

Excessive consumption of red or processed meat and risk of colon cancer

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ABSTRACT

Besides skin cancers, colon cancer is the most common type of cancer in developed countries. Cancer incidence in immigrants to developed countries is also very high, indicating that lifestyle or environmental factors likely play a large role.

Many epidemiological studies have shown a strong association between red meat or processed meats, with increased animal fat and protein consumption being strongly linked. Meta-analysis studies have shown that colon cancer risk is increased by 20–30% in people with high red and processed meat consumption.

Meat processing involves alteration by curing, fermentation, salting, and smoking. High cooking temperatures result in the production of mutagens like heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). Curing results in mutagens being produced by the body, in this case nitrites (NOC). High consumption of heme iron found in red meat has also been linked to changes in the colon flora, considered a risk factor for colon cancer.

In this thesis we explore the available data on this topic and provide a comprehensive analysis.

INTRODUCTION

According to the World Health Organization (WHO), colorectal cancer (abbreviated henceforth as colon cancer or CRC) is the third most common type of cancer in men and the second most common in women. It is also the fourth most common mortality-causing cancer in the world¹. 1.8 million people developed colon cancer worldwide in 2018². Colon cancer incidence in developed countries is higher than in developing countries, with 55% of cases diagnosed in developed countries² and factors like lifestyle, dietary, genetic and environmental factors resulting in variations in incidence rates of CRC across the world. Deaths from colon cancer exceed 373,600 for men and 320,300 in women³.

Nutritional deficiencies have been linked to the development of many different diseases. Cardiovascular diseases and 72% of CVD deaths are associated with poor diet⁴. Some studies have shown an association between depression and poor diet¹. In addition, many types of cancer have been related to diet⁵. Nutritional deficiency may also have a role on colon cancer. Colon carcinogenesis is a complex process with several steps. Inflammation, the immune response, obesity and malnutrition are believed to be key risk factors for CRC⁶. Epidemiologic studies have also demonstrated that the so-called “Western diet” rich in red meat may be a key factor for the development of colon cancer⁷.

One of the first pieces of epidemiologic evidence that there was an association between red meat and colon cancer risk was the demonstration of a strong correlation between per capita meat intake and incidence of colon cancer in women from 23 countries in 1975⁸. In 1999, a WHO committee suggested that increased risk of colon cancer development was associated with consumption of heated red meat⁹. This was

partly based on a strong association with intake of strongly heated meat found in epidemiological studies in North America and Europe¹⁰⁻¹⁴.

Sandhu *et al* concluded that the risk of CRC increased from 12% to 17% with an increase of 100 grams of daily consumption of red meat¹⁵. Another group concluded that consumption of meat in direct contact with flames may increase the risk of colon cancer in people who are genetically predisposed^{16,17}.

When meat is heated to high temperatures, various produced compounds have been suggested to play key roles in colon carcinogenesis. These compounds include heterocyclic aromatic amines and exogenously formed N-nitroso compounds, and polycyclic aromatic hydrocarbons. Sheila Anne Bingham's group at Cambridge showed that after consumption of red meat the fecal concentration of nitroso compounds in humans greatly increased¹⁸.

METHODS

For this review article I used systematic reviews and meta-analysis studies as well as basic science and clinical and preclinical research studies published from 1970 to 2021 using queries for the terms (“colorectal cancer” OR “colon cancer”) , (“red meat” OR “processed meat”), and (“nutrition” OR “diet”). I searched NCBI/PubMed, ScienceDirect, Springer, and the Iranian site <https://www.sid.ir/fa/journal/ViewPaper.aspx?id=234555>.

I studied a diverse set of articles from many countries and selecting those that I felt were of the highest quality.

RESULTS

Epidemiological and basic science studies are supportive of the hypothesis that consumption of processed meats and red meat may increase the risk of colon cancer, possibly because they are the source of chemical carcinogens. In contrast, consumption of vegetables and fiber may inhibit cell replication and reduce the formation of carcinogens and inhibit colon cancer¹⁹.

Oncogenesis, the process by which cells gradually become malignant, has both environmental components like high alcohol intake and cigarette smoking as well as genetic components. Over 10% of colon cancer cases are clearly associated with a genetic predisposition, with 1 in 200 individuals known to have a high risk allele²⁰. In addition, the western lifestyle and diet, associated with high rates of colon cancer, generally includes a high level of daily consumption of red meat (beef, pork, and lamb/mutton)²¹.

Association of diet and cancer

Diet is now known to be an important factor in the development of many diseases such as colon cancer. Consumption of Vitamin D, whole grains, Calcium, milk and fiber are all believed to reduce the risk of colon cancer⁶. In a landmark Chinese study of risk factors for colon cancer using various types of surveys, Gu *et al* found that 63,102 deaths from colon cancer could be attributed to tobacco smoking, alcohol drinking, overweight/obesity, physical inactivity, low vegetable intake, low fruit intake, and high red and processed meat intake. Low consumption of vegetables was associated with the biggest risk of 17.9% PAF. Ultimately, 46% of colon cancer incidence and mortality in China in 2012 could be attributed to these seven factors²².

60% of colon cancer cases are diagnosed in developed countries. Western Europe, North America, Australia/New Zealand and Asian countries like Singapore, Japan and South Korea that have experienced major changes in their dietary and nutrition habits have the highest rates of CRC incidence, with Latin America being intermediate, and South-Central Asia and Africa (with the exception of South Africa) having the lowest rate of CRC incidence. Women also universally have a lower rate of incidence and mortality than men. The lowest mortality rates are in Central Africa and the highest mortality rates are in Central and Eastern Europe. With better therapies and early detection and preventive measures such as colonoscopies, mortality from colon cancer has been decreasing in North America and Japan²³.

In a prospective study of the food habits of Japanese individuals aged 45-74, Takachi *et al* reported on a survey with questions about 138 kinds of food (the red meat items are listed in Table 1) and five years of follow-up, 1,145 cases of colon cancer were identified. Red meat consumption for men and women from the lowest to highest quintiles were 13.6–15.4 and 93–102 g/day, respectively. Red meat intake was linked to increased risk of colon cancer in the Japanese, a population with relatively low red meat consumption. They looked at both men and women, and found that in women, it was linked to proximal colon cancer, while in men it was linked to distal colon cancer. Japanese per capita meat consumption is lower than in western populations, but starting in the 1970's the mortality and incidence of colon cancer among both sexes increased, with women eating more beef and pork and men eating all types of red meat. A link between intake of processed meat and risk of colon cancer in both genders was not detected however²⁴.

Potential mechanisms

The association between processed meat or red meat with colon cancer has been attributed to many mechanisms. Older individuals have shown more clear positive associations between meat and colon cancer than younger participants, which could be attributed to many factors including gut pH or bacterial flora. A higher gut pH in older participants produces more secondary bile acids and increases the amount of endogenous NOC. After red meat intake, primary bile acids that are synthesized from cholesterol in the liver and stored in the gallbladder are secreted into the gut for digestion of animal fat. The activity and growth of 7 alpha-dehydroxylating bacteria is stimulated after secretion of primary bile acids and conversion into secondary bile acids. These bile acids are then converted to deoxycholic acid (DCA) which has been shown to have tumor-promoting activity²⁴⁻²⁶.

A second proposed mechanism for red meat-associated carcinogenesis relates to the high amounts of heme iron found in red meat. A third mechanism relates to the high temperatures used for cooking meat that produce carcinogenic heterocyclic amines. The fourth mechanism involves the production of exogenous and endogenous NOC, and relate in part to pH and substrate availability²⁶.

A pivotal study by Sheila Bingham *et al* showed that fecal concentrations of carcinogenic nitroso compounds in humans strongly increase after consumption of red meat, but not white meat. Volunteers consumed a specified amount of meat every day for 10–15 days and feces was collected every 48 hours and nitroso compounds quantified. Exogenous and endogenous nitroso compounds were both measured^{27,28}.

Cross *et al* found that it is the heme component of red meat and not the inorganic iron that results in the stimulation of endogenous formation of nitroso

compounds²⁹. Consistent with their mutagenic effects, processed meat and heme iron have been strongly associated with the risk of somatic mutations in the genes KRAS and APC3. Heme iron can induce NOC, oxidative stress and colonocyte proliferation which are all strong colon carcinogens⁶. About 20 years ago Massey *et al* in an experiment on germ-free rats demonstrated that only in the presence of normal intestinal microflora can endogenous nitroso compounds form³⁰.

Red meat protein intake also increases the production of heterocyclic amines (HCA) in the colon^{19,31}. When muscle meats are cooked at high temperatures such as by grilling directly over an open flame or pan frying, HCA form from the sugars, creatine, creatinine and amino acids. The most mass-abundant HCAs detected in cooked meats are 2-amino-3,8-dimethylimidazo(4,5-f) quinoxaline (MeIQx) and 2-amino-1-methyl-6-phenylimidazo(4,5-b) pyridine (PhIP), which are possibly carcinogenic to humans. Kobayashi *et al* (2007) found that the levels of HCA measured in hair samples was correlated with level of HCA exposure estimated using FFQ's (food frequency questionnaire) data. This study proposed that using FFQ's in epidemiological studies is a way that can be measure the levels of HCA intake.

A summary of some original studies are provided in Table 1. Various ways that the scientists used to examine red meat consumption included cooking methods, meat doneness and high temperatures. With the exception of a Swedish study³², most studies showed a positive association between HCA exposure and the risk of colon cancer and well-done meat intake. Studies by Nowell *et al* and Butler *et al* showed moderate to strong associations with certain HCAs, including MeIQx, DiMeIQx, and PhIP and well-done meat intake^{33,34}.

Table 1. Epidemiological studies of well-done meat intake and HCA exposure with cancer risk (1996-2008)

Author (year) Study population	No. of Cases/controls Cancer site	Major findings for highest	RR or OR V.s exposure	(95%CI) Lowest
Augustsson K, (1999) Sweden	352 (Colon) 249 (Rectum) 553 controls (colorectum)	Total HCA PhIP MeIQx DiMeIQx	Colon 0.6 (0.4–1.0) 0.6 (0.4–0.9) 0.6 (0.4–1.0) 0.6 (0.4–0.9)	Rectum 0.7 (0.4–1.1) 0.6 (0.4–1.1) 0.7 (0.4–1.2) 0.6 (0.4–1.1)
Kampman E, (1999) USA, California, Minnesota, Utah	868/989 Men 674/871 Women (Colon)	High-temp cooked Red meat White meat Mutagen index	Men 1.3 (0.9–1.7) 1.1 (0.8–1.6) 1.3 (1.0–1.7)	Womn 0.9 (0.6–1.3) 1.2 (0.9–1.6) 1.1 (0.8–1.4)
Le Marchand L, (2001) Hawaii, USA	349/467 (Colon)	Red meat Preference for well done red meat	1.0 (0.6–1.5) 1.1 (0.8–1.6)	
Nowell, S (2002) Arkansas/Tennessee USA	157/380 (Colorectum)	Well/very well-done meat MeIQx	4.4 (2.1–9.6)* 4.1 (1.9–9.1)	—
Butler LM, (2003) North Carolina, USA	African-American 274/427 Caucasian 346/611	Well/very well red meat	1.7 (1.2–2.5)	—

	(Colon)	Pan-fried red meat	2.0 (1.4–3.0)		
		Pan-fried white meat	1.4 (1.0–2.0)		
		DiMeIQx	1.8 (1.1–3.1)		
		Mutagenicity	1.4 (1.0–2.0)		
Navarro A, (2004) Argentina	296/597 (Colorectum)	Darkly-browned vs no preference	Red meat 2.9 (2.0–4.1)		
		Barbecued	1.1 (0.8–1.5)		
		Roasted	2.4 (1.7–3.5)		
		Iron-pan	1.7 (1.2–2.5)		
		Fried			
Murtaugh MA, (2004) Utah and California, USA	952/1205 (Rectum)	Total	Red meat 1.1 (0.8–1.5)		
		High-temperature	1.1 (0.8–1.9)		

Polycyclic aromatic hydrocarbons (PAH) form from the flames and smoke of heated fat and juices. PAH exist in smoke and stick to the surface of the meat. During food preparation processes, such as smoking of meats, PAHs can also be formed¹¹. Cooking methods and “doneness” level (rare, medium, or well done) and meat types are factors influencing formation of HCA and PAH. The HCA concentration in well-done or barbecued chicken and steak are high. Smoking of meat results in the formation of PAH like benzo[a]pyrene (BaP)^{35,36}.

In the body, PAH and HCA are bioactivated and metabolized by specific enzymes in the body, becoming capable of damaging DNA. Studies have found that association between cancer risk and exposure to these chemicals is related to the different levels of activity of these enzymes in people³⁷⁻⁴². The risk of developing adenomas, the precursor to colon cancer, is also associated with consumption of strongly browned meat⁴³

It should be borne in mind that although numerous epidemiologic studies using detailed questionnaires have found increased risks of colon cancer are associated with high consumption of well-done, fried, or barbecued meats^{44 3,45,46}, not all studies have⁴⁷.

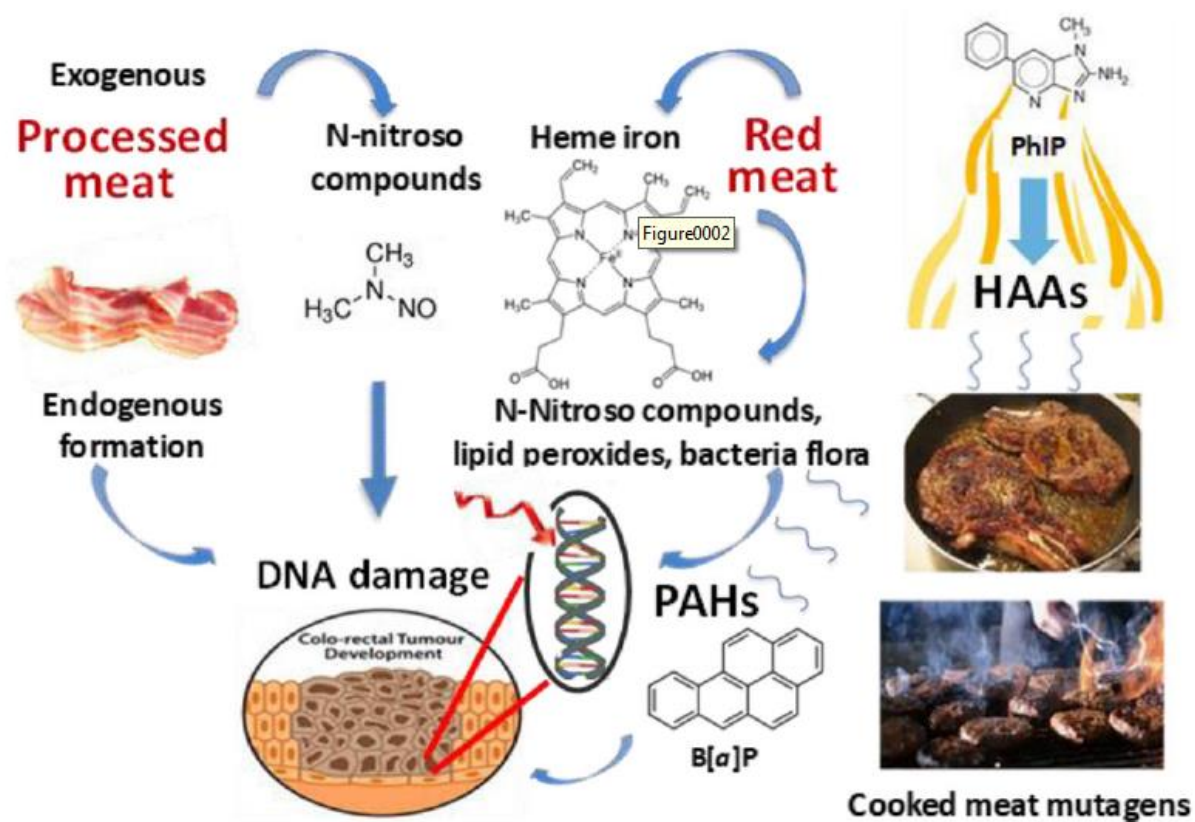


Figure 1. Cooked meat-associated mutagens.

DISCUSSION

In this review article, I summarize the literature that supports the hypothesis that greater consumption of red or processed meat increases the risk of colon cancer. I also discuss the potential mechanisms related to how the meat is cooked.

Alexander *et al* reported in their study that in the UK and US, an estimated 10–12% of new CRC cases may be related to consumption of processed meat, an estimate based on data from WCRF⁴⁸. Similarly, in Anika Knuppel and coworker's prospective analysis study, they found a positive association between processed meat and risk of rectal cancer (per 20 g/day higher intake HR was 1.26) and colon cancer (per 20 g/day higher intake HR was 1.18) but not colon cancer⁴⁹.

High-temperature cooking methods have been associated with increased risk of colon cancer. There was an increased risk of approximately 26% for every 10 g/day increase in consumption of grilled/barbecued red meat⁵⁰. A high consumption of heme iron (but not other forms of iron), N-nitroso compounds (NOC), HCA, and PAH have all been associated with increased risk of colon cancer⁵⁰. The relationship between processed meat consumption and CRC risk have been investigated in a sizable number of clinical studies which many of them reported that existing nitrite in processed meats, cause increasing risk of CRC⁵¹. Pierre *et al* demonstrated that a key event in the carcinogenesis promoting effect of processed meat in rats was heme nitrosylation⁵². Last but not least, processed meats are high fat sources that stimulate bile acid secretion which may influence colon cancer, and red meat is a big source of heme iron that causes cellular colonic mucosa proliferation, a precursor to carcinogenesis¹³.

Limitations

The articles we study for this paper have known limitations. For instance, most studies use food frequency questionnaires (FFQs) which have many limitations such as limited numbers of assays, questions, and types of food items and suffer from problems such as recall bias and sufficiently broad definition of meat types. It is also difficult to extract information on potential quantities of mutagens derived from the meat consumed. There is also great heterogeneity across studies regarding study design and instruments used to assess red and processed meat intake²². In addition, there is a small number of country studies, usually with a small number of patients and lack of controls, an important exception being Gu *et al*'s Chinese study. Some studies had limited follow-up, which may not be enough to observe an association between red meat consumption and colon risks. Some studies also likely have patient recall bias⁵⁰. Last but not least, another source of bias in a review such as this is that the same authors wrote many of the key papers. Drs. Cross and Sinha for instance are the leading authors of many of the papers I ended up citing.

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