Review Article

Recent evidence on modifiable and non-modifiable risk factors for colorectal cancer (CRC): a systematic synopsis of meta-analyses from 2015 to 2017

Teguh Kristian Perdamaian[1,2]

Author's affiliations:
[1]*Faculty of Medicine, Universitas Kristen Duta Wacana, Yogyakarta, Indonesia*
[2]*Centre of Population Health Sciences, The University of Edinburgh, Edinburgh, United Kingdom*

Corresponding author:
Teguh Kristian Perdamaian
Faculty of Medicine, Universitas Kristen Duta Wacana, Gedung Logos, Jalan Dr. Wahidin Sudirohusodo No. 5-25, Yogyakarta 55224, Indonesia
Tel/Fax: +62-274-563929
E-mail: teguh.kristian@staff.ukdw.ac.id

ABSTRACT

Colorectal cancer (CRC) is a common cancer with a huge impact on international public health. This review discusses recent evidence on modifiable and non-modifiable risk factors for CRC using a systematic review method. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines on systematic reviews and meta-analyses of observational studies. The literature search was performed on the Ovid MEDLINE database and included publications from 2015 to 2017, followed by a quality assessment and a narrative synthesis. Of the 90 identified articles, there were 13 meta-analyses with statistically significant results. Seven articles discussed modifiable risk factors and six articles discussed non-modifiable risk. The modifiable risk factors with the highest risk were radiotherapy of prostate cancer (pooled odds ratio 1.68; 95% confidence interval [CI] 1.33–2.12). The non-modifiable risk factors with the highest risk was Lynch syndrome (hazard ratio 135.49; 95% CI 111.55–164.57). This review discovered new and previously known risk factors for CRC. Recent evidence shows that research on CRC risk factors is continuing to grow indicating that more studies on risk factors are needed to optimize CRC prevention and early detection.

KEYWORDS colorectal cancer, genetic marker, metabolic diseases, meta-analysis, risk factors

Colorectal cancer (CRC) is a common cancer with a huge impact on public health worldwide. This cancer contributes to a large incidence and mortality second only to breast cancer. Evidance show higher incidence (>14.3 per 1,000) and mortality rates (>7.7 per 1,000) in Europe, North America, and the Western Pacific region. However, recent studies have reported an increasing trend of incidence and mortality in developing countries such as in Southeast Asia and South America.[1,2] Data from the global burden of disease (GBD) study showed similar results for middle-income countries, with up to a 3-fold increase in CRC rate over 25 years.[3] Advances in communicable disease management in these countries might prolong life expectancy and expose the population to more risk factors for CRC over their lifetime. Apart from geographical variability, CRC epidemiology appears to be influenced by socioeconomic inequalities, in which the highest deprived populations have the highest CRC incidence and mortality rates.[4]

Many reviews and meta-analyses have summarized important non-modifiable and modifiable risk factors for developing CRC. The 2015 GBD study reported that 52.57% of the colorectal cancer burden is attributable to behavioral and metabolic risk factors, including physical inactivity, a unhealthy diet, smoking, and obesity.[1] Some pre-existing diseases have also been reported to have a substantial risk on the development of CRC, such as hepatobiliary autoimmune disorders (i.e., primary sclerosing cholangitis) and inflammatory bowel diseases (i.e., ulcerative colitis).[5] Another growing area of CRC risk profiling is genetic studies, which have discovered several potential genetic polymorphisms that might be beneficial for CRC screening. For example, patients with Lynch syndrome and a mutation in the MSH1, MLH2, MSH6, or PMS2 genes are offered earlier colonoscopy screenings due to the high rate of future CRC development.[6,7] Yet, there could be more undiscovered risk factors, which might improve current prevention practices. This review will discuss recent evidence on modifiable and non-modifiable risk factors to complement existing knowledge, by systematically searching and summarizing the current best evidence. The method used in this review will guide future health practitioners when they conduct concise systematic reviews on meta-analyses with a broad topic. The results from this review will be useful as a guide to direct future research or practice recommendations.

METHODS

Search strategy and eligibility criteria

A systematic literature search was conducted to identify meta-analysis studies that summarized risk factors for developing colorectal cancer. The risk factors were categorized into two main groups

of modifiable and non-modifiable. The risks were not limited to one with evidence on causality, but we also considered other conditions related to the development of CRC. A modifiable risk factor was considered when there was any evidence of reduced risk from an intervention. Non-modifiable risk factors generally include aging, gender, ethnicity, and genetic characteristics.[8] The outcome of this study was the pooled risk of certain risk factors on the outcome of all types of CRC. The pooled risk could be a risk ratio (RR), odds ratio (OR), risk difference, or hazard ratio (HR), and should be complemented with its *p*-value and 95% confidence interval (CI). The types of CRC included in this study were colon cancer, rectal cancer, cecal cancer, sigmoid cancer, and hereditary nonpolyposis cancer. The search was conducted on the MEDLINE platform, using the subject headings, text words, and limitation features shown in Table 1.

No age, sex, or language limitations were followed. The search was limited by publication dates between January 1, 2015 and April 7, 2017. The search method for both types of risk factors was combined into one flow (Figure 1), in which the classification was developed after the full-text data were obtained. Based on the objective of this review, the literature search and screening included studies on humans, and the CRC diagnosis as the outcome. The type of study was restricted to a meta-analysis. This review excluded protective risk factors.

Data extraction, quality assessment, and data synthesis

Key information was extracted from the articles, and the results are presented in Table 2 and 3. The data included were authors, journal reference, studied risk factors and subsets, studies included (sample size, case and control number, association estimation (type of estimation [HR and RR], or OR and 95% CI], and corresponding *p*-value), heterogeneity of the studies

Table 1. Search strategy in the MEDLINE platform

| Search terms |
| --- |
| (exp cecal neoplasms/ or exp appendiceal neoplasms/ or exp colorectal neoplasms/ or exp adenomatous polyposis coli/ or exp gardner syndrome/ or exp colonic neoplasms/ or exp sigmoid neoplasms/ or exp colorectal neoplasms, hereditary nonpolyposis/ or exp rectal neoplasms/) or ((cecal neoplasms or appendiceal neoplasms or colorectal neoplasms or adenomatous polyposis coli or gardner syndrome or colonic neoplasms or sigmoid neoplasms or colorectal neoplasms or hereditary nonpolyposis or rectal neoplasms).tw) |
| (exp risk/ or exp risk assessment/ or exp risk factors/) or ((risk or risk assessment or risk factors).tw.) |
| 1 and 2ß |
| limit 3 to (humans and meta-analysis and "causation-etiology (maximizes specificity)" and yr="2015-Current") |
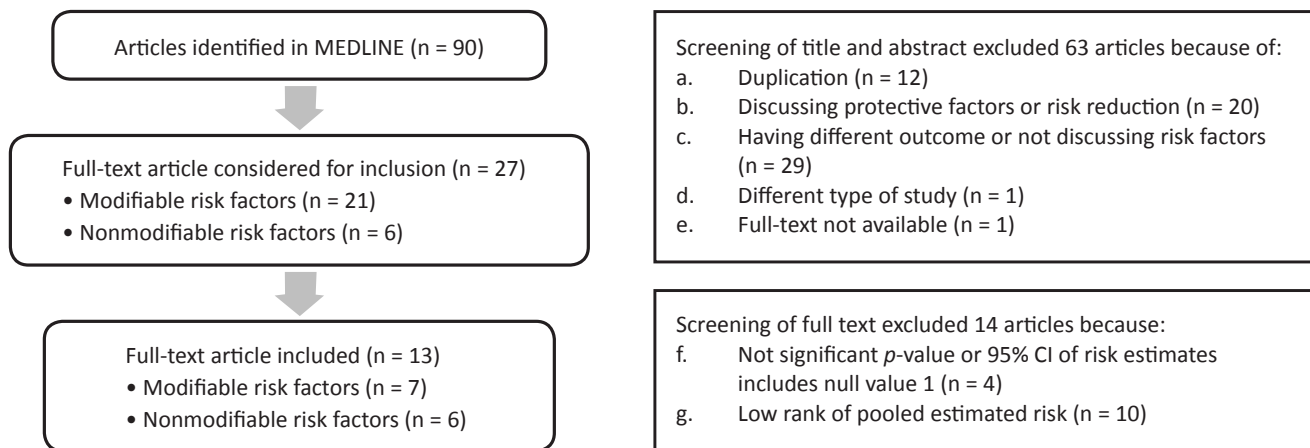
Figure 1. Flow diagram for the literature search and screening process

(I^2 and *p*-value), and quality of the meta-analysis. The trend or dose-response analysis was not inputted into the table or with the subgroup analysis and meta-regression results. The values of implicit information were calculated from published data on the included meta-analyses and their primary sources when possible. The quality of the meta-analysis was assessed with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines on systematic review and meta-analysis of observational studies reporting.[9]

RESULTS

Ninety articles were identified by the initial search strategy. Sixty-three papers were excluded due to failed eligibility criteria. Of the 27 studies remaining, 13 articles were included based on the focus on five risk factors in each group (Figure 1). These 10 risk factors were chosen based on their high rank on the magnitude of pooled risk estimates. Seven articles discussed five modifiable risk factors, such as abdominal radiation for other malignancies,[10] alcohol and beer consumption,[11,12] diabetes mellitus (DM),[13,14] *Helicobacter pylori* infection,[15] and gynecologic surgery.[13] The other six articles discussed non-modifiable genetic factors, including Lynch syndrome (polymorphisms in the MLH1 and MSH2 genes),[16,17] the rs16892766 polymorphism,[18] the rs4779584 polymorphism,[19] the XRCC1 gene polymorphism,[20] and the BMP4 gene polymorphism.[21] These studies are presented in Table 2 and 3 ordered by the earliest publication date. The publication quality of the seven included articles was exceptional, except for the articles by Guraya[14] and Jenkins et al[16] because of unavailable details on robust search methods and a

bias assessment. As expected from meta-analyses of observational studies, heterogeneity between studies was a common finding (8 of 18 results had substantial heterogeneity with $I^2 > 50\%$).

Modifiable risk factors

Some considerably increased risks were reported for abdominal radiation exposure (OR 1.68; 95% CI 1.33–2.12) and lifetime alcohol consumption (RR 1.49; 95% CI 1.27–1.74). Specifically, Zhang and Zhong[12] reported a significant association between the alcohol in beer and the incidence of CRC (RR 1.20; 95% CI 1.06–1.37). There was a 21% increased risk (95% CI 2–42%) of developing CRC in patients with type 2 diabetes mellitus (T2DM).[14] In addition, Luo et al[22] reported a 37% increased risk for diabetics, which was not limited to T2DM. A review by Zhao et al[15] suggested that a *H. pylori* infection can also play a role in the development of CRC (RR 1.33; 95% CI 1.01–1.77), and is not limited to upper gastrointestinal cancer as previously thought. An increased risk (22–30%) of CRC incidence was found in postsurgical women who had their ovaries removed (i.e., oophorectomy and hysterectomy). (Table 2)

Non-modifiable risk factors

Six of the included meta-analyses discussed genetic factors as non-modifiable risk factors. A substantial association was detected between a genetic mutation related to Lynch syndrome and one type of CRC (hereditary nonpolyposis colorectal cancer) (HR 135.49; 95% CI 111.55–164.57). MLH1 also showed significant increase in odds of developing all types of CRC (codominant polymorphism, OR 2.29; 95% CI 1.618–3.244). Two major single nucleotide polymorphisms (SNPs) had considerably increased

Table 2. Summary of evidence on modifiable risk factors

First author, year	Risk factors and comparison	Study design inclusion	No. of studies	Sample size included		Pooled risk estimates			Heterogeneity		Quality
				CRC event (exposed/not exposed)	Controls (exposed/not exposed)	Risk estimate	95% CI	p	I² (%)	p	
Zhang,[12] 2015	Alcohol (beer), any beer drinkers vs. non-drinkers	Case control and cohort studies	21	10,736 (NA)	NA	RR 1.20	1.06–1.37	NA	73.3	<0.001	High
Guraya,[14] 2015	T2DM, compared to without T2DM	Cohort studies	8	51,931 (5,229/46,702)	872,701 (108,639/764,062)	RR 1.21	1.02–1.42	0.03	96.0	<0.001	Low
Luo,[22] 2016	DM compared to without DM	Case control and cohort studies	20	30,133 (3,275/26,858)	2,579,043 (204,418/2,375,625)	RR 1.37	1.30–1.45	NA	45.1	0.012	High
Zhao,[15] 2016	Helicobacter pylori infection, compared to negative result	Case control studies	14	2,228 (940/1,288)	1,202 (437/765)	OR 1.33	1.01–1.77	0.05	67.0	<0.001	Medium
Jayasekara,[11] 2016	Lifetime alcohol consumption, highest vs. lowest intake	Case control and cohort studies	7	NA	NA	RR 1.49	1.27–1.74	NA	33.5	0.172	High
Luo,[13] 2016	Hysterectomy, compared to general population	Cohort studies	10	Total case and controls = 307,958		RR 1.24	1.17–1.32	<0.001	53.1	0.024	High
	Oophorectomy, compared to general population	Cohort studies	4			RR 1.30	1.27–1.34	<0.001	0.0	0.837	
	Oophorectomy and Hysterectomy, compared to hysterecto my only	Cohort studies	5			RR 1.22	1.06–1.40	<0.001	0.0	0.744	
Wallis,[10] 2016	Radiotherapy for prostate cancer	Cohort studies	10	1,984 (732/1,252)	228,785 (64,105/164,680)	OR 1.68	1.33–2.12	<0.001	72.0	<0.001	High

CRC=colorectal cancer; CI=confidence interval; NA=not applicable (could be caused by unavailable or unreported data or incomplete details; thus, the calculation was not feasible); RR=risk ratio; T2DM=type 2 diabetes mellitus; DM=diabetes mellitus; OR=odds ratio

Table 3. Summary of evidence on non-modifiable (genetic) risk factors

| First author, year | Risk factors | | Study design inclusion | No. of studies (datasets) | Sample size included | | Pooled risk estimates | | | Heterogeneity | | Quality |
	Gene (location)	Polymorphism			CRC event	Controls	Risk estimate	95% CI	p	I² (%)	p	y
Jenkins,[16] 2015	Lynch syndrome (MLH1 and MSH2)	Not specified	Cohort	4 (4)	1,114 Lynch families: MLH1 mutation: 508 MSH2 mutation: 606		HR 135.49*	111.55–164.57	NA	NA	NA	Low
Zhou,[21] 2015	BMP4 (14q22.2)	rs4444235	Case control	12 (36)	54,631	77,115	OR 1.06	1.04–1.08	<0.001	2.4	0.428	High
Li,[18] 2015	Unidentified gene (8q23.3)	rs16892766	Case control	11 (23)	41,728	44,393	OR 1.22	1.18–1.27	<0.001	5.0	0.393	High
Tu,[19] 2015	Unidentified gene (15q13.3)	rs4779584	Case control	20 (41)	48,468	85,105	OR 1.13	1.09–1.16	<0.001	49.1	0.001	High
		rs10318		4 (9)	8,947	9,218	OR 1.13	1.02–1.24	0.02	61.2	0.008	
Chen,[17] 2015	MLH1	rs63750447 codominant	Case cohort	7 (7)	1,396	1,326	OR 2.28	1.612–3.232	<0.001	0.0	0.56	High
		rs63750447 dominant	Case control				OR 2.29	1.618–3.244	<0.001	0.0	0.54	
Wang,[20] 2016	XRCC1	rs1799782 recessive	Case control	11 (11)	482	5,783	OR 1.32	1.04–1.67	<0.05	25.3	0.203	Medium
		rs1799782 dominant		11 (11)	3,011	3,221	OR 1.21	1.00–1.46	<0.05	66.7	0.001	
		rs1799782 homozygous		11 (11)	582	3,221	OR 1.43	1.07–1.91	<0.05	45.3	0.05	

CI=confidence interval; HR=hazard ratio; NA=not applicable (could be caused by unavailable or unreported data or incomplete details; thus, the calculation was not feasible); CRC=colorectal cancer; OR=odds ratio

*The study did not calculate overall risk estimates; the above value was the highest hazard ratio (HR) corresponding to the male group, aged 30 to 39 years

odds, which are rs1799782 in the XRCC1 gene (21–43%) and rs16892766 in chromosome 8q23.3. One SNP in the BMP4 gene (rs4444235) only showed a small increase in CRC odds (6% increase, 95% CI 4–8%). (Table 3)

DISCUSSION

This review discovered some new and previously known risk factors for developing CRC. Radiotherapy, in any dose and duration, is associated with the future development of cancer. Wallis et al[10] reported a notably increased risk, as opposed to a weak association reported by other primary research.[23,24] Surgical treatment for ovarian cancer by oophorectomy increases the risk of colorectal cancer by stopping the effects of hormones. Fortunately, previous meta-analyses have shown a potential benefit of hormone replacement therapy to prevent CRC in these patients.[25] DM has been extensively studied and results in an increased risk not only of CRC but also of developing other cancers, such as liver and gastric cancers.[26,27] This finding suggests a common cancer progenitor from digestive organs that should be studied further. Another shared digestive risk factor included in this review is *H. pylori* with a similar strength of association compared to previous reviews.[28,29] Alcohol consumption reviewed here is concordant with previous reviews in various populations with evidence of a dose-response relationship.[30,31]

The most prominent result of genetic studies is the role of mutation in Lynch syndrome (MSH2 and MLH1) and the future development of CRC from previous studies.[32,33] The increased risk for the XRCC1 and BMP4 gene mutations is comparable with a previous review.[34,35] The role of a genetic mutation in the 8q23.3 and 15q13.3 loci is a novel finding that might need future research.

Strength and limitations

The strengths of this review include its systematic approach and quality assessment using the PRISMA guidelines. Given a specified range of publication dates, this review additionally included some studies with a similar theme, such as beer consumption-alcohol intake, T2DM, and the Lynch syndrome-MLH1 mutation. Clear screening criteria contributed to producing a high impact meta-analysis. Some limitations should be considered when applying the

results, mainly regarding the search strategy and data synthesis. The search strategy within a short time limit on one platform (MEDLINE) probably missed some informative resources. Numerous hits of studies originating from East Asia (i.e., China and Japan). These countries have a high burden of CRC and correspondingly might not have published studies in English. A search strategy that includes the Global Health and Chinese national databases could discover more publications in specific populations. The aim to find only five themes for each risk factor group based on recentness excluded some interesting risk factors with a weak association in the screening process. This may have led to selection bias, although all eligibility criteria were thoroughly described. The results of each meta-analyses should be carefully generalized as they mostly have a high level of heterogeneity.

Implications for public health practice and health policy

The modifiable risk factors discovered in this study are important for primary prevention and consideration or stratification for early detection of CRC. The high rate of secondary CRC due to radiation should inform the oncologist and radiotherapist to consider the benefit-to-harm ratio of specific localized treatment, while the gynecologic surgeon should consider the need for hormone replacement after ovary removal procedures. The evidence in diabetic patients could lead to a contradictive decision, as use of insulin poses an increased risk for developing CRC,[36] while metformin therapy shows protective effects.[37,38] Nevertheless, this review suggests that the health practitioner should aim for well-controlled blood glucose but does not warrant a stricter glucose-lowering regimen than the current practice for T2DM treatment. The need for early CRC screening of diabetic patients requires more convincing evidence.

The evidence on Lynch syndrome would not change the current practice in high-income countries. Genetic testing is cost effective[39] and many countries, including the UK have integrated genetic testing of Lynch syndrome into the high-risk group, particularly in cases of a family history of a similar disease.[6] However, further information from corresponding meta-analyses regarding a decreased HR with increasing age should not directly decrease the screening effort. The cost-effectiveness of decreasing the screening effort according to

age in Lynch syndrome would probably alter the recommendation. Evidence on the remaining genetic risk factors could help find the best combination of risk predictors for early detection of CRC. The focus of genetic studies in a restricted population, such as a subgroup analysis performed by some of the meta-analyses, might find a stronger association. These approaches would improve the current screening program by including important genetic markers for certain high-risk groups, as combining universal and selective screening in one multi-stage program. The pitfall would be potentially increasing false negative results.

This review supports recent efforts for managing the CRC burden in lower to middle-income countries. Particularly for genetic screening, it poses the availability and affordability issues that might hinder these countries to implement CRC screening. Current evidence on CRC burden warrants a well-designed universal or targeted screening program, with at least a simple diagnostic test, such as a stool examination, in developing countries.

Based on these findings, future research should explore the impact of treatments for pre-existing diseases, as many behavioral, metabolic, and diet risk factors have been discovered without any effects on practice. Research on the best-fit genetic marker combination is still ongoing with promising results. Another option is to combine both modifiable and non-modifiable risk factors in one study to assess any overlap and to understand the underlying mechanism of their association.

Research on risk factors for CRC has been widely performed, with more evidence coming from high burden developing countries. Current practices may not be changed until the discovery of novel high impact factors. In conclusion, recent evidence shows that research on CRC risk factors is continuing to grow, demonstrating that more studies on risk factors are needed to optimize CRC prevention and early detection.

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