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Review

Risk prediction models for colorectal cancer: A scoping review

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Abstract

Background and objectives

Many risk prediction models have been developed globally to identify specific populations at high risk for colorectal cancer in specific settings. Documentation of available evidence from existing studies will serve as a useful information base. We performed a scoping review, to review and analyse published risk prediction models for colorectal cancer the world over.

Methods

A scoping review was undertaken to address the following question 'what are the existing risk prediction models to identify the risk of developing colorectal cancer among individuals in different countries and settings?' using the framework developed by Arksey and O'Malley for scoping reviews. Forty-one articles were included in this review from database searches and from additional searches. The titles and abstracts were reviewed using predetermined screening criteria. We limited our search to existing literature in English language and included both observational and interventional studies.

Results

Out of the 58 risk prediction models identified, most were developed for colorectal cancer followed by advanced colorectal cancer. Most of the articles reviewed were cross sectional studies 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 authors of the 58 risk prediction models have considered 77 different risk factors excluding the genetic variants.

Conclusions

This comprehensive scoping review demonstrates the capacity of the existing risk models to stratify the general population into risk categories, detailing the studies conducted, location, study design, outcome, overview of the methods, data source and the identified risk predictors. While striving to build on existing knowledge, the review also identifies the research gaps and the need for further improvement.

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Introduction

Globally, colorectal cancer is ranked as the third most common cancer in men and as the second most common cancer in women. [1]. The tests available to screen for colorectal cancers vary from simple tests, such as the faecal occult blood test to more technical and invasive methods, such as flexible sigmoidoscopy and colonoscopy which have better sensitivity and specificity than other methods [2]. The lifetime risk of having colorectal cancer in a Western country is about 5% in the population [1]. Thus, screening for colorectal cancer would benefit only this 5% whilst the remaining 95% might have to

undergo this invasive high cost procedure with no personal gain [2]. Evidence from developed countries 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 [3]. This has prompted many countries to explore the use of high-risk screening for colorectal cancer with appropriate risk stratification of individuals [4].

With the growing recognition of the potential harms of population-based cancer screening programs, screening based on risk stratification has been proposed as a method of reducing harm as well as a method of focusing on the risk population [5]. 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 [6]. Of the tools to assess the individualized cancer risk, risk prediction models which are simple and can be applied in a community setting by a trained person are considered as useful [7].

Risk prediction modelling is a mechanism which estimates the probability of an individual having a certain condition based on presence of multiple risk factors [7]. An essential feature of a risk prediction model is that it uses multiple predictors to assess individuals regarding their risk of future occurrence of a specific outcome [8]. In the development of risk prediction models, obtaining accurate risk estimates for genetic, environmental and behavioural factors and clinical biological markers etc. becomes important. This is usually achieved via cohort or case-control studies [9]. Furthermore, incorporation of variables from published data and expert opinion is another method of selecting risk predictors [10, 11].

There are many risk prediction models developed in different parts of the world to identify specific populations at high risk for colorectal cancer in specific settings. Knowledge regarding the different study designs and statistical methods used is useful for researchers and service providers in the field of colorectal cancer to identify the comprehensiveness and applicability of the various models developed in different parts of the world. Thus, documentation of available evidence from existing studies may serve as a useful information base. In this background, a scoping review was performed, to review and analyse the published risk prediction models for colorectal cancer, the world over. The methodologies used were also reviewed and summarized to facilitate researchers in the field.

Methods

Scoping reviews are distinguished from systematic reviews in their focus on providing an overview of the research landscape to propose a platform for future research. It differs from a systematic review as it does not evaluate research quality or provide a synthesis or meta-analysis of findings [12]. The present scoping review is conducted with the objective of identifying existing risk prediction models for colorectal cancer. In the methodology, Arksey and O'Malley's (2005) scoping review framework was used. This

model comprises four key stages which includes, identifying the research question, identifying relevant studies, selecting studies, charting of data and collating, summarizing and reporting results [13].

1. Identifying the research question

The review focused on the research question, 'what are the existing risk prediction models to identify the risk of developing colorectal cancer among individuals in different countries and settings?'

2. Identifying relevant studies

The review included a search of the scientific literature via PubMed/Medline and Cochrane database. Aligned with the research question, broad search terms were used. These included 'colorectal neoplasm,' 'risk/risk factor/risk assessment,' and 'prediction/model/score.' The search filtered the articles published in peer reviewed journals between 1st of January 2000 to 20th May 2017. Searches were limited to papers in the English language. As guided by Arksey O' Malley's (2005) framework, all articles were screened for relevance to the research question. To capture any missed articles, including those in non-medical databases, a secondary Google Scholar search was initiated that fitted the research question. The selection process is shown in Figure 1.

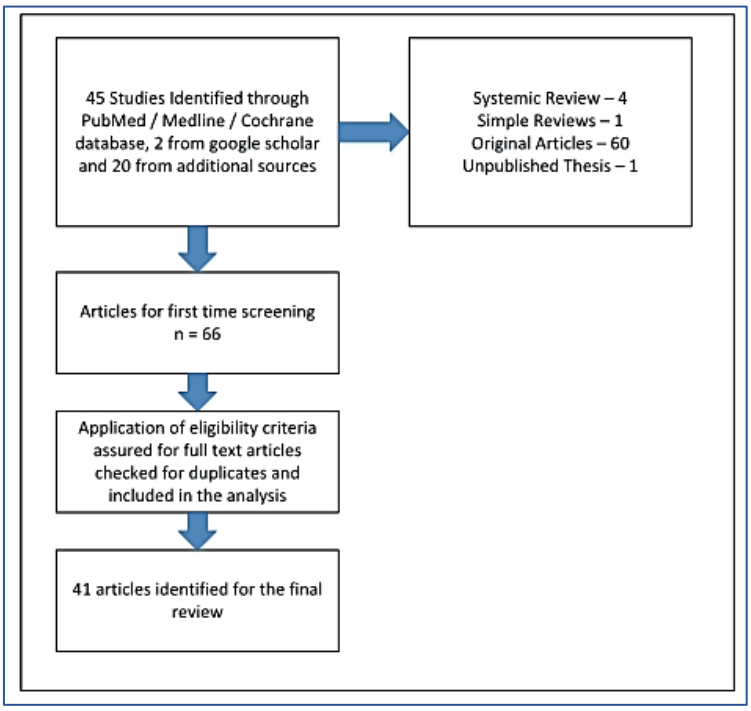

Figure 1: Selection process in the Scoping Review

3. Selecting studies

The titles and abstracts were reviewed using predetermined screening criteria. Inclusion and exclusion criteria are listed in Table 1.

Table 1: Eligibility criteria for selecting studies

Inclusion criteria	1	Adult populations more than 18 years of age
	2	Intervention studies
	3	Observational studies
	4	Risk prediction models on behavioral factors
	5	Risk prediction models on genetic factors
	6	Models in any setting
	7	Risk prediction models for either colon, rectal or colorectal cancer
Exclusion criteria	1	Risk prediction models developed for already diagnosed patients
	2	Risk prediction models developed for symptomatic patients

Following the identification of the relevant articles, the first author reviewed the full text of each article, confirming the relevance and reviewing overall themes. After applying the screening criteria, forty-one articles were retained for the scoping review. Once the duplicates were removed, the search identified forty-one articles for the final review. Agreement was obtained on overall patterns and gaps.

4. Charting of data and collating, summarizing and reporting results

Each of the forty-one articles was charted according to the author (year), study location, study design, outcome of the model, overview of the methods and data source. Because the aim of this scoping review is to identify the existing risk prediction models and does not seek to evaluate quality, charting emphasized the basic characteristics of articles while the validation details of the models (which correspond to the quality of the models) were not reviewed. For studies which included multiple models such as separate models for men and women or for different sub sites, all were included separately.

Results

Identified risk prediction models

Forty-one eligible articles were included in the present scoping review and they described fifty-eight risk prediction models. Table 2 summarizes the basic characteristics of the identified risk prediction models.

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Table 2: The basic characteristics of the included articles on colorectal risk prediction models

Authors (year)	Study location	Study design	Outcome	Overview of methods	Factors Identified	Data Source
1. Park et al, 2017 [14]	South Korea	Hospital based cross sectional study	Advanced colorectal cancer (ACRC)	Risk factors were identified from cross sectional study via multiple logistic regression. Individual risk factors were transformed into risk points and overall risk was calculated by summing up the risk points	Older age, male sex, positive serology of Helicobacter pylori, high triglyceride levels, low high-density lipoprotein levels	Medical records
2. Samarakoon, 2016 [15]	Sri Lanka	Case control study	Colorectal cancer (CRC)	Risk factors were identified from a case-control study via multiple logistic regression and from consensus method. Individual risk factors were transformed into risk points and overall risk was calculated by summing up the risk points	Older age, frequent deep-fried food, frequent red meat consumption, having a first degree relative with colorectal cancer and/or other cancers diagnosed at or before 60 years of age, history of hypertension for 10 years, history of inflammatory bowel disease before 10 years and history of polyps before 10 years	Questionnaire and medical records
1. Li et al, 2015 [16]	China	Population based case control study	CRC	Genetic variants and other non-genetic risk factors were identified as risk factors via a case control study. Multiple models combining genetic and non-genetic factors were established and receiver operating characteristic curve analysis was used to compare the discriminatory power of different predictive models	Seven single-nucleotide polymorphisms (SNP) as genetic variants, age, sex, cigarette smoking and alcohol drinking	Blood tests for genetics and Questionnaire
2. Jung et al, 2015 [17]	Korea	Case cohort design drawn from an underlying large prospective cohort study	CRC and rectal cancer (RC)	Genetic risk factors were identified in case-cohort design. A genetic risk score was calculated by summing the number of risk alleles over all SNPs based on the cox proportional hazard regression models.	Seven SNPs identified for colorectal cancer and rectal cancer excluding colon cancer alone	Blood tests for genetics and Questionnaire

3. Schroy et al, 2015 [18]	United States	Hospital based cross sectional study	ACRC	Risk factors were identified from cross sectional study via multiple logistic regression. Individual risk factors were transformed into risk points and overall risk was calculated by summing up the risk points	Age, smoking, alcohol intake, height, combined sex/race/ethnicity variable	Questionnaire
4. Steffen et al, 2014 [19]	Australia	Cohort study	CRC	Risk factors identified from cohort study. Risk prediction equations were developed from cox proportional hazards regression	Age, sex, body mass index (BMI), prevalent diabetes, ever having undergone colorectal cancer screening, smoking, alcohol intake	Questionnaire
5. Shin et al, 2014 [20]	Korea	Population based cross sectional study	CRC	Risk factors identified from population based cohort study. Prediction equations developed from cox-proportional hazard regression models	Age, BMI, serum cholesterol, family history of cancer and alcohol consumption, meat consumption, height, fasting serum glucose	Questionnaire and blood test
6. Shin et al, 2014 [20]	Korea	Population based cross sectional study	CRC	Risk factors identified from population based cohort study. Prediction equations developed from cox-proportional hazard regression models	Age, height family history of cancer, fasting serum glucose and meat consumption	Questionnaire and blood test
7. Shin et al, 2014 [20]	Korea	Population based cross sectional study	RC	Risk factors identified from population based cohort study. Prediction equations developed from cox-proportional hazard regression models	Age, BMI, family history of cancer, height, fasting serum glucose, total serum cholesterol, alcohol, meat consumption	Questionnaire and blood test
8. Shin et al, 2014 [20]	Korea	Population based cross sectional study	RC	Risk factors identified from population based cohort study. Prediction equations developed from cox-proportional hazard regression models	Age, family history of cancer, height, fasting serum glucose, meat consumption	Questionnaire and blood test
9. Shin et al, 2014 [20]	Korea	Population based cross sectional study	Colon cancer (CC)	Risk factors identified from population based cohort study. Prediction equations developed from cox-proportional hazard regression models	Age, BMI, family history of cancer, height, fasting serum glucose, total serum cholesterol, alcohol, meat consumption	Questionnaire and blood test
10. Shin et al, 2014 [20]	Korea	Population based cross sectional study	CC	Risk factors identified from population based cohort study. Prediction equations developed from cox-proportional hazard regression models	Age, family history of cancer, height, fasting serum glucose, meat consumption	Questionnaire and blood test

11. Tao et al, 2014 [21]	Germany	Hospital based cross sectional study	ACRC	Multiple logistic regression was used to develop the algorithm. Regression coefficients based scores were used to calculate the individual risk	Sex, age, first degree relatives with history of colorectal cancer, cigarette smoking, alcohol, red meat consumption, ever regular use of non-steroidal anti-inflammatory drugs (NSAIDS), previous colonoscopy, previous detection of polyps	Questionnaire
12. Tao et al, 2014 [21]	Germany	Hospital based cross sectional study	CRC	Multiple logistic regression was used to develop the algorithm. Regression coefficients based scores were used to calculate the individual risk	Sex, age, first degree relatives with history of colorectal cancer, cigarette smoking, alcohol, red meat consumption, ever regular use of NSAIDS, previous colonoscopy, previous detection of polyps	Questionnaire
13. Wells et al, 2014 [22]	California and Hawaii	Cohort study	CRC	Forward stepwise regression was used to select the most important variables for use in Cox proportional regression model for men	Age, BMI, smoking status, first degree relative with colon cancer, alcohol consumption, race/ethnicity, years of education, regular use of aspirin, multivitamins, red meat intake, physical activity, history of diabetes	Questionnaire
14. Wells et al, 2014 [22]	California and Hawaii	Cohort study	CRC	Forward stepwise regression was used to select the most important variables for use in Cox proportional regression model for women	Age, BMI, smoking status, first degree relative with colon cancer, alcohol consumption, race/ethnicity, years of education, regular use of NSAIDS, multivitamins, use of oestrogen, history of diabetes	Questionnaire
15. Chen et al, 2014 [23]	China	Hospital based cross sectional study	ACRC	Risk factors identified via multiple logistic regression. Risk scores assigned according to the beta values of the risk factors	Age, gender, history of coronary heart disease, egg intake, stool frequency	Questionnaire
16. Kaminski et al, 2014 [24]	Poland	Hospital based cross sectional study	ACRC	Risk factors were identified from multiple logistic regression. Risk level derived from a scoring method based on regression coefficients	Age, sex, family history of colorectal cancer, cigarette smoking, BMI	Questionnaire

17. Stegeman et al, 2014 [25]	Netherlands	Cross sectional study	ACRC	Risk questionnaire was developed from a non-statistical method (undefined). Based on the risk questionnaire and Faecal immunochemical testing a risk model was developed	Age, first degree relative with colorectal cancer, smoking, faecal immunochemical test, calcium intake	Questionnaire
18. Stegeman et al, 2013 [26]	Netherlands	Cross sectional study	ACRC	Risk factors were identified from a cross sectional analysis via bivariate analysis	Age, BMI, gender, first degree relative with colorectal cancer, menopausal status (women), smoking, sleep, vigorous exercise, alcohol, fiber intake, aspirin/NSAIDS use	Questionnaire
19. Dunlop et al, 2013 [27]	Worldwide	Case-control studies	CRC	Binary logistic regression was used to identify the risk predictors	Age, first degree relative with colorectal cancer, sex, 10 SNPs	Questionnaire and blood test for genetics
20. Wrong et al, 2013 [28]	Hong Kong	Hospital based cross sectional study	CRC	Risk factors were determined from binary logistic regression	Age, gender, smoking, family history, BMI, self-reported diabetes,	Medical records
21. Hassan et al, 2013 [29]	Italy	Hospital based cross sectional study	ACRC	Risk predictors were determined from multiple logistic regression	Age, gender	Medical records
22. Johnson et al, 2013 [30]	Worldwide	Risk factors identified from published literature from meta-analysis	CRC	Random effect models of the logarithms of risks across the studies was used to quantify each factor's impact on colorectal cancer risk	BMI, first degree relative with colorectal cancer, smoking status, physical activity, alcohol, Inflammatory bowel disease, current or former hormone therapy, aspirin/NSAIDS, processed meat/red meat/fruit/vegetable intake	Questionnaire
23. Yarnall et al, 2013 [31]	United Kindom	Genetic variants and environmental factors were identified from literature	CRC	Through a simulation study, using a risk modelling software risk prediction model was developed	14 SNPs, BMI, smoking status, alcohol consumption, red meat consumption, fiber intake, physical activity	Questionnaire and blood test for genetics

24. Wang et al, 2013 [32]	Taiwan	Case Control study and published literature	CRC	Prediction model was constructed by applying Jackknife feature selection and ANOVA testing	16 SNPs	Blood test for genetics
25. Lin et al, 2013 [33]	United States	Cohort study	ACRC	Risk predictors and the risk score developed via a penalized logistic regression method	Age, BMI, smoking, previous sigmoidoscopy or colonoscopy, number of first degree relatives with colorectal cancer, polyp history in past 10 years, physical activity, vegetable consumption, NSAID use, oestrogen use	Questionnaire
26. Lubbe et al, 2012 [34]	United Kingdom	Population based cross sectional study	CRC	Risk factors identified from a cross sectional study. The risk associated with genetic variants was calculated by unconditional logistic regression	14 SNPs	Blood test for genetics
27. Jo et al, 2012 [35]	Korea	Cohort study	CRC	Risk predictors were identified from logistic regression methods.	Age, family history of colorectal cancer, 3 SNPs	Questionnaire and blood test for genetics
28. Jo et al, 2012 [35]	Korea	Cohort study	CRC	Risk predictors were identified from logistic regression methods	Age, family history of colorectal cancer, 5 SNPs	Questionnaire and blood test for genetics
29. Cai et al, 2012 [36]	China	Hospital based cross sectional study	ACRC	Risk factors were identified from multiple logistic regression. Risk level derived from a scoring method based on regression coefficients	Age, sex, smoking, diabetes mellitus, green vegetables, pickled food, fried food, white meat	Questionnaire
30. Yeoh et al, 2011 [37]	Asia	Hospital based cross sectional study	ACRC	Predictors identified from multiple logistic regression. Risk scores were allocated based on the odds ratios	Age, gender, family history, smoking	Questionnaire
31. Taylor et al, 2011 [38]	United States	Population based cohort study	CRC	Predictors identified based on the Cox regression and Harrell's C	Age, first/second/third degree relative with colorectal cance	Questionnaire

32. Marshall et al, 2010 [39]	Canada and United States	Cross sectional study	CRC	Panel performance characteristics and disease prevalence were used to develop a scale assessing an individual's current risk of having colorectal cancer based on his/her gene signature via multiple logistic regression	Seven genes	Blood test for genetics
33. Ma et al, 2010 [40]	Japan	Population based Cohort study	CRC	Risk factors identified from cohort study by Cox proportion hazard regression	Age, BMI, alcohol, smoking status, daily physical activity	Questionnaire
34. Ma et al, 2010 [40]	Japan	Population based Cohort study	CC	Risk factors identified from cohort study by Cox proportion hazard regression	Age, BMI, alcohol, smoking status, daily physical activity	Questionnaire
35. Ma et al, 2010 [40]	Japan	Population based Cohort study	RR	Risk factors identified from cohort study by Cox proportion hazard regression	Age, BMI, alcohol, smoking status, daily physical activity	Questionnaire
36. Bener et al, 2010 [41]	Qatar	Hospital based case-control study	CRC	Risk predictors developed from multivariate stepwise logistic regression	Family history of colorectal cancer, BMI, smoking status, soft drinks, bakery products	Questionnaire
37. Wei et al, 2009 [42]	United States	Cohort study	CC	Risk factors derived from cohort study. Relative risk based on cumulative incidence of colon cancer by the age of 70 years. Colon cancer risk was determined by multivariate non-linear poison regression	Smoking, consistent high relative weight, daily consumption of red or processed meat, low physical activity level, being never screened low daily folate, current or past HRT, first degree relative with colon cancer, aspirin use,	Questionnaire
38. Almurshed et al, 2009 [43]	Saudi Arabia	Hospital-based case control study	CRC	Risk factors were identified from a case control study and the model was developed from multiple logistic regression	Region, education level, marital status, employment status, physical activity, activity level, knowledge on high-fiber diet	Questionnaire

39. Kastrinos et al, 2009 [44]	United States	Hospital based cross sectional study	CRC	Risk assessed from an algorithm of three questions developed from recursive partitioning analysis	First degree relative with colorectal cancer or Lynch syndrome related cancer diagnosed before 50 years of age, colorectal cancer or polyps diagnosed before 50 years of age, having three or more relatives diagnosed with colorectal cancer	Simple three question model
40. Freedman et al, 2009 [45]	United States	Population based case control study	Distal CC	Risk factors were identified from the case control studies. Relative risks and attributable risks were combined with the baseline age specific cancer hazard rates and the mortality rates to estimate the individual risk	BMI, number of first degree relatives with colorectal cancer, polyp history for the last 10 years, history of previous negative sigmoidoscopy/colonoscopy for the last 10 years, NSAIDS use	Questionnaire
41. Freedman et al, 2009 [45]	United States	Population based case control study	Distal CC	Risk factors were identified from the case control studies. Relative risks and attributable risks were combined with the baseline age specific cancer hazard rates and the mortality rates to estimate the individual risk	Cancer-negative sigmoidoscopy/colonoscopy in the last 10 years, polyp history in the last 10 years, history of colorectal cancer in first degree relatives, aspirin and NSAIDS drug use, oestrogen exposure in last two years	Questionnaire
42. Freedman et al, 2009 [45]	United States	Population based case control study	Proximal CC	Risk factors were identified from the case control studies. Relative risks and attributable risks were combined with the baseline age specific cancer hazard rates and the mortality rates to estimate the individual risk	Cancer-negative sigmoidoscopy/colonoscopy in the last 10 years, polyp history in the last 10 years, history of CRC in first degree relatives, aspirin and NSAIDS use, cigarette smoking, BMI, vegetable consumption	Questionnaire

43. Freedman et al, 2009 [45]	United States	Population based case control study	Proximal CC	Risk factors were identified from the case control studies. Relative risks and attributable risks were combined with the baseline age specific cancer hazard rates and the mortality rates to estimate the individual risk	Cancer-negative sigmoidoscopy/colonoscopy in the last 10 years, polyp history in the last 10 years, history of colorectal cancer in first degree relatives, aspirin and NSAID use, current leisure-time vigorous activity, vegetable consumption, oestrogen exposure for last 2 years	Questionnaire
44. Freedman et al, 2009 [45]	United States	Population based case control study	RC	Risk factors were identified from the case control studies. Relative risks and attributable risks were combined with the baseline age specific cancer hazard rates and the mortality rates to estimate the individual risk	Cancer-negative sigmoidoscopy/colonoscopy in the last 10 years, polyp history in the last 10 years, history of CRC in first degree relatives, aspirin and NSAID use, current leisure-time vigorous activity	Questionnaire
45. Freedman et al, 2009 [45]	United States	Population based case control study	RR	Risk factors were identified from the case control studies. Relative risks and attributable risks were combined with the baseline age specific cancer hazard rates and the mortality rates to estimate the individual risk	Cancer-negative sigmoidoscopy/colonoscopy in the last 10 years, polyp history in the last 10 years, history of colorectal cancer in first degree relatives, aspirin and NSIAD use, BMI, current leisure-time vigorous activity, oestrogen exposure in last two years	Questionnaire
46. Liu et al, 2008 [46]	Taiwan	Population based case control study	CRC	Multivariate logistic regression was used to identify the risk factors. Individual risk factors were transformed into risk points and overall risk was calculated by summing up the risk points	Race, occupation, physical activity, coffee intake, consumption of white meat, seafood, vegetables and fruits, method of cooking of meat, alcohol consumption in males only	Questionnaire
47. Han et al, 2008 [47	Not given	Not defined	CRC	Logistic regression was used to identify the genetic predictors for colorectal cancer	Five genes	Blood test for genetics

48. Driver et al, 2007 [48]	United States	Prospective cohort study	CRC	Logistic regression was used to determine the independent predictors of incident colorectal cancer over the follow-up period. Risk scores were created from the sum of the odds ratios and used to divide the cohort into categories of increasing relative risk	Age, history of smoking, BMI	Medical Records
49. Driver et al, 2007 [48]	United States	Prospective cohort study	CC	Logistic regression was used to determine the independent predictors of incident colorectal cancer over the follow-up period. Risk scores were created from the sum of the odds ratios and used to divide the cohort into categories of increasing relative risk	Age, weekly or daily alcohol use, smoking status, BMI	Medical Records
50. Lin et al, 2006 [49]	United States	Predetermined risk factors were used to develop the model	CRC	Predetermined risk factors were given scores based on a previously validated scoring system	Age, sex, first degree relative with colorectal cancer or second degree relative with adenoma	Questionnaire
51. Wei et al, 2004 [50]	United States	Cohort studies	CC	Risk factors were identified from cohort studies and the risk prediction model was developed based on the pooled logistic regression to identify the multivariate risk predictors	Age, BMI, sex, alcohol, smoking, first degree relative with colon cancer, height, physical activity, processed meat, pork/lamb, servings of beef calcium intake, folate intake,	Questionnaire
52. Wei et al, 2004 [50]	United States	Cohort studies	RR	Risk factors were identified from cohort studies and the risk prediction model was developed based on the pooled logistic regression to identify the multivariate risk predictors	Age, BMI, sex, alcohol, smoking, first degree relative with colon cancer, height, physical activity, processed meat, pork/lamb, servings of beef calcium intake, folate intake,	Questionnaire
53. Imperiale et al, 2003 [51]	United States	Cross sectional study	ACRC	A clinical index of three variables were created based on the information of persons. Risk score was created by allocating points to variables (method for scoring undefined)	Age, sex, distal findings of colonoscopy	Questionnaire

54. Betes et al, 2003 [52]	Spain	Hospital based cross sectional study	CRC	Risk factors and the risk score was developed from multiple logistic regression based on the results from the cross-sectional study	Age, BMI, gender	Medical records
55. Camp et al, 2002 [53]	United States	Population based case-control study	CC	Classification tree analysis was used to identify the interactions between risk factors	Age, first degree relative with colorectal cancer, BMI, NSAID use, long term vigorous activity, western diet, calcium intake, lutein intake, folic acid, refined grain intake, prudent dietary pattern	Questionnaire
56. Colditz et al, 2000 [54]	United States	Consensus process	CC	Risk factors identified from group consensus and relative risks identified from different studies. Risk points were allocated according to the strength of the causal association and summed. Population average risk of cancer and cumulative 10-year risk was obtained from SEER data. Individual ranking relative to the population average was determined. The risk was evaluated for validity using colon cancer incidence in prospective cohort data.	Family history of colon, BMI, screening (FOBT and sigmoidoscopy), aspirin, inflammatory bowel disease, folate, vegetables, alcohol, height, physical activity, oestrogen replacement, Oral contraceptives, red meat, fruits, fiber, saturated fat, cigarette smoking	Questionnaire

Among the identified models, 29 have colorectal cancer, 12 have advanced colorectal cancer (defined as either having an invasive cancer, an adenoma of 10mm or more, a villous adenoma or having an adenoma with high grade dysplasia), 11 have colon cancer and six, rectal cancer as the outcome.

Socio-demographic characteristics of the study populations

A majority of the risk prediction models have been developed in United States of America [18, 22, 33, 38, 39, 42, 44, 45, 48, 49,50, 51, 53, 54] followed by Korea [14, 17, 20, 35]. Three models have been developed in China [16, 23, 36] and Japan [40] while, Netherlands [25, 26], Germany [21], Taiwan[32, 46] and United Kingdom [31, 34] have developed two models each. Many other countries, such as Australia [19], Poland [24], Hong Kong [28], Italy [29], Qatar [41], Saudi Arabia [43], Spain [52] and Sri Lanka [15] have also developed country-specific risk prediction models for colorectal cancer. When considering the global approach two models have been developed globally [27, 30] while another has been developed for Asia [37].

Most of the risk prediction models address both men and women. However, 11 models are specific for females [20, 22, 35, 42, 45, 50] while 10 models are specific for males [20, 22, 35, 45, 48]. Although many models have not restricted application to a specific age limit, 11 models have been developed from populations aged 30 years and above [15, 20, 42, 43, 50], 10 from populations aged 50 years and above [18, 25, 26, 45, 51] and seven from populations aged 40 years and above [14, 19, 23, 24, 36, 38, 52]. In addition, one model has used a population above 20 years [35] while another, populations lower than 80 years [34].

Development of the models

Determination of risk factors was performed via various study designs in these risk prediction models. A total of twenty-three were developed from hospital based (n=14) or population based (n=9) cross sectional studies in participants undergoing screening colonoscopy, while another 13 models were developed from case control studies. The cases were identified from hospitals (n=6) or population registries (n=7) while controls were identified from hospitals, primary care or from the community. Sixteen models were developed using cohort designs where most of the cases were identified through cancer registries over a period of follow-up. Four risk prediction models were developed from reviewing published literature [30, 31, 32, 49], while one model was developed using a consensus procedure [54].

A total of six models include only variables that are routinely available in the medical records [14,28, 29, 48, 52]. A majority (n=35) of models include variables obtained through a questionnaire [18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 30, 33, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 49, 50, 51, 53, 54]. The questionnaires range from those with only one or two simple questions to those with detailed questions on factors such as diet, physical activity, alcohol and smoking habits and past medical facts. Three purely genetic models have used only a blood test for genetic biomarkers [32, 34, 39], while thirteen models have

used data from a questionnaire and the results of blood tests for genetic biomarkers and other biochemical tests [16, 17, 20, 27, 31, 35, 47]. One model has obtained data both from a questionnaire and medical records [15].

The prominent method of developing the risk prediction models was via statistical methods. A majority of the studies have used multiple logistic regression to identify the risk predictors [16, 27, 28, 30, 33, 34, 35, 41, 43, 47, 50, 52] followed by the allocation of the risk points, based on the values of beta-coefficients [14, 15, 18, 21, 23, 24, 36, 37, 39, 45, 46, 48]. Fourteen models have incorporated Cox proportional hazards regression to develop the risk model and the score [17, 19, 20, 22, 38, 40]. One model [30] was developed from meta-analysis of various studies, one [31] used risk modelling software in a simulated population and one [26] used pure bivariate analysis. Several other statistical methods were used in the development of models such as jackknife feature selection and ANOVA testing [32], multivariate non-linear Poisson regression [42], recursive portioning analysis [44] and classification tree analysis [53]. However, four models were identified as developed from non-statistical methods such as consensus method [25, 51], extracting data from previously published validated models [49] or from previous studies [54].

Risk predictors in the developed models

The risk prediction models identified can be broadly categorized as non-genetic, genetic and mixed models with both genetic and non-genetic predictors. Among the models four were purely genetic [17, 32, 34, 47], seven models have both components [16, 27, 31, 35, 39] while the rest of the models are non-genetic (n=48). The authors of the 58 risk prediction models have considered 77 different risk factors (excluding genetic factors) as shown in Table 3.

Table 3: Seventy-seven risk factors identified across all included studies (excluding genetic factors)

Socio-demographic characteristics	**Diet**
Age	Meat consumption
Male Sex	Red meat consumption
Gender	Deep fried food consumption
Sex/race/ethnicity variable	Egg intake
Race/ethnicity	Calcium intake
Years of education/education level	Fiber intake
Region	Processed meat intake
Marital status	Fruits intake
Employment status	Vegetable intake
Anthropometric measurements	Green vegetable intake
Height	Prickled food intake
Consistent high relative weight	Fried food intake
BMI	White meat intake
Genetic characteristics	Soft drinks intake
Family history of cancer	Bakery products intake

First degree relatives with history of colorectal cancer	Low daily folate intake
First degree relatives with history of other cancer	Coffee intake
Relatives with colon cancer	Seafood intake
First/second/third degree relative with colorectal cancer	Pork/lamb intake
First degree relatives with Lynch Syndrome related cancer diagnosed before 50 years	Servings of beef
Having three or more relatives diagnosed with colorectal cancer	Western diet
Second degree relatives with adenoma	Lutein intake
Personal Medical History	Refined grain intake
Diabetes/History of diabetes	Prudent dietary pattern
History of hypertension/History of hypertension for 10 years	**Female hormonal factors**
History of inflammatory bowel disease	Use of oestrogen
History of coronary heart disease	Menopausal status
Stool frequency	Current or former hormone therapy
Self-reported diabetes	Current or past HRT
History of polyps	**Drugs**
Polyp history for last 10 years	Ever regular use of non-steroidal anti-inflammatory drugs
Biomarkers	Regular use of aspirin
Positive serology of Helicobacter pylori	Regular use of multivitamins
High triglyceride levels	Aspirin/NSAID use
Low high-density lipoprotein level	**Lifestyle related factors**
Total serum cholesterol	Cigarette smoking
Fasting serum glucose	Alcohol drinking
Other tests	Physical activity
Prior sigmoidoscopy or colonoscopy	Sleep
Faecal immunochemical test	Vigorous exercise
Distal findings of colonoscopy	Activity level
Faecal occult blood test	Current leisure time vigorous activity
Personal Medical History	Method of cooking of meat
Diabetes/History of diabetes	
History of hypertension/History of hypertension for 10 years	
History of inflammatory bowel disease	
History of coronary heart disease	
Stool frequency	
Self-reported diabetes	
History of polyps	
Polyp history for last 10 years	

Discussion

A comprehensive review was performed that identified 58 risk prediction models in forty-one studies. This scoping review demonstrates that multiple risk prediction models exist for predicting the risk of developing colorectal cancer, advanced colorectal cancer, colon cancer and rectal cancer among asymptomatic male and female population groups. A majority had been developed using data from analytical cross-sectional studies. The other contributions are from case-control studies and cohort studies, in this order. Though many have used multiple logistic regression statistical methods in developing the model, a minority have incorporated non-statistical methods such as consensus processes and reviewing literature. The identified models ranged from pure non-genetic models to pure genetic models including a small number of models with both components.

The main strength of this review is the extensive search strategy and careful screening of the studies applicable to the research question. Use of a broad search strategy has allowed us to identify many more risk models than reported in previous reviews in the area of risk prediction in colorectal cancer. Therefore, this review is more comprehensive and up to date. However, the inclusion criteria included only asymptomatic individuals, excluding symptomatic and already diagnosed populations, limiting the applicability of models for those with familial syndromes such as hereditary non-polyposis colorectal cancer or familial adenomatous polyposis. Furthermore, since the research question in this review was to identify existing models, the performance of the risk prediction models was not evaluated with respect to their discriminative power and calibration properties which is a drawback as the usefulness of the models in terms of validity could not be shown.

This scoping review demonstrates that the existing risk models have the capacity to stratify the general population into risk categories. Risk stratification applied through these models can help to identify the populations who may benefit from invasive screening preventing those at low risk of disease from being exposed to the direct and indirect harms of screening procedures. This may also address the issues of cost effectiveness of screening programmes using colonoscopy since this risk stratification can limit the number of individuals referred for screening. The use of risk prediction models can also increase the screening behaviour of the public as well as provide an opportunity to encourage lifestyle changes.

However, several challenges can be anticipated when implementing the existing models in clinical practice. Many require collection of dietary information using food frequency questionnaires. Though these can be used to generate accurate estimates in the research setting, practical applicability at population level is questionable. With assessment of lifetime physical activity, recall bias becomes an issue. Furthermore, information collected other than from routine medical reports, becomes questionable with regards to accuracy. On the other hand, access to medical reports also becomes a practical

challenge when applying these modules at community level. Furthermore, models including genetic variants, require blood sample collection as well as processing which is not so user friendly or feasible at population level, in addition to increased cost.

It is necessary to evaluate the performance of these models with respect to their discriminative and calibration properties. Evaluation of the utility of these models in. The role of the currently available models in clinical practice will be defined when comparative data on the performance of different models becomes available. However, the choice of which risk model is applicable to each country will be based on validation studies in the population of interest. Furthermore, research is needed to identify optimal implementation strategies, where feasibility, accessibility, cost-effectiveness and impact on morbidity and mortality in comparison to the already existing programmes is assessed. Finally, it is necessary to assess the advantages and disadvantages of implementing these risk models in clinical practice via randomized controlled trials.

Conclusions

This comprehensive and up-to-date scoping review describes this emergent body of literature, detailing the studies conducted, location, study design, outcome of the model, overview of the methods, data source and risk predictors identified, demonstrating the capacity of the existing risk models to stratify the general population into risk categories. While striving to build on existing knowledge, the review also identifies the research gaps and the need for further improvement.

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