

Impact of Red Meat Intake to Colorectal Cancer Pathogenesis

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Abstract

Colorectal cancer is considered an important public health challenge since it ranks as the second most frequently diagnosed cancer and the fourth cause of cancer-related death worldwide. Influence of consumption of red meat on colorectal cancer risk is unclear. We attempted to provide an overview of published observational studies, meta-analysis and bi-directional case control studies from different geographical region to prove the association of red meat intake and colorectal cancer risk in this review article. Most published data indicated, with few exceptions, that, an increase of either the dose or the frequency of total red meat consumption is associated with a higher risk of colorectal cancer. In estimating cancer risk, confounding factor adjustments are made for age, sex, physical activity, smoking, alcohol consumption, BMI, family history of colorectal or other cancer etc.

Keywords: Red Meat, Colorectal Cancer, Correlation.

I. INTRODUCTION

According to the World Health Organization (WHO), "Cancer is a broad term used to refer to a variety of diseases that befall the body at any point. The other terminology used are Malignant tumors and Neoplasms. Cancer is characterized by the rapid creation of many abnormal cells, whose growth surpasses that of nearby normal tissues; these malignant cells can invade adjacent parts of the body and spread to other organs, a process known as metastasis. Metastasis-induced death is the major culprit of cancer mortality. According to Centers for Disease Control and Prevention cancer is defined as, "Cancer is a term for diseases in which abnormal cells divide without control and can invade other tissues. 'The blood and lymph systems are part of the body's system for disposing of dangerous materials, and this give cancer cells a chance of spreading to other areas of the body. They proposed this new definition of cancer: Cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection (1) Colorectal cancer (CRC) is among the leading causes of cancer related death burden worldwide. Due to the fast westernized diet and lifestyle of fast economic growing countries, CRC incidence and mortality rate is higher

there. Another reason is due to other non-modifiable factors, which are genetic and environmental factors. In high income countries CRC are largely from increased animal protein intake. Other factors that contribute to the CRC, collectively referred to as environmental factors, which are external to humaneome, include physical inactivity, smoking, alcohol, age, gender, family history of CRC, poor nutrition (++ fat content), obesity and other chronic diseases (2). According to GLOBOCAN 2018, colorectal cancer (CRC) accounted for 10.2% of all cancers and 9.2% of all cancer-related decedents. Highest incidence of colon and rectum cancer is reported in Europe, Australia, New Zealand, Northern America and Eastern Asia but lowest in Africa and Southern Asia. One of the results of this research is being colorectal cancer plays an important marker for socioeconomic development. (3)

In high-income countries, particularly in North America, Europe, and Australia, colorectal cancer rates have traditionally been higher due to factors such as aging populations, dietary patterns rich in red and processed meats, and lower levels of physical activity (4)

However, in recent years, several lower-income and middle-income nations have witnessed a disturbing rise in CRC incidence. Westernized lifestyles, urbanization, and changes in dietary habits, alongside improvements in healthcare systems which ultimately allow for better detection and reporting are the probable reasons of this shifting. (3,5)

Effective prevention, screening, and treatment strategies across different regions are immediately needed (6).

Colorectal cancer (CRC) is one of the most prevalent cancers globally with diet being a major contributing factor. Although CRC risk is influenced by genetics and other factors including physical activity and environmental exposures, the extent to which diet influences both the development and progression of the disease has been investigated in considerable depth. Intake of various dietary components, and other dietary factors associated with colorectal cancer.

➤ *Consumption of High Amounts of Red and Processed Meat-*

One of the other most consistent dietary factors associated with colorectal cancer is high total intake of red and processed meats. A large body of evidence has consistently found that the high intake of these meats, in fact, substantially raises the risk for CRC. In the case of red meats like beef, lamb and pork, they provide heme iron, which in turn could be harmful to your intestinal linings. Bacon, sausage, hot dogs, and other processed meats include preservatives called nitrates and nitrites that are transformed in the body into carcinogenic compounds.

Processed meats are Group 1 carcinogen (known to cause cancer), and red meats are Group 2A carcinogen (probable human carcinogen) according to World Health Organization (WHO), and International Agency for Research on Cancer (IARC) classification systems 1. Consumption of more than 50 grams of processed meat daily is associated with an about 18% increased risk of CRC.

➤ *Dietary Fiber and Protective Effects-*

Conversely, a diet rich in dietary fiber has been shown to have protective effects against colorectal cancer. Fiber, particularly from whole grains, fruits, and vegetables, is thought to reduce cancer risk through several mechanisms. It promotes regular bowel movements, which may help flush out potential carcinogens from the digestive tract. Additionally, fiber is fermented in the colon into short-chain fatty acids, which may exert anti-inflammatory effects and reduce cancer cell growth.

Those who have the highest intake of fiber per day in their diet, have a risk of developing CRC intel all but 15%. For example, foods that contain at least 25 — 30 grams of fiber per day reduce the risk of colorectal cancer, says the American Cancer Society (7).

➤ *Dietary fat and CRC risk—*

The association between dietary fat and CRC is multifaceted. Dietary saturated fats, which are primarily derived from animal products and high-fat processed foods, have been linked with an increased risk of CRC. Well these fats increase bile acid production may cause cancer.

On the contrary, high intakes of unsaturated fatty acids (e.g., from olive oil, nuts, and fatty fish) may protect against CRC. These fats are thought to be anti-inflammatory in nature and may reduce the growth of cancerous lesions in the colon (8).

➤ *Consuming Alcohol is Yet Another Dietary Characteristic Associated with an Increased Risk of Colorectal Cancer-*

Alcohol and Colorectal Cancer Research suggests that individuals with a heavy and regular alcohol intake experience an increased risk of CRC, specifically if they have a family history of the disease. Alcohol is also known to damage the cell in the colon and initiate the mutations that begin the cancerous processes.

This risk rises with increased alcohol intake, demonstrating a 7% higher CRC risk per additional drink consumed per day according to some studies (9). According to the American Cancer Society, limiting alcohol to no more than one drink per day for women and two drinks per day for men will lower cancer risk.

➤ *The Mediterranean Diet and Cancer Prevention-*

The Mediterranean diet is linked with lower colorectal cancer risk. This diet is high in antioxidants, polyphenols, and many other anti-inflammatory and anticancer bioactive components. The attractiveness of the potential protective effects of Mediterranean-style dietary components on CRC has been confirmed by several studies whereby lower CRC risk is documented among those eating a Mediterranean-type diet compared to other diets, likely mediated through healthy fat sources, fiber and phytonutrients (10).

In this article, we re-evaluate the association of red meat intake with colorectal cancer risk. The condition itself is not an independent factor which can cause colorectal cancer, but is one of the most important single factors which can eventually lead to colorectal cancer.

II. METHOD

In this review article we have tried to cover a variety of geographical regions e.g., United states, Canada, Japan, India, Bangladesh, China, Australia, etc. and make an association of red meat intake and the occurrence of colorectal cancer. We have included prospective cohort studies , meta analyses and case controlled studies. We used to search using “red meat and colorectal cancer”, “association of red meat and colorectal cancer risk”, “red meat and colorectal cancer in women”, “red meat and colorectal cancer in men”. We did not mention any timeline for articles collection. We

analyze both types of articles which include positive and negative association between red meat and colorectal cancer.

In this review, we used 'red meat' term which include beef, pork and mutton or lamb. Here we analyzed univariate or multivariate relative risk at 95% confidence interval and p value for trend was analyzed. Other attributable factors are adjusted for example age, body mass index (BMI), sex, physical activity, tobacco smoking pattern, alcohol consumption, education level, income, social class, total nutrients intake, family history of colorectal cancer, hormone therapy etc.

CRC =Colorectal cancer, CC=colon cancer, DTC=distal colon cancer, RC=rectum cancer, RR=relative risk, CI= confidence interval.

III. RESULTS

➤ *Red Meat and Colorectal Cancer in Women:*

Willett *et al.* (1990) found a significant association of red meat intake and colorectal cancer (CRC) risk in both consumption frequency and serving amount in women by conducting a cohort study of 88751 women of 34-59 years in United States. The age-adjusted relative risk (RR) for colon cancer in women who consumed red meat as a main dish ≥ 1 time per day was 2.49 (95% CI: 1.24–5.03; $p = 0.01$). Similarly, for those in the highest quintile of red meat consumption ($\geq 134\text{g/day}$), the age-adjusted RR for colon cancer was 1.77 (95% CI: 1.09–2.88; $p = 0.03$). Additionally, the ratio of red meat to chicken and fish was positively associated with CRC risk, with an age-adjusted RR of 2.49 (95% CI: 1.50–4.13; $p = 0.0005$) for a ratio ≥ 5.2 (8)

Bostick *et al.*, (1994) conducted a prospective cohort study in the United States and found no significant association between red meat intake and CRC. After adjusting other confounding variables (age, dietary intake, height), the relative risk (RR) of colon cancer 1.04 (95% CI: 0.62–1.76; $p = 0.78$) for highest consumption of red meat vs lowest consumption of red meat (11).

Kato *et al.* (1997) a prospective cohort study of 14727 women from New York and Florida in the United States to investigate the role of diet in CRC. For women, they observed a positive association between red meat intake and CRC, which was not statistically significant. Relative risk (RR) of colorectal cancer for highest quintile vs lowest quintile red meat consumption multivariate-adjusted RR 1.23 (95% CI: 0.68–2.22; p for trend = 0.545) Potential confounding variables were adjusted for relative risk estimation, including age, total calorie intake, education level, and place of study (12).

Flood *et al.* (2003) conducted a prospective cohort study Red meat was associated positively but non-significant with Colorectal cancer risk (CRC) in women, in United states,(2003) based on proportional hazard ratio. Colorectal cancer (highest quintile intake of red

meat vs lowest quintile intake of red meat: adjusted energy RR = 1.10 (95% CI: 0.83–1.45; $p = 0.39$), food (energy- and total meat) adjusted RR for red meat = 1.04 (95% CI: 0.77–1.41; $p = 0.73$) The current study could not refute the absence of an association between red meat intake and CRC, but at present we cannot dismiss the idea that such a link may not exist (13).

Lin *et al.* (2004) A population based cohort study of 37547 women of United states revealed a statistically significant though borderline positive association between red meat consumption and risk for colorectal cancer in women. Instead of calculating red meat consumption on a serving basis, the study measured how much red meat contributed to the total intake of animal fat. The multivariate relative risk (RR) for CRC for red meat consumption at the highest quintile of intake was 0.66 (95% CI: 0.40–1.09; $p = 0.05$), after adjustment for age, random treatment, BMI, family history of CRC, previous history of colorectal polyps, physical activity, smoking, alcohol, post menopausal hormone therapy, and total energy intake (14).

Larson *et al.* (2005) found a statistically significant positive correlation between CRC and the consumption of red meat of Swedish women aged 40–75 years. They found positive associations between red meat intake and risk for DTC, but no significant associations for PCC or RC. The multivariate RR for CRC was 1.32 (95% CI: 1.03–1.68; $p = 0.03$)z and for RC was 1.28 (95% CI: 0.83–1.98; $p = 0.32$) for intake of $\geq 94\text{g}$ red meat vs $< 50\text{gm}$ per day. Values were further adjusted for age, BMI, education, total energy intake, alcohol consumption as well as intake of saturated fat, calcium, folate, fruits, vegetables, and whole grains (15).

Lee *et al.* (2009) conducted a prospective cohort study on 40-70 years aged Chinese women and found no positive association between red meat consumption and colorectal cancer CRC risk.

After adjusting for animal food intake, the relative risk (RR) for CRC was 0.8 (95% CI: 0.6–1.1; $p = 0.53$), for colon cancer (CC) the RR was 0.9 (95% CI: 0.6–1.5; $p = 0.31$), and for those consuming $\geq 67\text{g}$ of red meat per day, the RR was 0.6 (95% CI: 0.3–1.1; $p = 0.79$) (16)

Table 1 Summary of Included Studies on Red Meat Consumption and Colorectal Cancer in Women

Study Location	Study Time	Sample Size	Age (Years)	Analytical Comparison	Cancer Location	Relative risk (95% CI)	p value	References
United States	1986-1990	35,215	55-69	Servings per week <4.0 vs >11.0 gm	Colon	1.04 (0.62 - 1.76)	0.78	Bostick <i>et al.</i> 1994
United States	1987-1998	45,496	<50-≥80	Quantile of total red meat intake <26.5 vs ≥77.8gm	Colorectal	1.04(0.77-1.41)	0.73	Flood <i>et al.</i> 2003
New Work, Florida	1985-1994	14,727	34-65	Highest vs lowest quintile of red meat intake	Colorectal	1.23 (0.68-2.22)	0.545	Kato <i>et al.</i> 1997
United States	1993-2003	37,547	≥45	Highest vs lowest quintile of red meat intake	Colorectal	0.66 (0.40-1.09)	0.05	Lin <i>et al.</i> 2004
Central Sweden	1987-1990	61,433	40-75	Highest vs lowest quintile of red meat intake	Colorectal	1.32(1.03-1.68)	0.03	Larson <i>et al.</i> 2005
United States	1980-1986	88751	34-59	Highest vs lowest quintile of red meat intake	Colon	1.77(1.09-2.88)	0.03	Willett <i>et al.</i> 1990
China	1997-2000	73224	40-70	Highest vs lowest quintile of red meat intake	Colorectal	0.8(0.6-1.1)	0.53	Lee <i>et al.</i> 2009

➤ *Red Meat and Colorectal Cancer in Men:*

Giovannucci et al. A cohort study conducted on 40–75 years old men from the US for ages between 1986 to 1994 found a significant association between red meat consumption and CRC (6). The highest category of red meat intake was associated with increased risk of four different types of CRC, and had a relative risk (RR) of 1.71 (95% CI: 1.15-2.55; p=0.005). Additionally, men with red meat as the main dish five or more times per week had a significantly greater risk of CRC (RR = 3.57; 95% CI: 1.58–8.06; p = 0.01). Clearly, both the amount and frequency of eating red meat were strongly correlated with elevated CRC risk. In addition, an increased ratio of red meat intake to chicken or fish consumption was also significantly related to higher CRC risk (RR = 1.83; 95% CI: 1.17–2.85; p = 0.015) (17)

Chen et al. Source: A Prospective Case Control Study of Men 40-84 Years Old, United States. A positive association which bordered on statistical significance was documented in those ≥60 yr from red meat consumption and CRC with an RR of CRC 2.15 (95% CI: 0.95–4.86; p = 0.06) for >1+/day red meat. In particular, the RR for CRC with red meat consumption >1+/day was 3.70 (95% CI: 1.08–12.7; p = 0.03) for NAT1 rapid acetylators and 4.10 (95% CI: 0.96–17.5; p = 0.05) for NAT2 rapid acetylators. For the 43 individuals identified as rapid acetylators of both NAT1 and NAT2 the RR increased substantially to 5.82 (95% CI: 1.11–30.6; p = 0.02). Results: For slow acetylators of NAT1, no associations were seen (18).

Hsing et al. In addition, Luo et al., (1998) found a non-significant positive association with CRC and red meat consumption in a US cohort of white men who were aged >35 years. Adjusted for age, alcohol, and total energy intake, and cigarette smoking in red meat consumers ≥60 times per month, the multivariate RR for colon cancer was 1.8 (95% CI: 0.8–4.4; p = 0.3) 12. Similarly, the RR for colon and rectal cancer combined was 1.9 (95% CI: 0.9–4.3; p = 0.1), and the RR However, these results were not statistically significant and thus require further investigation (19).

Pietinen et al.(1999) A positive association between the risk of CRC and red meat intake was found in a cohort study conducted among Finnish male smokers aged 50–69 at the time of dietary assessment, but the association was not statistically significant (Ronn 1999). The corresponding multivariate RRs of CRC for the highest median intake group in comparison to the lowest were 0.9 (95% CI: 0.6–1.3; p = 0.69) for the total DM and red meat (80 g/person/day), 1.0 (95% CI: 0.7–1.5; p = 0.82) for processed meat (0.4 g/person/day), and 0.9 (95% CI: 0.6–1.2; p = 0.20) for all meat data sets (203 g/day of red meat, consumed on non-red meat days). That is, this experience is different from previous studies in that there was the positive relationship between the consumption of red meat and CRC (8,17). As red meat in this cohort was typically cooked using low-temperature methods and served within a mixed-dish rather than as a centerpiece (20), we believe that differences in cooking methods may contribute to the null association found in this cohort.

Table 2 Summary of Studies on Red Meat Consumption and Colorectal Cancer in Men

Study Location	Study Time	Sample Size	Age (Years)	Analytical Comparison	Cancer Location	Relative risk (95% CI)	p value	References
United States	1982-1995	22071	40-84	Red meat intake <0.5 vs 1+/day	Colorectal	1.17(0.68-2.02)	0.59	Chen et al.1998
United States	1986-1992	47949	40-75	Red meat intake 18.5 vs 129.5 g/day	Colon	1.71(1.15-2.55)	0.005	Giovannucci et al. 1994
United States	1966-1986	17,633	>35	Red meat intake frequency <15 vs 60+ times/month	Colon	1.8 (0.8–4.4)	0.3	Hsing et al. 1998
Finland	1987-1995	27111	50-69	Total red meat intake 80 vs 203g	Colon	1.1(0.7-1.7)	0.73	Pietinen et al.1999

➤ *Red Meat and Colorectal Cancer in Men and Women:*

Fraser (1999): A cohort study of Seventh-day Adventists ≥ 25 years who had high vegetable French fries intake and a general abstained from alcohol and tobacco Red meat consumption was extensively related to the risk of colon cancer. The group of participants who consumed red meat ≥ 1 /week and white meat < 1 /week had a RR for colon cancer of 1.86 (CI 95%: 1.15–3.02; p-trend = 0.01). Moreover, vegetarians had a substantially lower risk of colon cancer than non-vegetarians (RR adjusted for age and sex was 1.88 (95% CI: 1.24–2.87; p-trend = 0.0032) (21).

In a Finnish cohort study by Jarvinen et al. (2001) In further support of this lack of association, the large population-based cohort study by Parker (2001), which studied both men and women, did not find a significant association between red meat consumption and CRC risk. Compared with the lowest quintile of red meat intake Level 5, multivariate adjusted relative risk RR for CRC was 1.50 95% CI: 0.77–2.94 in the highest quintile of intake Level 1 III. Data from the respective site-specific analyses also demonstrated an RR of 1.34 (95% CI: 0.57–3.15) for CC and 1.82 (95% CI: 0.60–5.52) for RC, reflecting similar lack of significant associations (22)

Norat et al (2003) conducted a meta-analysis of epidemiological studies found a positive association of CRC with red meat (Smith-Warner et al. The analysed studies of the highest vs lowest levels of red meat consumption showed a pooled risk for CRC of 1.35 (95% CI: 1.21–1.51; $p < 0.001$). The association was no longer statistically significant in subgroup analyses, and the reverse was seen for case-control studies (RR: 1.36; 95% CI: 1.17–1.59; $p < 0.001$). The association was somewhat stronger among men (RR = 1.40; 95% CI: 1.20–1.64; $p = 0.64$) than among women (RR = 1.13; 95% CI: 0.85–1.50; $p = 0.03$) with statistical significance varying accordingly. Further, positive relations between red meat consumption and CRC risk were significant in both U.S. and Europe based studies, but the positive association was stronger in U.S. than in Europe based studies ($p = 0.002$) (23)

Chiu et al. (2003) performed a population-based case-control study on men and women in Shanghai, China, ages 30–74 years and found a statistically significant positive association between red meat and risk of colorectal cancer (CRC). The association was

particularly striking for colon cancer and statistically significant in men. Although the adjusted relative risk (RR) for colon cancer among those in the highest quintile of red meat intake was 1.5 for both sexes combined (men: RR = 1.5, 95% CI: 1.0 to 2.1, $p = 0.03$; women: RR = 1.5, 95% CI: 1.0 to 2.2, $p = 0.08$), the association was statistically significant in men only. Age, total energy intake, education, BMI, income, and physical activity was adjusted in relative risk estimates (24)

Kojima et al. A study for example, (2004) performed a prospective cohort study of meat consumption and colorectal cancer (CRC) risk of 45,181 men and 62,643 women ages 40–79 years in Japan. In the current study, meat intake including red meat and processed accounted for the upper limit of CRC in obese men, but no significant positive association of red meat intake with CRC risk was found (25)

English et al. (2004) investigated the association between red meat consumption and CRC in a cohort of Australian residents aged 27 to 75 years. It found a non significant positive association between intake of fresh red meat and risk of rectal cancer. The relative risk (RR) of rectal cancer for the highest versus lowest quintile of fresh red meat consumption was 2.3 (95% CI: 1.2–4.2; $p = 0.07$) when controlled for multiple variables including sex, country of birth, and energy, fat and cereal products intake. The adjusted RR for colon cancer was 1.4 (95 percent CI, 1.0 to 1.9; $p = 0.2$) and for total CRC, it was 1.1 (95 percent CI, 0.7 to 1.6; $p = 0.9$), suggesting that the association was more pronounced for rectal versus colon cancer. Higher red meat to white meat ratio accounted also contributes to CRC by RR 1.3 [95% CI: 1.0 – 1.7, $p=0.05$] (26)

Norat et al. (2005) A multicenter study assessed the relationship between meat consumption and colorectal cancer (CRC) risk among men and women aged 35–70 years from 10 European countries. The multivariate relative risk (RR) for red meat consumption and colorectal cancer was 1.28 (95% CI: 1.10–1.64; $p = 0.008$) after adjustment for age, sex and energy from fat and non-fat sources. There was a significant association found between CRC incidence and intake of red meat. (27)

Chao et al. (2005) conducted a prospective cohort study among U.S. men and women aged 50–74 years,

reporting a marginal but statistically significant positive association between red meat consumption and colorectal cancer (CRC) risk. Individuals in the highest quintile of red meat intake exhibited a 15% increased risk of colon cancer compared to those in the lowest quintile (RR = 1.15, 95% CI: 0.90–1.46, $p = 0.04$). Furthermore, a significantly elevated CRC risk was observed among participants with the highest quintile ratio of red meat to poultry and fish consumption (RR = 1.27, 95% CI: 1.06–1.53, $p < 0.001$). This association appeared stronger in women (RR = 1.37, 95% CI: 1.06–1.76, $p < 0.001$) than in men (RR = 1.18, 95% CI: 0.90–1.54, $p = 0.03$). Relative risk estimates were adjusted for age, total energy intake, education level, BMI, smoking, physical activity, use of multivitamins or aspirin, and hormone therapy, as well as relevant dietary factors(28)

Brink et al. (2005) conducted a case-cohort study in the Netherlands, which found a statistically non-significant positive association between beef consumption and colorectal cancer (CRC). After adjusting for age, sex, body mass index (BMI), smoking status, energy intake, and family history of CRC, the relative risk (RR) for colon cancer associated with each additional 15 grams of beef consumed per day was 1.28 (95% CI: 0.96–1.72, $p = 0.06$) (29)

Oba et al. (2006) conducted a community-based cohort study in Japan to evaluate the association between red meat consumption and colorectal cancer (CRC) risk in both men and women. After adjusting for height, body mass index (BMI), smoking, alcohol consumption, and physical activity, red meat intake was not significantly associated with CRC in either sex. The adjusted relative risk was 1.03 (95% CI: 0.64–1.66; $p = 0.86$) for men and 0.79 (95% CI: 0.49–1.28; $p = 0.20$) for women (30)

Kimura et al. Another hospital-based case-control study in Japan that included 782 cases of colorectal cancer (CRC) was published by (2007). No significant dose response with red-meat intake and CRC was demonstrated. Participants in the highest quintile of red meat intake had 1.14 (95% CI = 0.90-1.54) times the CRC risk compared to those in the lowest quintile, and this association was not statistically significant ($p=0.97$). The absence of a strong correlation might be caused by the relatively low level of average red meat consumption in their population (mean: 50 g/day, 31)

Butler et al. Zhao et al (2008) studied dietary patterns and risk of colorectal cancer among the Singapore Chinese Health Study population, a prospective cohort study of men and women aged 45-74 years residing in public housing estates in Singapore. Nonetheless, they did not observe any significant relationship between red meat and CRC risk. The models for relative risk (RR) estimates included age- and sex for rate in model 1, with additional adjustment for diabetes (yes/no), smoking habits (current/past/never smoker), body mass index, alcohol consumption, physical activity and family history of CRC among first-degree relatives; and total energy intake was reported. The RR (95% CI)

of CRC comparing the highest quintile with the lowest for red meat was 1.01 (0.82–1.26; p -value = 0.60). This is in contrast to previously reported data, which showed a favorable association with CRC for red meat intake (8, 17). The investigators speculated that variations in cooking methods and the overall dietary pattern could account for the discrepancy. On the other hand, grilling red meat using an open flame (a frequent practice in Western diets) can result in potentially poisonous and carcinogenic compounds formation; this is not common practice in their diets (32).The Asian diet type is very rich in fruits and vegetables' consumption as well as in deep frying techniques.

In a hospital-based case-control study conducted in Kerala, India, Nayak et al. (2009) identified a significant positive association between beef consumption and colorectal cancer (CRC) risk. Both univariate and multivariate analyses exhibited increased risk associated with higher beef intake. In univariate analysis, individuals who consume the highest quintile of beef had a relative risk (RR) of CRC 5.89 (95% CI: 2.80–12.50) compared to those in the lowest quintile. In multivariate analysis, adjusting for potential confounders, consuming beef more than once per week was associated with a markedly increased risk of CRC compared to non-consumers (RR = 4.25, 95% CI: 2.02–8.94, $p = 0.00$) (33)

Cross et al. A large prospective cohort study of U.S. men and women age 50–71 years (2009) reported a significant positive association of red meat with colorectal cancer (CRO), however, results were statistically significant ($p<0.05$). Compared with individuals in the lowest quintile, those in the highest quintile of red meat intake had a 24% higher CRC risk (multivariate RR = 1.24; 95% CI: 1.09–1.42, $p < 0.001$). The link was especially strong for colon cancer (RR = 1.21, 95% CI: 1.03–1.41, $p < 0.001$), but there was also a significant association with rectal cancer (RR = 1.35, 95% CI: 1.03–1.76, $p = 0.024$). Relative risk estimates were adjusted for sex, education, BMI, smoking, total energy intake, dietary fiber, and calcium intake (4).

Chan et al. Further significant positive associations between the consumption of red meat and the risk of colorectal cancer were found (CRC) (2011). The highest versus lowest level of red meat intake were associated with a relative risk (RR) for any CRC of 1.10 (95% CI: 1.00–1.21; $p = 0.04$), and for CC, the RR was 1.18 (95% CI: 1.04–1.35; $p = 0.01$). Red meat was ranked as the most important dietary exposure for CRC (RR = 1.23; 95% CI: 1.08--1.40; $p = 0.00$) and CC (RR = 1.29; 95% CI: 1.08--1.54; $p = 0.01$) jointly, after controlling for gender, ancestry, study site, body mass index, smoking status, alcohol consumption, and dietary factors within individual studies, but this ranking was observed only human mammary tumor in European but not in non-European and population samples. Moreover, dose-response meta-analysis has found that compared with increase in red meat consumption of 100 g/day, significantly associated with increase CRC risk (RR = 1.17; 95%CI: 1.05–1.31; $p = 0.01$) (34).

Takachi et al. A promise cohort study of 45–74 aged Japanese male/female population in 2011 (n=6586) found risks of colon cancer with red meat consumption. In multivariate analysis, women in the highest quintile of red meat consumption had a significantly increased risk of colon cancer (RR = 1.48, 95% CI: 1.01–2.17, $p = 0.03$), but the corresponding association for men was not statistically significant (RR = 1.27, 95% CI: 0.93–1.74, $p = 0.15$). Additionally, for individual meat type, a strong positive association was observed for high beef and pork consumption and colon cancer in women. For colon cancer, the relative risk for beef in women was 1.62 (95% CI: 1.12–2.34, $p = 0.04$) and for pork was 1.42 (95% CI: 0.99–2.04, $p = 0.05$). All risk estimates were adjusted for age, Public Health Center area, BMI, smoking, alcohol consumption, physical activity, diabetes history and medication use, cancer screening participation, and dietary intake variables (total energy and calcium, vitamin D, vitamin B₆, folate, dietary fiber, and dried and salted fish) (35)

Ferrucci et al. (2012) reported a marginal but statistically significant positive association between red meat consumption and the risk of colorectal adenoma. The study assessed multivariate relative risk (RR) for incident colorectal adenomas, adjusting for a comprehensive set of covariates, including age, study center, sex, ethnicity, education, family history of CRC, BMI, use of NSAIDs, physical activity, smoking status, alcohol intake, calcium intake, dietary fiber intake, and total energy intake. For individuals in the highest category of red meat consumption, the adjusted relative risks were as follows: distal adenoma, RR = 1.22 (95% CI: 0.98–1.52, $p = 0.12$); colon adenoma, RR = 1.22 (95% CI: 0.95–1.56, $p = 0.12$); and rectal adenoma, RR = 1.33 (95% CI: 0.87–2.04, $p = 0.24$). Although these findings did not reach statistical significance, they suggest a potential trend toward increased risk. Notably, the method of meat preparation also influenced adenoma risk. Participants with the highest intake of grilled red meat exhibited a significantly increased risk of rectal adenoma compared to those in the lowest intake category (RR = 1.56, 95% CI: 1.04–2.36, $p = 0.05$) (36)

Bernstein et al. (2015) conducted a cohort study in the United States, which reported a statistically non-significant positive association between red meat intake and colorectal cancer (CRC). Notably, processed red meat showed a statistically significant association with CRC, whereas no significant association was found for total red meat or unprocessed red meat. In multivariate analysis, each additional serving per day of processed red meat was associated with a 15% increased risk of CRC (RR = 1.15, 95% CI: 1.01–1.32, $p = 0.03$), while the relative risk for total red meat was 1.06 (95% CI: 0.97–1.16, $p = 0.19$). Unprocessed red meat significantly elevated the proximal colon cancer risk as RR 1.25 (95% CI: 1.06–1.47, $p = 0.008$). The relative risk estimates were adjusted for a range of factors, including age, family history of CRC, prior lower gastrointestinal endoscopy,

smoking, BMI, physical activity, use of multivitamins, aspirin or NSAIDs, alcohol consumption, energy intake, and intake of calcium, folate, vitamins, and fiber (37)

Iswarya et al. (2016) conducted a case-control study involving Indian men and women aged <40 to ≥ 70 years, investigating the association between red meat consumption and colorectal cancer (CRC). A statistically significant positive association was observed. In the univariate model, individuals who consumed mutton more than 2–3 times/month had a markedly increased risk of CRC compared to those who rarely or never consumed mutton (RR = 7.4, 95% CI: 2.93–3.45, $p = 0.001$). After adjusting for dietary habits, smoking, alcohol consumption, and physical activity in the multivariate model, the risk remained significantly increased (RR = 5.41, 95% CI: 1.55–19.05, $p = 0.008$) (38)

Wada et al. Methods: A prospective cohort study in Japan among both genders 35 years and older (2017). Consuming high levels of red meat was associated with a 1.44-fold increase (95% CI: 1.10–1.89, $p = 0.009$) in risk for colorectal cancer (CRC) in men with no significant association noted for women (RR = 1.07, 95% CI: 0.79–1.46, $p = 0.98$). Among men, the association between red meat consumption and CRC risk was much stronger when considering rectal cancer (RR = 1.65; 95% CI: 1.06–2.58; $p = 0.023$; Table (1C) but not among women (RR = 0.95; 95% CI: 0.54–1.68; $p = 0.97$; Table (1D) These associations persisted after controlling for potential confounders including age, height, BMI, physical activity, smoking status, education level, history of aspirin use, alcohol consumption, menopausal status, total fiber intake, calcium and vitamin D intake, and total energy intake (39).

Luo et al. Guo et al., (2019) conducted a case-control study in China among 2,138 cases of colorectal cancer (CRC) patients and 2,144 matched controls in both men and women. There was a significant positive association between CRC risk and iron intake from red meat. Compared with those in the lowest quartile, the highest quartile of iron intake from red meat was associated with a significant increase in risk of CRC (RR = 1.83, 95% CI: 1.49–2.24, $p = 0.001$). In particular, a high intake of red meat was positively associated with CRC among 42.7% of younger (20–50-year old) patients versus 21.3% of older (>50-year old) patients (43).

De Zoysa et al. (2024) conducted a hospital-based case-control study in Sri Lanka, which found a statistically significant association between red meat consumption and colorectal cancer (CRC). After adjusting for age, educational level, ethnicity, body weight, physical activity, and average daily sleep, the relative risk (RR) for CRC associated with beef consumption was 1.76 (95% CI: 1.12–2.78, $p = 0.015$) (44)

Table 3 Summary of Studies on Red Meat Consumption and Colorectal Cancer in Both Gender

Study Location	Study Time	Sample Size	Age (Years)	Analytical Comparison	Cancer Location	Relative risk (95% CI)	p value	References
Singapore	1993-1998	63257	45-74	Quartiles of red meat intake 4 vs 1	Colorectal	1.01 (0.82 – 1.26)	0.6	Butler,et,al 2008
California, USA	1976–1988	59,801	≥25	Vegetarians vs Non vegetarians	Colon	1.88(1.24-2.87)	0.0032	Fraser et al 1999
Finland	1966–1972	62440	-	Quartiles of red meat intake 4 vs 1	colorectal	1.50 (0.77–2.94)	NR	Jarvinen et al. 2001
Europe	1992–1998	478,040	35–70	Quartiles of red meat intake 10 vs 80+g/day	Colorectal	1.28(1.10-1.64)	0.008	Norat et al.2005
United States	1993-2001	17,072	55-74	Quartiles of red meat intake 4 vs 1	Distal adenoma	1.22(0.98-1.22)	0.12	Ferrucci et al 2012
Kerala, India	2003-2006	Case-108 Control-324	18-35	Quartiles of red meat intake 4 vs 1	Colorectal	4.25 (2.02–8.94)	0	Nayak et al 2009
Japan	1995-2006	758,116	45-74	Quartiles of red meat intake 4 vs 1	Colon	1.27 (0.93, 1.74) (men) 1.48 (1.01, 2.17)(women)	0.15 (men) 0.03 (women)	Takachi et al 2011
United States	1992-2001	148,610	50-74	Quartiles of red meat intake 5 vs 1	Colon	1.15 (0.90-1.46)	0.04	Chao et al 2005
China	1990-1993	Case-932 Control-1552	30-74	Quartiles of red meat intake 4 vs 1	Colon	1.5 (1.0–2.1) (men) 1.5 (1.0-2.2) (women)	0.03 (men) 0.08 (women)	Chiu et al 2003
United States	1992-1993	300,948	50-71	Quartiles of red meat intake 5 vs 1	Colorectal	1.24 (1.09-1.42)	<0.001	Cross et al 2010
India	NR	Case-94 Control-94	<40- ≥70	Tertile 3 vs 1 red meat intake	Colorectal	5.41 (1.55-19.05)	0.008	Iswarya et al 2016
China	2010-2017	Case-2138 Control-2144	30–75	Quintile 4 vs 1 intake of iron from red meat	Colorectal	1.83 (1.49, 2.24)	<0.001	Luo et al 2019
Japan	1992-2008	30,331	≥35	Quartiles of red meat intake 4 vs 1	Colorectal	1.44 1.10–1.89	0.009	Wada et al 2017
Sri Lanka	NR	Case-200 Control-200	<50->70	Bee consumption	Colorectal	1.76 1.12 - 2.78	0.015	De Zoysa et al 2024
United States	1986-2010	51,529 (men) 121,700 (women)	40–75 (men) 30–55 (women)	Increase 1 serving of red meat/day	Colorectal	1.06 (0.97–1.16)	0.19	Bernstein et al. 2015
United Kingdom	2006-2010	475 581	40–69	50g/day red meat intake	Colorectal	1.18 (1.00-1.39)	0.049	Bradbury et al. 2020
Netherlands	1994-2001	120,852	55 – 69	Quartiles of red meat intake 4 vs 1	Colorectal	1.28 (0.96 – 1.72)	0.06	Brink et al 2005
Japan	2000-2003	Case-782 Control-793	20–74	Quartiles of red meat intake 5 vs 1	Colorectal	1.14 (0.81–1.62)	0.97	Kimura et al 2007

Japan	1988-1990	107,824	40-79	Beef and pork consumption highest vs lowest	Colon	1.46 (0.74-2.86) (beef) 1.14 (0.61-2.14) (pork)	0.96 (beef) 0.31 (pork)	Kojima et al. 2004
Japan	1992-2000	30,221	≥35	Red meat intake highest vs lowest	Colon	1.03 (0.64-1.66) (men) 0.79 (0.49-1.28) (women)	0.86 (men) 0.20 (women)	Oba et al. 2006
Goa, India	2014-2016	Case-110 Control-110	NR	Consuming red meat yes or no	Colorectal	2.52 (95% CI: 1.38-4.58)	0.0009	Ferreira et al. 2021
Melbourne, Australia	1990-1994	37,112	40-69	Quartiles of red meat intake 4 vs 1	Colorectal	1.4 (1.0 - 1.9)	0.2	English et al. 2004

IV. DISCUSSION

The association between red meat consumption has been studied extensively from the past decade with a variety of epidemiological evidence which include large prospective cohort studies, nested case control studies and meta-analyses. With a very few exceptions, other studies consistently suggested the positive correlation

Heterocyclic amines and polycyclic aromatic hydrocarbons- other pro-cancer factors in red meat were heterocyclic amines and polycyclic aromatic hydrocarbons due to cooking red meat at high temperature or in open flame. Several studies showed that high consumption of heterocyclic amines and polycyclic aromatic hydrocarbons were related to increased colorectal cancer risk.

N-nitroso compounds- Different nitroso compounds were formed in red meat by nitrosation of organic compounds. Among them some of were carcinogens and can cause mutation in the DNA.

Gut microbiota modulation- Gut microbiota composition may alter by red meat consumption supporting the growth of bacteria that convert dietary components into pro-carcinogenic metabolites which were related to both onset and progression of colorectal cancer.

Rather than any single mechanism, combination of multiple from above mechanisms were responsible for the carcinogenesis by red meat consumption.

After reviewing the epidemiological studies, majority of data supports the statistically significant positive association between red meat consumption and colorectal cancer risk in women (8,14,15), men (18,19) and in both gender (4,21,23,24,27,33-44). A few of them suggested modest or non-significant positive associations (12,13,20,26,29), which can be explained considering the potential cofounding variable. Some of data suggested no association between red meat consumption and CRC (11,16,22,25,30-32).

between red meat consumption and colorectal cancer. A dose response relationship has been also established. International Agency for Research on Cancer (IARC) classified red meat as group 2A carcinogen that refers to probably carcinogenic to humans. Several mechanisms were proposed at different times for this relationship (45-49)

Positive association has been found among both men and women, but statistical significance has reached among women(50). In some cases, no statistical significance has been found among men and women, though the risk has been higher in men (51). Finland, Germany, Italy, Spain and the Netherlands showed positive correlations between the red meat consumption and colorectal cancer among men; positive correlations were observed in women of Finland, Germany, Italy, Spain and Sweden(52)

By geography, North America showed more positive association of red meat and colorectal cancer than Europe. In Europe, colorectal cancer incidence has been rising since the last decade due to increased protein intake from meat source (52). For Asia, no statistically significant difference has been observed for colorectal cancer regarding the red meat consumption. This can be happened due to a variety of reasons eg. low sample size, overall low meat intake, cooking method etc. By conducting larger studies, conclusion can be made (50,51)

Consideration of confounding factor has much importance in all of the studies as colorectal cancer has also been associated with age, gender, dietary pattern, physical activity, smoking, alcohol consumption, family history of colorectal or other cancer, education, BMI, use of other medications etc.

Table 4 Association Pattern of CRC with Statistical Significance

Association pattern	Gender	Reference	Remarks
Positive	Women	Willett et al. (1990)	
		Kato et al. (1997)	Statistically non significant
		Flood et al. (2003)	Statistically non significant
		Lin et al. (2004)	
		Larson et al. (2005)	
	Men	Chen et al. (1998)	
		Hsing et al. (1998)	
		Pietinen et al. (1999)	Statistically non significant
	Both	Fraser (1999)	
		Norat et al. (2002)	
		Chiu et al. (2003)	Statistically significant for men
		English et al. (2004)	Statistically non significant
		Norat et al. (2005)	
		Chao et al. (2005)	Statistical significance stronger among women than men
		Brink et al. (2005)	Statistically non significant
		Nayak et al. (2009)	
		Cross et al. (2010)	
		Chan et al. (2011)	
		Takachi et al. (2011)	Statistically significant for women
		Ferrucci et al. (2012)	Statistically significant (colorectal adenoma)
		Bernstein et al. (2015)	Statistically significant (proximal colon cancer)
		Iswarya et al. (2016)	
		Wada et al. (2017)	Statistically significant for men
		Luo et al. (2019)	
Bradbury et al. (2020)			
Ferreira et al. (2021)			
Rahman et al. (2024)			
De Zoysa et al. (2024)			

V. CONCLUSION

The present review represents that there is a positive association of red meat intake and colorectal cancer incidence, though the risk depend on other contributing factors. By minimizing red meat intake, colorectal cancer risk can be minimized. Red meat a enriched source of iron ad protein but there is a lot of healthy alternative of these nutrients. White meat and egg can be good source of protein while salmon, tuna, beetroot, spinach, beans etc are good choices for iron. We found that people who are consuming the highest quintile of red meat in a certain time are at high risk, so eventually by reducing the frequency as well as amount of red meat, colorectal cancer incidence can be minimized.

➤ List of abbreviations:

- CRC= colorectal cancer,
- CC=colorectal cancer,
- DTC=distal colon cancer
- RC= rectum cancer,
- RR=relative risk and
- CI= confidence interval.

➤ Declarations:

- *Ethics Approval and consent to participate- Not applicable*

- *Clinical Trial Number- Not applicable*
- *Consent for publication- Not applicable*
- *Availability of data and materials- Not applicable*
- *Competing interest: The authors declare that they have no competing interests.*
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