

Review Article



A systematic review on the risk of colorectal cancer in association with red meat intake

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ABSTRACT

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The evolution in lifestyle and the food intake have become the main reasons behind the increase of colorectal cancer worldwide. Though red meat is marked as a great contributor to form this type of cancer according to the World Cancer Fund Organization, some researchers found that negative. The main focus of this study is to understand the basic relation between red meat intake and the probability of this type of cancer occurrence. The accessible resources in English were taken for this study up to the year of 2022. According to some criteria 10 research works were taken from 371 works. Our study found no relation between red meat and the risk of colorectal cancer. Beside this, a relation between processed meat intake and highly boiled meat intake was found to be responsible for colorectal cancer and its growth. In some cases, the genetic makeup of the individuals was found to have some relation with the influence of red meat intake on colorectal cancer. What we got from this review recognizes an extended intake of processed meat (>100g/day) as a risk factor for colorectal cancer.



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INTRODUCTION

It is found that colorectal cancer is one of the most commonly occurred cancers. It contributes about 700,000 deaths globally each year (Patil *et al.*, 2017). In case of males (23.6), the incidence rate is found higher than that of females (16.3) individuals (Rawla *et al.*, 2019). In India, it is reported

contrarily including lower rate for males (7.2) and higher rate for females (5.1) (Pathy *et al.*, 2012). Before 2025, the overall number of cases and deaths from CRC were predicted to be increased about 60% and 71.5%, respectively (Douaiher *et al.*, 2017).

Colorectal cancer is developed according to the heredity, style of living and some natural factors. Prominent risk factors encompass a family or individual background of cancer, colon polyps, diabetes mellitus, cholecystectomy (Henrikson *et al.*, 2015), age, gender, way of living that includes food intake, smoking, alcohol consumption, tardiness (Harriss *et al.*, 2009) as well as social and economic factors (Sawicki *et al.*, 2021). The increased risk of CRC has been attributed to daily food intake, particularly the consumption of red meat and processed meats (Van Blarigan *et al.*, 2022). Pork, beef and lamb meat are categorized in the section of "probably carcinogenic" (2A group) by the International Agency for Research on Cancer. On the other hand, processed meats preserved with added chemical preservatives or by smoking or salting are referred as "carcinogenic to humans" (Group 1) (Bouvard *et al.*, 2015; Turesky, 2018). Before this, it was established that an intake of 100g red meat or only 50g of processed meat daily can create 18% more risk of colorectal cancer (Aykan, 2015). Although the underlying mechanism of how red meat contribute to CRC development is not well understood but it is widely accepted that point mutations can be induced by substances which are formed while boiling, including N-nitroso compounds, heterocyclic amines, and polycyclic aromatic hydrocarbons (Cross *et al.*, 2010; Hur *et al.*, 2019). Furthermore, it has been indicated by animal studies that the presence of nitrates and nitrites in processed meat, along with red meat iron, could potentially add substantial implications in the development of cancer (Santarelli *et al.*, 2008; Sharma *et al.*, 2018; Sinha *et al.*, 2005). In the year of 2007, the World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR) determined the actual proof related to the influence of red meat on CRC. They found the evidence to be "convincing" and recommended reducing the weekly consumption of meat to not more than 500 g, without completely eliminating it from the diet (Clinton *et al.*, 2020). Nevertheless, a few researchers questioned this finding, leading to a reassessment of the evidence pertaining to the exact impact of red meat on the development of CRC (Boyle *et al.*, 2008; Truswell, 2009). Moreover, variations in epidemiological data have resulted in certain studies indicating the absence of a significant correlation between the red meat intake and the occurrence of CRC (Alexander *et al.*, 2010; Alexander & Cushing, 2011). Hence, the objective of our study was to serve a dependable analysis of the scientific methodologies utilized in investigating the correlation between CRC and red meat. Additionally, this systematic review intended to create a concise scenario of the existing epidemiological evidence pertaining to this correlation.

METHODS

Literature search

This study focused on the determination of relation between red meat and CRC. This study was performed following the guidelines set by PRISMA- systematic review and meta-analysis (Page *et al.*, 2021). Studies focussing on the relationship between red meat intake and CRC development were screened. Randomized trials, laboratory-based studies, and case reports were excluded based on predetermined exclusion criteria. The scope of the search was restricted to databases in the English language including publications spanning the years 2015 to 2022. The key words used in the

PubMed database encompassed "red meat," "processed red meat," "colorectal cancer," and "colorectal carcinoma," in conjunction with pertinent medical subject headings (MeSH) such as "Colorectal Neoplasms"[Mesh], "Red Meat"[Mesh], and "Processed Red Meat"[Mesh]. We used the search terms "colorectal neoplasm" or "colorectal cancer" in conjunction with the terms "red meat" and "processed red meat" on Google Scholar. Additional studies were identified by reviewing the references of selected papers, prioritizing the papers that dealt with a large sample size or conducted recently.

Selection and screening

The article screening process was conducted by two researchers in an independent manner. At first, the titles and abstracts were examined to identify articles that met the specified criteria for inclusion. The articles were thereafter taken for a comprehensive examination. Those which could not fulfill the established screening process were discarded. Exclusion rules encompassed studies that particularly examined fish or poultry meat, randomized trials, or case reports. A standardized data collection form was used to retrieve pertinent data from the studies included in the analysis. This form was specifically designed to capture information on the title of the articles, authors, publication year, the name of country, the pathway of study, sample size, population, methodology, outcomes, and conclusions. The resolution of inconsistencies in data extraction was achieved through discussion.

The process of screening was conducted distinctly by two researchers. At the beginning studies were included or excluded through the observation on their titles and the abstract. Only the articles that meet the selection criteria were included. Some articles were focused on fish or poultry meat which were discarded. Randomized trials or case reports were also excluded. At last, they could screen the desired database from the resources independently. When any confusion arose, it was solved by discussion. The data collection form included title, name of the authors, publication year, name of the country, design of the study, article selection criteria, sample and population size, methodology, results and discussion or conclusion of the study.

To observe the quality of the selected studies, the Cochrane Risk of Bias Tool for Non-Randomized Studies of Interventions (RoB 2) was a valuable tool. This tool can measure several facts that are crucial for maintaining the integrity of the study, including perplexity, selection, planning, deviations from the plan, problem with the results and discussion. The biasness risk was evaluated for every areas, and the assessments were classified as either "Yes" (indicating a high risk) or "No" (indicating a low risk). The findings were then presented in a supplementary table (Table 1 Suppl).

Table 1 Supplement: ROB analysis of the selected articles

Reference	Confounding					Selection			Classification of Intervention			Deviations from intended interventions				Missing data			Measurement of Outcome				
	Is there potential for confounding undig of the effect of intervention in this study ?	Were interventions discontinued or switched to be related to factors that are prognostic for the outcome?	Did the author use appropriate analysis methods that controlled for the important confounding undig domains?	Did the author use appropriate analysis methods that controlled for the important confounding undig domains?	Did the author use appropriate analysis methods that controlled for the important confounding undig domains and for time-varying confounding?	Were confounding domains adjusted for validly and reliably by the undig variables available in the study?	Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Do start of follow-up and the start of intervention coincide for most participants?	Were interventions clearly defined at the start of the intervention?	Was the information used to define intervention groups recorded at the start of the intervention?	Could classification of interventions be affected by knowledge of the outcome?	Were there deviations from intended interventions?	Were important co-interventions balanced across intervention groups?	Was the study participant adherence to the intervention ascertained?	Did the study participants adhere to the intervention?	Were outcome data available for all, or nearly all, participants?	Were participants excluded due to missing data on other variables needed for the analysis?	Could the outcome measure have been influenced by the intervention?	Were outcome assessors aware of the intervention received by participants?	Were the methods of outcome assessment able to measure the outcome of interest across the study?	Were any systematic errors in measurement of the outcome related to intervention received?		
(Gharbi <i>et al.</i> , n.d.)	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No		
(Mehta <i>et al.</i> , 2020)	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	
(S Deoula <i>et al.</i> , 2020)	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	
(Klusek <i>et al.</i> , 2019)	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	
(Andersen <i>et al.</i> , 2019)	No	No	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	
(Saliba <i>et al.</i> , 2019)	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	
(Kim <i>et al.</i> , 2019)	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	
(Carr <i>et al.</i> , 2017)	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	
(Ward <i>et al.</i> , 2016)	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	
(Carr <i>et al.</i> , 2016)	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	

RESULTS

Finding literature and selection of studies

The way of searching studies and the inclusion-exclusion process was described in a flowchart (Figure 1). Out of 371 studies that were initially assessed, 48 were found to be duplicates. After proper screening, 296 articles were discarded. 17 articles were found to be non-relevant. Finally, 10 research articles were selected for the final study. Among them, 8 were related to case control (Carr *et al.*, 2016) and 2 were of prospective cohort study (Mehta *et al.*, 2020).

Study characteristics

This study has a sample size of 74, 877 with studies selected globally. Notably, one study conducted as a prospective cohort study covering 10 countries (i.e., Denmark, Sweden, Norway, UK, Netherlands, Greece, Italy, Spain, Germany, France) (Ward *et al.*, 2016). The remaining studies were carried out in Tunisia (Gharbi *et al.*, 2020), United states of America (Mehta *et al.*, 2020), Morocco (Deoula *et al.*, 2020), Poland (Andersen *et al.*, 2019; Klusek *et al.*, 2019), Israel (Saliba *et al.*, 2019), South Korea (Kim *et al.*, 2019) and Germany (Carr *et al.*, 2017; Chan *et al.*, 2011) (Table 1).

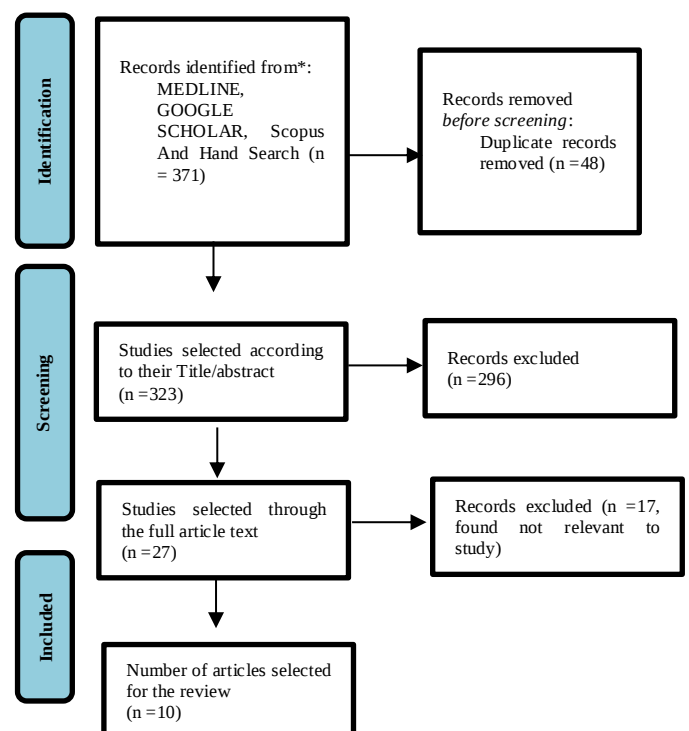


Figure 1: PRISMA flow chart of searching database for this review

Combined effect of red meat and processed meat on colorectal

Red meat from pork, beef, goat, lamb and horse and processed meat like ham, sausages, minced ready-to-eat meat, bacon were studied in the selected studies. [Mehta *et al.* \(2020\)](#) noticed that processed meat specifically sausages and red meat cooked by grilling such as hamburgers, barbequed or grilled meat were positively correlated with the risk of CRC (hazard ratio; HRadj= 1.85 to 2.23) ([Mehta *et al.* \(2020\)](#)). Similarly, [Deoula *et al.* \(2020\)](#) found processed meat (kaddid and khlii) prepared using traditional methods did not cause CRC, whereas the meat which was processed industrially was regarded as significantly responsible for the CRC ([Deoula *et al.* \(2020\)](#)).

Quantity of meat consumption

In most cases, an increased intake of red meat and processed red meat resulted in an increase of CRC risk. [Gharbi *et al.* \(2020\)](#) noticed that people having a daily consumption of 100 g red meat were significantly at higher risk than the people with daily consumption of more than 50 g of meat ([Gharbi *et al.* \(2020\)](#)). Considering different types of meat in correlation with CRC, beef was found to be less harmful whereas pork, lamb and the meat that was processed, exhibited moderate association with higher risk of CRC among population with high intake rates ([Saliba *et al.* \(2019\)](#)).

Table 1: Study characteristics of the selected articles

Topics	Study_Design	Country	Goal	Inclusion_Criteria	Way of Exclusion	N_Study	Study_Population	Method	Results	Significance	Conclusion	Reference
Red and processed meat intake and the occurrence of Colorectal Cancer	Case-control	Tunisia	To identify the effects of red meat, processed meat on the risk of CRC	Tunisian patients were diagnosed for CRC. They were the case group. People having to previous cancer history were the control group.	Firstly, people having a history of other cancers were excluded. And, people who did not meet the general conditions	102	cases-CRC; control-CRC free		The case group had 52.9% men as well as 47.1% women. On the other hand the control group was combined with 49%men and 51% women. Median age was found 56 years. People having stage 1-3 disease were 63% and the other 37% had a metastatic disease. The CRC group had an average Body mass index (BMI) of 24. 76 Kg/m2. In the control group, it was 27.39Kg/m2. Families having poor educational background and a history of CRC occurrence exhibited more risk of CRC than the control group. The socio-economic factors and regional factors created a difference between the two groups. There was no significant relationship found between red meat intake and colorectal cancer risk (p 0,063). But a higher daily intake (> 100 g) of meat was found to be significantly related to a higher risk of CRC (<50 g) (p=0.023). No significant relation was found observing different cooking methods. Among the case group, 51% of people consume processed meat and it is 23. 5% in the control group. This factor was found positive for the occurrence of CRC (p 0,004).	Red meat consumption in the case and control groups was 90.2% and 76.5%, respectively. There is no significant relation between moderate red meat intake and CRC risk (p 0,063). But a higher daily meat intake (> 100 g) was related significantly with CRC than a lower daily meat intake (<50 g) (p=0.023). Processed meat was found positive for the occurrence of CRC (p 0,004).	A high intake of red meat and industrially processed meat results in a higher risk of CRC.	(Gharbi <i>et al.</i> , n.d.)
Analysis on Red and Processed Meat intake and probability of CRC in Women	Prospective cohort study	USA	To analyse the relation between red and processed meat consumption and risk of CRC U.S. women	No proven breast cancer in women but have a sister with breast cancer	Anyone who discontinued the process, lacked FFQ and lacked information on meat intake, or lacked CRC	48704	women	Data were collected from another Study. It included women from 35-74 years old. The target countries were U.S. and Puerto	216 CRC cases were examined. After analysis, in the highest quartile of processed meat intake, CRC risk was found to be increased [HRadj]=1.52 (95%CI: 1.01-2.30); p-trend: 0.02]. It was found in case of different meat products, that included breakfast sausages	The HR was adjusted and found 1.04(95%CI: 0.68-1.60) in case of the highest quartile.	CRC risk for women can be increased if higher red meat products or processed meat is consumed daily.	(Mehta <i>et al.</i> , 2020)

Topics	Study_Design	Country	Goal	Inclusion_Criteria	Way of Exclusion	N_Study	Study_Population	Method	Results	Significance	Conclusion	Reference
					information. CRC patients were excluded.			Rico. Data were taken from those women who had a sister having breast cancer. A questionnaire was used to collect different level of information (N=48,704). The hazard ratio was multivariable and the confidence interval was 95%.	(HRadj=1.85 [95%CI: 1.30-2.64]) and bacon (HRadj=1.46 [95%CI: 1.01-2.11]). Beside this, some evidence was found due to cooking types and red meat doneness. If we take cooking style as a consideration, a positive association is found for CRC and red meat products. ; e.g., grilled/ barbequed steaks (HRadj=2.23 [95%CI: 1.20-4.14]) and hamburgers (HRadj=1.98 [95%CI: 1.00-3.91])			
Consumption of meat, traditional and modern processed meat and the risk of colorectal cancer	Case-control	Morocco	To understand the effects of different types of meat and industrially processed meat on CRC risk	People having diagnosed CRC and found positive in the last three months before the interview were added in case group. But they should not have started a therapeutic process. Healthy people from the same location were taken as control group.	People having no specified cancer (n = 7), old biopsies (six cases), lack of dietary data (n = 10), duplicate records (n = 2), records that were unmatched (n = 8) and lowest and highest 1% of the distribution of the ratio between energy consumption and energy need (n = 30)	1453	cases-CRC; control-CRC free	The study included 2,906 matched case-control pairs taken from five large university hospitals. A questionnaire was used for collecting data. The confidence interval to determine the relation of CRC risk with meat consumption was 95% (high vs. low intake). It was measured by conditional logistic regression models.	There was a positive relation between red meat intake and colon cancer and CRC risk (OR = 1.23, 95% CI = 1.05-1.44; OR = 1.14, 95% CI = 1.02-1.27, respectively), but no significant relationship was found with rectal cancer (OR = 1.05, 95% CI = 0.90-1.23). Beef was found responsible for colon cancer and CRC risk (OR = 1.23, 95% CI = 1.05-1.44; OR = 1.11, 95% CI = 1.01-1.24, respectively). On the other hand, no significant relation was found between lamb meat intake and cancer.	A positive relation was found between colon cancer and CRC risk (OR = 1.23, 95% CI = 1.05-1.44; OR = 1.14, 95% CI = 1.02-1.27, respectively). On the other hand, there was no significant relation between the intake of red meat and rectal cancer risk (OR = 1.05, 95% CI = 0.90-1.23). Industrially processed meat was positively related to colon cancer, rectal cancer and CRC (OR = 1.61, 95% CI = 1.27-2.04; OR = 1.73, 95% CI = 1.34-2.23; OR = 1.67, 95% CI = 1.41-1.98), traditional processed meat was inversely connected to colon cancer and CRC risk (OR = 0.74, 95% CI = 0.57-0.98; OR = 0.77, 95% CI = 0.64-0.93), respectively	It exhibits the same connection between the intake of red meat and CRC risk in Morocco as in other first world nations, while a different scenario was found for traditional processed meat products. This study examined the effects of traditional vs. modern processed products in a developing country.	(S Deoula <i>et al.</i> , 2020)
Red Meat, risk of CRC and Genetic Polymorphisms of S-Glutathione Transferase Genes	case-control	Poland	To measure the influence of GST gene polymorphism and rate of red meat intake on CRC.	The case group contained 197 patients with confirmed colorectal cancer. It was confirmed through diagnosis. The control group included 104 non-cancer patients.		301	cases-CRC; control-CRC free	The rate of red meat intake was measured through the FFQ. The questions were about the rate of red meat intake, consisting of the intake of beef, pork, veal, mutton, and venison. DNA was taken from blood samples by using the Genomic	A high meat intake rate resulted in more than 2-fold increase in the risk of CRC. The odds ratio (OR) was adjusted according to sex and age = 2.4, 95% confidence interval (CI); 1.3-4.4). However, after detailing the genetic makeup, not including the polymorphisms of all three genes, there was no relation between a high rate of meat intake and the risk of CRC.	For GSTM1 gene polymorphism, the high rate of meat intake resulted in an increased risk of CRC by almost more than 4 times (OR for sex and age = 3.8, 95% CI: 1.6-9.1). There was a 3-fold higher risk, in GSTP1, of CRC was found with a high rate of meat intake (OR for sex and age = 3.4, 95% CI: 1.4-8.1). For GSTT1 gene polymorphism,	The rate of red meat consumption in the people who don't smoke resulted in a higher risk of colon cancer if considered the GST gene polymorphisms	(Klusek <i>et al.</i> , 2019)

Topics	Study_Design	Country	Goal	Inclusion_Criteria	Way of Exclusion	N_Study	Study_Population	Method	Results	Significance	Conclusion	Reference
Red and Processed Meat consumption, using different drugs(non-steroid anti-inflammatory drugs, different genetic types and occurrence of CRC	case-cohort study	Poland	To investigate how a person's unique genetics related to inflammation and fat metabolism and their consumption of red and processed meat to influence the risk of developing colorectal cancer.	1038 CRC cases and 1857-person sub-cohort from the Danish "Diet, Cancer and Health" study.		2895	case- CRC Confirmed ; control- healthy	Micro AX Blood Gravity kit from AA Biotechnology (Gdynia, Poland) A nested case-cohort design within the Danish prospective "Diet, Cancer and Health" study.	They investigated the association of genetic variants in fatty acid metabolism and NSAID pathway genes (<i>SLC25A20</i> , <i>PRKAB1</i> , <i>LPCAT1</i> , <i>PLA2G4A</i> , <i>ALOX5</i> , <i>PTGER3</i> , <i>TP53</i> , <i>CCAT2</i> , <i>TCF7L2</i> , <i>BCL2</i>) with colorectal cancer (CRC) risk, and their interaction with diet and NSAID use. The variant <i>CCAT2</i> rs6983267 was significantly associated with CRC risk ($p < 0.01$). Several significant gene-environment interactions were identified. Notably, the intake of red and processed meat influenced the risk associated with variants in <i>CCAT2</i> (rs6983267), <i>TP53</i> (rs1042522), <i>LPCAT1</i> (rs7737692), and <i>SLC25A20</i> (rs7623023) (all p -interaction < 0.05). The effect of the <i>TP53</i> rs1042522 variant on CRC risk was influenced by both NSAID use and alcohol intake (p -interaction = 0.04 for both). No other consistent associations or interactions were observed.	the higher risk of CRC was not statistically significant (OR adjusted for sex and age = 1.9, 95% CI: 0.4–8.5) Significant gene-environment interactions were identified. The association between red and processed meat intake and CRC risk was modified by variants in <i>CCAT2</i> (rs6983267; p -interaction=0.04), <i>TP53</i> (rs1042522; $p=0.04$), <i>LPCAT1</i> (rs7737692; $p=0.02$), and <i>SLC25A20</i> (rs7623023; $p=0.03$). The relationship between the <i>TP53</i> rs1042522 variant and CRC risk was modified by both NSAID use and alcohol intake (p -interaction=0.04 for each).	The results indicate that red meat intake and NSAID use share common pathways in colorectal cancer development. The novel gene-environment interactions identified require replication. Future studies on NSAID chemoprevention should include genetic and dietary assessments.	(Andersen <i>et al.</i> , 2019)
A population based study on red and processed meat intake and its relation to CRC	case-control	Israel	This study aims to investigate the relation between the intake of red meat and the risk of colorectal cancer, comparing Jewish and Arab populations within a shared Mediterranean environment.	All consecutive patients diagnosed with colorectal cancer (CRC) residing in a geographically defined area of northern Israel at the time of diagnosis were eligible to participate as cases. CRC-free controls were randomly selected from the same source population, using the Health Services (CHS) population		10026	cases- CRC; control- CRC free	This study uses data from the Molecular Epidemiology of Colorectal Cancer (MECC) study, a prospective, population-based case-control study in northern Israel (N=10,026). All participants completed in-person interviews using a detailed questionnaire, which included a food-frequency questionnaire (FFQ) to assess dietary intake, comprehens	Consumption patterns and CRC risk associated with red meat differed significantly by ethnicity. Jews consumed less red meat but more processed meat than Arabs. Each weekly serving of total red meat increased CRC odds in Jews (OR=1.05, 95% CI: 1.01-1.08) but not Arabs (OR=0.94, 0.88-1.01). Among Jews, lamb, pork, and processed meat were significantly associated with higher risk; no such associations were found for any subtype in Arabs, despite their higher overall intake.		Overall red meat consumption showed a weak positive relation to colorectal cancer (CRC) risk. Lamb and pork consumption were significantly related to an increased risk of CRC, whereas beef consumption was not. Processed meat consumption was consistently associated with a significant CRC risk. No association was found between red meat subtypes and	(Saliba <i>et al.</i> , 2019)

Topics	Study_Design	Country	Goal	Inclusion_Criteria	Way of Exclusion	N_Study	Study_Population	Method	Results	Significance	Conclusion	Reference
				register, and were frequency-matched to cases on key demographics.	—			ive lifestyle and demographic data.			risk based on specific tumor location.	
Role of common genetic variants in the <i>CYP2E1</i> and <i>PPARγ</i> genes in modifying the association between red meat consumption and the risk of colorectal cancer	case-control study	South Korea	This study aims to examine the associations between polymorphisms in the <i>CYP2E1</i> and <i>PPARγ</i> genes, red meat intake, and colorectal cancer (CRC) risk.			2036	cases-CRC; control-CRC free	971 colorectal cancer patients and 658 controls (1995–2004) were taken. Red meat intake was measured by a food frequency questionnaire, and polymorphisms in <i>CYP2E1</i> (rs3813867) and <i>PPARγ</i> (rs1801282, rs3856806) were genotyped.	The analysis revealed a significant gene–diet interaction, where the association between red meat intake and colorectal cancer (CRC) risk was modified by <i>CYP2E1</i> genotype. The odds ratio (OR) for high red meat consumption (≥ 5 times/week vs. < 1 time/week) was 2.77 (95% CI: 1.23–6.25) among individuals carrying a C allele of <i>CYP2E1</i> rs3813867, but 0.89 (0.51–1.54) among those with the GG genotype (P -interaction = 0.05). A similar, though non-significant, trend was observed for the <i>PPARγ</i> rs3856806 (C161T) polymorphism. These data provide evidence that East Asian individuals with the <i>CYP2E1</i> variant allele may have a genetically heightened susceptibility to CRC associated with red meat consumption.	The effect of red meat consumption on CRC risk differed significantly by <i>CYP2E1</i> genotype. Compared to infrequent consumption (< 1 time/week), high intake (≥ 5 times/week) was associated with a 2.77-fold increased risk (95% CI: 1.23–6.25) among individuals carrying a C allele, whereas no significant association was observed among those with the GG genotype (OR=0.89; 95% CI: 0.51–1.54; P for interaction = 0.05).	These findings provide evidence that genetic polymorphisms in <i>CYP2E1</i> modulate the association between red meat intake and colorectal cancer (CRC) risk. The observed gene-diet interaction indicates that individuals with certain genotypes may be more susceptible to the carcinogenic effects of high red meat consumption. The possibility of a population-specific interaction between red meat intake and <i>CYP2E1</i> variants in relation to CRC risk warrants further investigation in other Asian cohorts.	(Kim <i>et al.</i> , 2019)
Associations of red and processed meat intake with major molecular pathological features of colorectal cancer	case-control study	Germany	To investigate the association between meat consumption and colorectal cancer (CRC) risk and assess potential variations in this risk by precise tumor anatomical location and key molecular pathological subtypes.	Patients with a histologically confirmed, first diagnosis of colorectal cancer (ICD-10 codes C18–C20) are eligible to participate. Inclusion criteria are: (1) age 30 years or older, (2) ability to communicate in German, and (3) physical and cognitive fitness to		2449	cases-CRC; control-CRC free	2,449 colorectal cancer (CRC) cases and 2,479 controls provided detailed risk factor data and completed a food frequency questionnaire. Using multivariable logistic regression, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the associations between meat intake	High intake of red and processed meat was associated with a significantly increased risk of colorectal cancer overall, as well as for colon and rectal cancers specifically. This elevated risk was largely consistent across most molecular subtypes examined, including tumors defined by microsatellite instability, CIMP status, and mutations in <i>BRAF</i> , <i>p53</i> , and <i>ER-β</i> . However, the association was significantly weaker for <i>KRAS</i> -mutated tumors compared to <i>KRAS</i> -wild type tumors, suggesting that the mechanism linking meat consumption to carcinogenesis may differ in tumors driven by <i>KRAS</i> mutations.		These findings found an association between high red and processed meat intake and increased colorectal cancer risk, which appears across most major molecular subtypes. Preliminary evidence suggests an attenuated association for <i>KRAS</i> -mutated tumors. While the results assure the role of meat as a broad risk	(Carr <i>et al.</i> , 2017)

Topics	Study_Design	Country	Goal	Inclusion_Criteria	Way of Exclusion	N_Study	Study_Population	Method	Results	Significance	Conclusion	Reference
				complete the study procedures				and CRC risk, with analyses stratified by molecular pathological features (e.g., microsatellite instability, KRAS/BRAF mutations) and specific tumor subtypes.			factor, the observed heterogeneity in specific subtype analyses indicates that underlying mechanisms may differ. This warrants further investigation in large, well-characterized cohorts to confirm these subtype-specific differences and elucidate the distinct biological pathways involved.	
Pre-diagnostic Intake of Meat and Dietary fiber in Relation to Colorectal Cancer Survival in the European Prospective Investigation into Cancer and Nutrition.	prospective cohort study	Sweden, Denmark, Norway, The Netherlands, UK, France, Germany, Spain, Italy and Greece	This study aims to investigate whether pre-diagnostic intakes of these dietary components are associated with overall and colorectal cancer.	The European Prospective Investigation into Cancer and Nutrition (EPIC) is a multi-center, prospective cohort study conducted across twenty-three centers in ten European countries. Between 1992 and 2000, the cohort recruited 519,978 volunteers, aged 25–70 years at baseline. The cohort's design and methodology have been described in detail previously.		3789	cases-CRC; control-CRC free		Individuals with higher red and processed meat intake had, on average, higher waist circumference, a greater proportion of smokers, and lower educational attainment. A higher proportion of rectal cancer was observed among men in the highest intake quartile. In substitution analyses, replacing red and processed meat with poultry was not significantly associated with all-cause or CRC-specific mortality, and dietary fiber intake from major sources was not associated with mortality outcomes.		This prospective analysis within the EPIC cohort found no evidence to support an association between pre-diagnostic intakes of red and processed meat or dietary fibers and survival outcomes after a colorectal cancer diagnosis.	(Ward <i>et al.</i> , 2016)
Associations of Red and Processed Meat Intake with Survival after Colorectal Cancer: Does the Timing of Dietary Assessment Matter?	case-control study	Germany	This study aimed to investigate the associations of red and processed meat intake, as measured at cohort baseline, with overall and colorectal cancer (CRC)-specific survival. It was also investigated how intake			3122	cases-CRC; control-CRC free	This analysis included 3,122 patients diagnosed with colorectal cancer (CRC) between 2003 and 2010 from the DACHS study. They were followed for a median of 4.8 years. Dietary intake,	In patients with stage I–III colorectal cancer (CRC), baseline red and processed meat intake (≥ 1 time/d vs. < 1 time/d) was not associated with overall survival (HR: 0.85; 95% CI: 0.67, 1.09), CRC-specific survival (HR: 0.83; 0.61, 1.14), or other cause-specific outcomes; results were comparable for stage IV patients. However, a significant adverse association was observed in the molecular subgroup of patients with KRAS-mutated tumors (HR		The findings suggest that pre-diagnostic red and processed meat intake is not associated with poorer survival outcomes in the overall colorectal cancer (CRC) patient population. However, the significant	(Carr <i>et al.</i> , 2016)

Topics	Study_Design	Country	Goal	Inclusion_Criteria	Way of Exclusion	N_Study	Study_Population	Method	Results	Significance	Conclusion	Reference
			levels changed among CRC survivors approximately five years after diagnosis.					including red and processed meat consumption, and other lifestyle factors were assessed via standardized questionnaire at baseline (around the time of diagnosis) at a 5-year follow-up. Multivariable Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between baseline meat intake and survival outcomes was used.	for overall survival: 1.99; 95% CI: 1.10, 3.56), but not in tumors with microsatellite instability or CpG island methylator phenotype (CIMP) positivity. Notably, a substantially lower proportion of survivors reported daily meat consumption at the 5-year follow-up compared to baseline (concordance rate: 39%; $\kappa = 0.10$; 95% CI: 0.07, 0.13), indicating a marked decline in intake after diagnosis.		adverse association observed specifically in patients with <i>KRAS</i> -mutated tumors warrants further investigation. Importantly, the substantial reduction in meat consumption reported at the 5-year follow-up suggests that post-diagnostic dietary changes may have influenced survival, potentially attenuating the observable effect of baseline diet.	

Pre-diagnostic evaluation and survival

Two research studies were conducted to understand the effect of initial dietary intake of red and processed red meat on individuals who were later diagnosed for CRC. Both studies denied any significant association between the intake of red meat and growing colorectal cancer (Carr *et al.*, 2016). However, a decrease in the intake of red and processed red meat after the diagnosis was linked to a better prognosis and survival rate in patients (Carr *et al.*, 2016).

Gene polymorphisms and molecular pathologies

The consequences of gene polymorphisms in connection to high red meat diet and the activation of carcinogenic pathways were investigated in three separate studies (Andersen *et al.*, 2019; Kim *et al.*, 2019; Klusek *et al.*, 2019). Andersen *et al.* (2019) studied CCAT2 gene polymorphism and its association with CRC (Andersen *et al.*, 2019). The study found that four polymorphisms who were found to be positively related to red meat consumption and initiate carcinogens in CRC (Andersen *et al.*, 2019). They were CCAT2 rs6983267, LPCAT1 rs7737692, TP53 rs1042522 and SLC2A20 rs7623023. Kim *et al.* (2018) investigated cytochrome P450 (CYP2E1) and proliferator-activated receptor gamma (PPAR γ) gene polymorphism in red meat intake and CRC development and found that individual who consumed red meat 4 or 5 times and carried the C allele variants of CYP2E1 and T allele variants of PPAR γ were positively associated with CRC (Kim *et al.*, 2019). Similarly Klusek *et al.*, (2019) studied S-glutathione transferase gene polymorphism of three genes-GSTM1, GSTP1, GSTT1. Gene polymorphism in GSTM1 and GSTP1 were related to high frequency consumption of red meat. It

resulted in a significant 4 and 3 fold growth of CRC risk, respectively whereas GSTT1 did not have any significant effect on CRC (Klusek *et al.*, 2019). Furthermore, research conducted by Carr *et al.* (2017) investigating the molecular pathologies associated with colorectal cancer (CRC) demonstrated that a substantial consumption of red meat has the potential to modify gene functions related to the phenotype of CpG island methylator(CIMP), BRAF, p53, or induce instability in chromosomes and microsatellites (Carr *et al.*, 2017). Consequently, this may contribute to an increased susceptibility to CRC.

DISCUSSION

The increasing rate of CRC worldwide is related to the changes in lifestyle, diet of people, and the consumption of refined food items. Understanding the correlation between red meat intake and CRC occurrence was the main focus of this study (Gharbi *et al.*, 2020; Mehta *et al.*, 2020; Deoula *et al.*, 2020; Saliba *et al.*, 2019). This review found that an increased intake of red meat and processed red meat can increase the probability of an increased risk of CRC (Chan *et al.*, 2011). This finding aligns with a previous meta-analysis that indicated a fifty gram regular consumption of processed red meat grows the CRC risk by 18%. This increase may be attributed to the presence of carcinogenic substances like nitroso compounds, heme iron, aromatic hydrocarbons, and heterocyclic amines, which are formed while cooking (Helmus *et al.*, 2013).

In terms of pre-diagnostic and post-diagnostic or postoperative dietary red meat and processed red meat intake, the selected studies showed no positive correlation with the pre-diagnostic red meat diet whereas postoperative

prognosis and survival rate moderately increased on low intake of red meat and processed meat (Carr *et al.*, 2017; Ward *et al.*, 2016). The connection between diet and the advancement of cancer is closely tied to the production of insulin. Diets excluding red meat are linked to reduced insulin production, while diets that are high in red meat, processed foods, and fast food make the insulin levels high. There exists a direct correlation between elevated levels of IGF-1 and the advancement of tumors (Fung *et al.*, 2001; Wu *et al.*, 2002).

In the current study, it was found that genotype of the person or gene polymorphism plays an important role for growing CRC (Andersen *et al.*, 2019; Kim *et al.*, 2019; Klusek *et al.*, 2019). For example, individuals with specific gene variations have impaired metabolism of carcinogenic nitroso compounds by cytochrome P450 enzymes (CYP2E1), resulting in an elevated CRC risk due to consuming red meat and processed meat in substantial amounts (Hayashi *et al.*, 1991; Kim *et al.*, 2019). Moreover, variations in the glutathione S-transferases gene family, which is responsible for the elimination of cancer-causing substances, have been associated with an elevated CRC risk when having an increased red meat intake. Single nucleotide polymorphism (i.e., transversion of adenine base to guanine base leads to change in base substitution), thereby enhances CRC risk from a higher intake of red meat (Klusek *et al.*, 2019). In recent years, many gene polymorphism (NAT2 G857A, MutS T1036A, XPC Lys939Gln, COX-2 rs20417) and molecular pathogens (chromosome and microsatellite instability, p53) were noticed to be related to red meat intake and development of CRC. Nevertheless, additional research is required to clearly define several subtypes of CRC, assess the influence of cooking techniques, and analyze the effect of different meat variations on CRC risk (Carr *et al.*, 2017; Ho *et al.*, 2014). Although this study has a large sample size, there are limitations because it cannot thoroughly investigate different types of meat, the way of processing and CRC subtypes. This gap makes the researchers understand that further research in order to gain a specific understanding of the correlation between the intake of red meat and an increased risk growth of CRC.

CONCLUSION

This study emphasizes the significant role of lifestyle and dietary changes in lowering the chance of getting colorectal cancer. This review's findings support the hypothesis that limiting red and processed meat diet could be a significant preventive approach against the initiation and progression of colorectal cancer. The findings presented the need for additional study to develop a thorough knowledge of the relationship between genetic variation and particular subtypes of colorectal cancer and red meat diet. Future research is crucial in determining the optimal amount of red meat consumption that is associated with a lower risk of cancer. This study has the potential to strengthen colorectal cancer prevention tactics and improve dietary recommendations.

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Declaration of Interests

None

Data Sharing

Data described in the manuscript will be made available upon request pending.

Authorship

The authors' responsibilities were as follows – Syed Mohammad Ehsanur Rahman developed the overall review plan; Hasan Mohammad Murshed and Md. Atikur Rahman devised and executed the literature search; Md. Ashikur Rahman and Ramachandran Chelliah performed the title/abstract as well as the full-text screening; Selvakumar Vijayalakshmi and Lingyue Shan performed the risk of bias, construction of data tables and summary and reporting of results; Deog-Hwan Oh, Shiddhartha Chakrabartty and Anindita Bhattacharjee reviewed and edited the manuscript; Syed Mohammad Ehsanur Rahman had primary responsibility for final content; all authors read and approved the final manuscript.

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