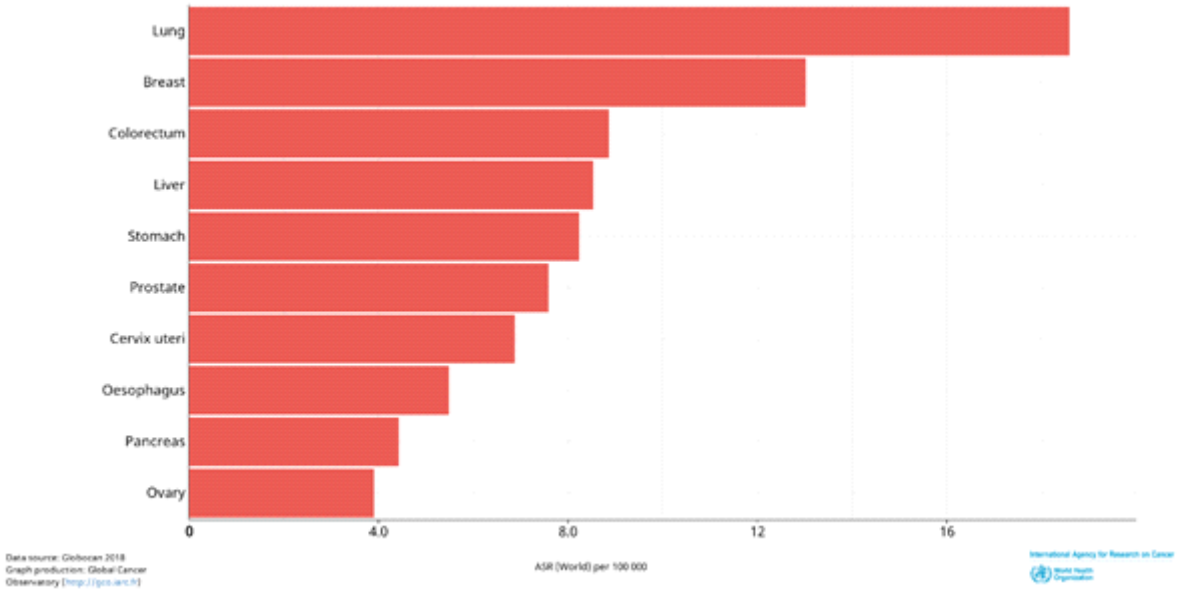

Figure 2. Estimated age standardised mortality rates of cancer in 2018, worldwide among both sexes, all ages

Source: GLOBOCAN 2018, International Agency for Research on Cancer, WHO

Colorectal cancer in Sri Lanka

Though considered as a disease in the West, the incidence of colorectal cancer in Sri Lanka has increased markedly in recent years. The latest data (2014) indicate that colorectal cancer is ranked as the fourth common cancer among men (ASR of 6.9/ 100,000 population) and the fifth among women (ASR of 6.9/ 100,000 population) (3). The incidence of colorectal cancer has reported an alarming increase, when considering its change over the years (Figure 3).

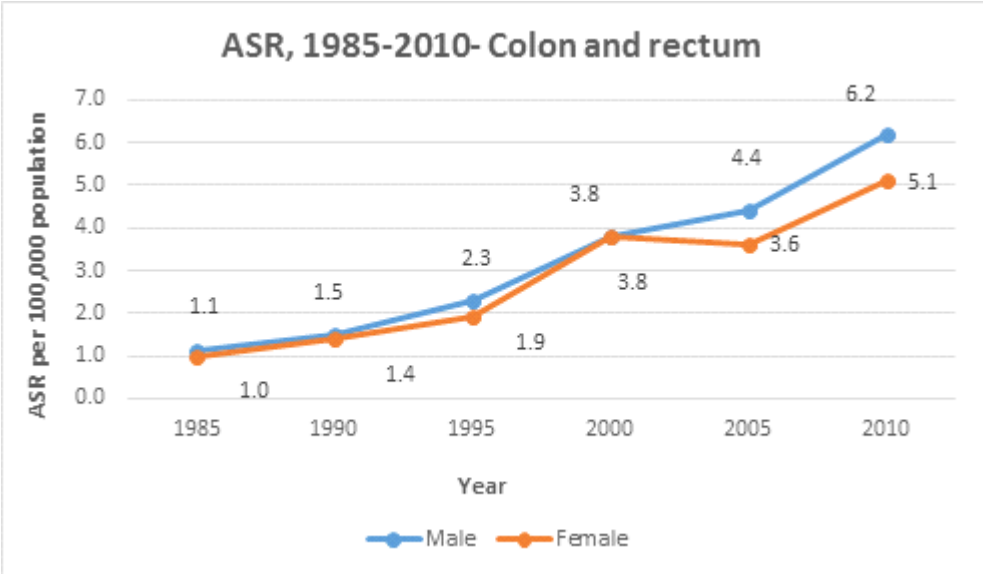

Figure 3. Age standardised incidence rates of colorectal cancer 1985-2010

Source: Cancer incidence data 2010, National Cancer Control Programme, Ministry of Health, Sri Lanka

Colorectal cancer prevention

Despite being one of the leading causes of morbidity and mortality worldwide, colorectal cancer is a preventable disease. Several genetic, environmental and lifestyle related risk factors are identified in the pathogenesis of colorectal cancer (Table 1), while many studies have also established a number of protective factors against its development.

Table 1. Risk factors for colorectal cancer

Modifiable risk factors	Non-modifiable risk factors
Red meat	Increased age
Excess alcohol	Male sex
Smoking	Family history/known genetic risk
Obesity	Inflammatory bowel disease
Lack of dietary fibre	
Lack of physical activity	

Identification of these risk factors and subsequent lifestyle modifications can aid in primary prevention of colorectal cancer. However, several cohort and case-control studies investigating the risk factors of colorectal cancer have shown geographical variation. With regards to Sri Lanka, though colorectal cancer is considered a disease of public health importance, there has been no evidence on its risk factors, highlighting the necessity of local evidence which could be applied as primary prevention strategies. On the other, colorectal cancer can largely be prevented by early detection and removal of adenomatous polyps, where survival becomes significantly better when it is diagnosed at an early stage, highlighting the importance of screening.

Colorectal cancer screening

Secondary prevention via screening has shown to be one of the controversial areas in digestive diseases. The potential for reducing the burden via early detection has become significant due to the slow progression of the disease from detectable precancerous lesions and improved prognosis of patients diagnosed at early stages. There are mainly two goals in colorectal cancer screening programmes. One is to identify and remove precancerous polyps, and thereby reduce its incidence, while the other is to detect disease at an early stage when curative therapy is most likely possible and thereby reduce its mortality.

The argument of colorectal cancer screening is based on the survival rates, which are based on the stage of disease at the time of diagnosis. The five-year survival of an early stage colorectal cancer which has not extended beyond the bowel wall is seen in more than 90% of the patients. However, it decreases up to 60% for patients with tumours with lymph node involvement; and to less than 10% with metastases, highlighting improved survival with early detection and treatment (4).

It is noted that the global incidence and mortality rates of colorectal cancer have significantly declined in the past few decades. This trend is mainly attributed to the adoption of effective screening programmes (5), based on flexible colonoscopy (FS), guaiac-based fecal occult blood test (gFOBT), faecal immunochemical test (FIT) and ccomputed tomographic colonography (CTC).

The FS screens for adenomas as far as in splenic flexure. Randomized trials show favourable results (6-7), with risk reduction of 18% in incidence and 28% in deaths related to colorectal cancer (8). Further, FS has a higher detection rate of advanced neoplasia

compared to gFOBT or FIT, but a lower specificity and sensitivity than colonoscopy for both advanced adenomas and neoplasm (9). Colonoscopy is considered the gold standard for colorectal cancer screening, which could detect and resect neoplasia and precancerous lesions across the entire large bowel. It is relatively safe with recent data suggesting less than 1 per 1000 perforation rate. However, currently there is proof only from observational studies of its superiority over FS in terms of mortality reduction, while cohort studies showing reduction of colorectal cancer incidence up to 90% has been noted only in symptomatic patients (10). On the other, gFOBT is an inexpensive, simple and widely available test, which demonstrates a relative reduction in colorectal cancer mortality by 15% (11). Globally, five countries have established gFOBT based screening programs but show lesser uptake (12), most likely due to the nature of the test procedure itself (12). This has resulted in moving to FIT-based screening, which is simpler and easier with fewer fecal samples required. Trials show that FIT has a greater sensitivity for detecting advanced adenomas and colorectal cancer than gFOBT (13). Further, CTC is a rapid radiographic non-invasive imaging test, which requires no sedation and has lower procedural risks compared to colonoscopy (14), but lacks data on its impact on colorectal cancer incidence and mortality. In most countries, colonoscopy is used as the second step in screening after FS or gFOBT (with gFOBT or FIT), as a cost-effective measure for cost and resource constraints (15).

Risk prediction in colorectal cancer

Despite the wide range of screening options available that could noticeably reduce the risk of colorectal cancer associated mortality, screening rates remain around 60% since 2010 (16) creating a dilemma in adopting screening programs for colorectal cancer in many countries.

The effectiveness of screening programs could be jeopardized by a multitude of complex factors. These include elevated cost, lack of proper education regarding colorectal cancer, under appreciation of the benefit of screening, a sense of fatalism or simply fear of the screening tests (17). Especially in low-resource settings, it is affected by lack of accessibility, limitations of test performance and sub-optimal screening compliance, which may subsequently result in marked variation in the colorectal cancer incidence and mortality globally (18). Furthermore, the lifetime risk of having colorectal cancer even in a Western country is about 5% in the population (19). Thus, screening for colorectal cancer would benefit only this 5%, whilst the remaining 95% would have to undergo this invasive high cost procedure with no personal gain (4). This evidence suggests that it is more efficient to offer colorectal cancer screening using colonoscopy or flexible sigmoidoscopy to high-risk population groups rather than to all as a routine screening test (20). This has prompted many countries to explore the use of high-risk screening for colorectal cancer with appropriate risk stratification of individuals (21). If risk-stratified cancer prevention is to be implemented, it requires risk assessment tools that can be used in primary care to identify those most likely to benefit from this intervention (22). Of such tools, risk prediction models which are simple and can be applied in a community setting by a trained person are considered as useful (23).

Prediction of colorectal cancer risk in Sri Lanka

Samarakoon et al. (2017) conducted a comprehensive scoping review on the available risk models and scores for colorectal cancer, and thereby identify the need for further improvement (24). Out of the 58 risk prediction models identified, most had been developed for advanced colorectal cancer. Most of the articles reviewed were cross-sectional or cohort studies. Statistical methods such as multiple logistic regression was used by a majority, while few have incorporated non-statistical methods such as consensus method and extracting data from published literature. The models have considered 77 different risk factors excluding the genetic variants. Thus, the currently available models have the potential to stratify the general population into risk categories; and allow screening and preventive strategies to be targeted at those most likely to benefit, while leaving those at low risk unexposed to the adverse effects of screening programs.

Clear evidence on its high burden and better survival associated with early detection using colonoscopy or flexible sigmoidoscopy signifies that Sri Lanka will benefit from introduction of a cost effective and affordable screening programme for colorectal cancer. However, being a low- and middle-

income country, Sri Lanka cannot afford to initiate a national screening program for all above 50 years of age, thus provides flexible sigmoidoscopy or colonoscopy for diagnosing colorectal cancer in patients with symptoms. As an alternative, evidence suggests that a two-step process where population groups at risk of colorectal cancer can be identified using a risk prediction tool is more effective. For this purpose, a risk prediction tool needs to be developed based on the knowledge on country-specific risk factors, in order to stratify and identify those 'being at risk' for whom the colonoscopy or flexible sigmoidoscopy are offered subsequently.

Risk prediction modelling is a mechanism which estimates the probability of an individual having a certain condition based on the presence of multiple risk factors (23). When developing such risk prediction models, obtaining country-specific accurate risk estimates for genetic, environmental and behavioural factors and clinical biological markers identified via cohort or case-control studies is vital (25). Incorporation of variables from published data and expert opinion is another method of selecting the risk predictors (26).

Country-specific risk factors for colorectal cancer

Samarakoon et al. (2018) further conducted a case-control study among 325 participants (65 incident colorectal cancer cases, 130 hospital and 130 community controls) in five major health care institutions and communities in areas with high incidence in Sri Lanka. Behavioural, genetic and co-morbid risk factors were assessed through an interviewer-administered questionnaire. Risk factors were evaluated using bivariate and multivariate logistic regression.

The results showed that the frequent consumption of red meat (adjusted odds ratio (aOR)=3.06; 95% CI=1.26, 7.43) and deep fried food (aOR=2.54; 95% CI=1.22, 5.39), hypertension for 10 years (aOR=3.3; 95% CI=1.3, 8.6), colorectal cancer (aOR=4.91; 95% CI=1.7, 14.18) and other cancers (aOR=3.0; 95% CI=1.14, 7.81) among first degree relatives and age >50 years (aOR=2.6; 95% CI=1.1, 5.9) were significant risk factors compared to hospital controls. Frequent consumption of deep-fried food (aOR=4.2; 95% CI=1.7, 10.1), being an ever smoker (aOR=3.2; 95% CI=1.1, 9.3), a current or former drinker (aOR=5.4; 95% CI=1.1, 27.8) and hypertension for 10 years (aOR=5.1; 95% CI=1.7, 15.6) were risk factors compared to community controls (27).

Development and validation of a country specific risk prediction model

Samarakoon (2016) developed a risk prediction model to estimate the risk of an adult developing colorectal cancer, which was based on the logistic regression model and expert opinion; and further refined with receiver operator characteristic (ROC) curve performance. Assessment of the criterion validity and reliability of the model was performed using a case-control design utilizing 65 colorectal cancer new cases and 65 hospital controls aged 30 years or more using an interviewer-administered questionnaire. A risk score was developed for the risk prediction model, by assigning a weighted score for each predictor included in the model. The adjusted ORs were taken as the weighted scores for these predictors, while the other weighted scores were decided based on the pooled OR from meta-analysis from other published literature (28). Table 2 shows the validated risk prediction model with the assigned categories and scores.

The developed and validated model consists of eight predictors with an area under the curve of 0.849 (95% CI=0.8, 0.9; $p<0.001$). The model demonstrated a sensitivity of 76.9% (95% CI=66.7, 87.1), specificity of 83.1% (95% CI=74.0, 92.2), positive predictive value of 82.0% (95% CI=72.3, 91.6) and negative predictive value of 79.3% (95% CI=68.5, 88.0) with positive and negative likelihood ratios of 4.6 (95% CI=2.6, 7.9) and 0.3 (95% CI=0.2, 0.4); and Kappa coefficient of 0.88 with respect to test re-test reliability.

This model, proven to be valid and reliable among adults aged 30 years and above can be easily administered in a community or a clinical setting by a trained person. It consisted of eight closed-ended questions that can be readily answered by a person when administered through an interviewer. The scoring system to identify those 'at risk' is indicated in the tool for easy use, thus suitable as a screening instrument in Sri Lanka.

Table 2. Validated risk prediction model with the assigned categories and scores

Predictor variable	Categories	Score
Age	Less than 50 years	0
	50 years or more	3
Frequent consumption of deep-fried food (3 times or more) per week for the period of last 20 years and beyond	Rare or never: less than 3 times per week or never	0
	Frequent: 3 or more times per week	2
Frequent consumption of red meat (3 times or more) per week for the period of 20 years and beyond	Rare or never: less than 3 times per week or never	0
	Frequent: 3 or more times per week	3
Diagnosis of colorectal cancer at or before 60 years among first degree relatives	No	0
	Yes	5
Diagnosis of other cancer at or before 60 years (breast, endometrial, ovary) among first degree relatives	No	0
	Yes	3
Personal history of intestinal polyps diagnosed before 10 years (histologically confirmed)	No	0
	Yes	3
Personal history of hypertension for more than 10 years (medically confirmed)	No	0
	Yes	3
Diagnosis of inflammatory bowel disease before 10 years (histologically confirmed)	No	0
	Yes	3
Total		**25**

Prevalence of the population 'at risk' of developing colorectal cancer in Sri Lanka

Samarakoon et al. (2017) also estimated the prevalence of population at risk of developing colorectal cancer based on the validated risk prediction model developed for Sri Lanka.

A community-based cross-sectional, descriptive study was conducted among a representative sample of 811 adults aged 30 years and above in the districts of Colombo and Gampaha, selected using a multi-stage cluster sampling technique. The validated risk prediction model was used in the form of an interviewer-administered questionnaire. The prevalence of those 'at risk' of colorectal cancer was assessed based on the validated cut-off score, while they were further divided as 'moderate' and 'high' risk based on cut-off values agreed upon by the experts.

The age-adjusted prevalence of those 'at risk' was 12.5% (95% CI=12.3, 12.7). Age-adjusted prevalence of those at 'moderate' and 'high' risk were 11.8% (95% CI=11.6, 12.0) and 0.72% (95% CI=0.7, 0.8), respectively. The high prevalence indicates the public health importance of the problem and the necessity for screening for colorectal cancer in Sri Lanka. The prevalence also highlights the logistical difficulties in offering the follow-up diagnostic colonoscopy examinations to those screened positive. Considering the logistic difficulties in offering follow-up diagnostic colonoscopy examinations for all, the study recommends that those found to be at 'high-risk' to be referred for colonoscopy (29).

Future perspectives and recommendations

Addressing dietary risk factors for colorectal cancers, mainly long-term frequent consumption of deep-fried food and red meat is recommended as a primary preventive measure. Noting that these foods are discouraged in the existing national dietary guidelines and school canteen policy, the evidence recommends strengthening their implementation. Furthermore, other co-morbid conditions such as hypertension, should be addressed by measures to prevent such conditions. Adopting healthy lifestyles, specifically healthy dietary practices of less salt and more fiber can be considered as specific recommendations, which can be strengthened in primary care setting.

Sri Lanka offers free healthcare services and has initiated healthy lifestyle centres (HLCs) at the lowest level of primary care institutions since 2011 to offer adults structured non-communicable disease screening (30). More than 900 such centres are distributed throughout the country at present. The main service objective of HLCs is to reduce the risk of NCDs of 40-65-year-old adults by early detection of risk factors and to improve the access for specialized care of those found to be at high-risk.

With the availability of a local risk prediction model, the scope of HLC can be extended for early detection of colorectal cancer in Sri Lanka. This prevalence of being 'at risk' denotes the burden of colorectal cancer on the health system in future. Such an initiation should be accompanied by informing the general public about the importance of getting their risk estimated, so that they could undergo FS or colonoscopy examination if required to diagnose the condition early, enabling successful treatment. With regards to persons identified as being 'at risk', they should be directed for diagnostic colonoscopy examination and further management, while those at 'moderate risk' should be advised on simple screening tests such as FOBTs or modifying the risk factors at primary care level. A further step in introducing a screening program in Sri Lanka is establishing a referral system for those 'at risk'. This information would form the basis to advocate for a policy decision to evaluate the need for a screening program among the high-risk population during HLCs in Sri Lanka.

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