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## Review Article

# Processed meat and its relationship with cancer: Literature review

Surabhi Jain<sup>1,\*</sup>

<sup>1</sup>Dept. of Therapeutic Nutrition, Nutriwell India, Lucknow, Uttar Pradesh, India



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### ABSTRACT

Large number of observational scientific studies and numerous research papers, has suggested that high consumption of red meat and processed meat products has an adverse effect on human health. These findings have led advocacy groups around the world to recommend that the general population should reduce use of processed meats and meat products, with the overall goal of reducing the risk of disease, especially cancer. Even World Health Organization (WHO)'s International Agency for Research on Cancer (IARC) stated that consuming processed meat is found to be "carcinogenic to humans (Group I)," and that consuming Red meat is "probably carcinogenic to humans (Group 2A)." So the present article reviews the research and data available regarding relationship between processed meat and cancer.

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## 1. Background

Based on a large number of observational scientific studies and numerous research papers, it has been suggested that a high consumption of red meat and processed meat products has an adverse effect on human health. These findings have led advocacy groups around the world to recommend that the general population should reduce use of processed meats and meat products, with the overall goal of reducing the risk of disease, especially cancer.

World Health Organization (WHO)'s International Agency for Research on Cancer (IARC) stated that consuming processed meat is found to be "carcinogenic to humans (Group I)," and that consuming Red meat is "probably carcinogenic to humans (Group 2A)."<sup>1</sup>

The two meats are differentiated like this.

**Processed meat** – The meat that has been processed by salting, curing, fermentation, smoking, or some other processes to enhance the flavour of the meat or improve its preservation.

India also produces processed meat Products which include beef, buffalo, pork, rabbit, mutton and poultry. The processed and semi-cooked products include corn beef, meat loaf, sausages, curries, bacon, ham, cutlet-mix, chicken-n-ham and salami.<sup>2</sup>

Processed meats consist mainly of pork or beef which has been preserved by methods other than freezing and which undergoes treatment to improve the taste. Processed meat worldwide includes bacon, ham (raw, smoked or cooked), heated sausages such as hot dogs (frankfurters), raw sausages (such as salami), bologna, black pudding (UK black pudding), liver pâté (or frankfurters) and other pâtés and meat spreads, cold meats and other deli meats, corned beef and canned meats. This list is not exhaustive and many other specific products are made all over the world, according to traditional recipes.<sup>3–5</sup>

Curing and smoking, two meat-specific processes, is described here.

Dry salting is the ancient method of salting meat. The pieces of meat are placed on heaps of salt and rubbed with salt or a mixture of salt, sugar and salt and pepper. This

\* Corresponding author.

E-mail address: [drsiyajain@gmail.com](mailto:drsiyajain@gmail.com) (S. Jain).

treatment is simple, but long, and its effectiveness depends on the diffusion of salt in the meat. It is necessary to maintain a low temperature until the centre of the piece of meat is salty enough to prevent internal spoilage.<sup>4,6,7</sup>

1. Seasoning in vats is faster than dry salting: the pieces of meat are placed in brine, water saturated with salt which may also contain sugar and nitrites.
2. Methods have been developed to accelerate the rate of diffusion of cured meats through both the use of the arterial needle injection system and the multi-needle system. Additionally, new additives have been used in brine to improve the colour formation and stability with reducing agents such as sodium ascorbate or erythorbate.<sup>5,6</sup>
3. Smoking is the process of exposing meat to the smoke of incomplete pyrolysis of wood. This gives the meat a brown colour, changes its flavor and helps preserve it because the smoke contains phenols, aldehydes, acetic acid and other carboxylic acids. Wood pyrolysis can generate carcinogenic polycyclic aromatic hydrocarbons (PAHs) and the process is difficult to control. A more controlled process is achieved by immersing the meat pieces in a "**smoke solution**", which gives it a smoky flavour without IPA contamination and improves meat preservation as it contains acetic acid.<sup>8</sup>

Of the many existing processed meat products, we have chosen to describe ham and sausages which contribute the most to overall processed meat consumption. Ham is obtained by refining the upper quarter (thigh and sirloin) of a pig and can be boiled (Parigi ham), dried (country ham) and/or smoked. Sausages are made with minced meat (usually pork or a mixture of pork and beef), lard, salt and other additives (eg wine, saltpeter, garlic, herbs, spices). This preparation is generally packaged in a packaging (historically the intestines of the animal, although now often collagen, cellulosic or polymeric). Sausages can be cured (salami type), cooked (hot dog type) and/or smoked., lard, and vegetable filling (bread, barley, onions), in three equal parts, with salt and spices. This preparation is packaged in a pork casing and cooked until it becomes thick.<sup>6</sup>

Red meat – It refers to the unprocessed mammalian muscle meat such as beef, veal, pork, lamb, mutton, horse and goat meat.

Consumption of the processed meat was classified to be carcinogenic and red meat to probably be carcinogenic after the Working Group IARC which comprises of 22 scientists belonging to 10 countries who had evaluated more than 800 studies. The Conclusions provided by them were majorly on the basis of proof generated for colorectal cancer. Moreover, the Data also showed some positive associations between processed meat consumption and stomach cancer, and also between the red meat consumption and pancreatic and

prostate cancer.<sup>7,9</sup>

Many meat processing activities like curing (e.g. by adding nitrates or nitrites) or smoking can most probably lead to the formation of the cancer-causing (carcinogenic) chemicals like N-nitroso-compounds (NOC) and polycyclic aromatic hydrocarbons (PAH).<sup>9–11</sup>

Meat also has heme iron present in it, which can further facilitate the production of carcinogenic NOCs.

Cooking specially in high-temperature like cooking the meat over a flame (e.g., pan-frying, grilling, barbecuing) can also produce carcinogenic chemicals, including heterocyclic aromatic amines (HAA) and PAHs.

But now also we can see, some advertisements in the media particularly that from the meat industry, promotes processed meat consumption as a major component of a healthy and balanced diet.

So as we can see from the report previously discussed, processed meat was classified as a Group 1 carcinogen by the IARC/WHO, belonging to the same category as tobacco smoking and asbestos. The International Agency for Cancer Research (IARC) uses clear and defined guidelines to identify the hazards (qualitative evaluation), i.e. whether cancer can be caused by an agent, but the IARC does not evaluate the level or the intensity of risk (quantitative assessment). In other words, the IARC/WHO evaluates the evidence not the risks that are associated. After all these reports even the US Dietary Guidelines Committee did issue a review of diet and health, amongst the conclusions it was stated that the consumption of red meat should be less for both human and planet health.<sup>10</sup>

Greater consumption of red or processed meat also enhances the risk of other chronic diseases and death.

It is well known that besides increasing the risk of some cancers, higher intake of processed meat can also increase the risk of other chronic and potentially life threatening diseases such as coronary heart disease, stroke and type II diabetes According to the data from the Global Burden of Disease Project collected in 2013, the number of total deaths (including deaths from cardiovascular disease or diabetes and colorectal cancers) caused due to a diet high in processed meat were 644,000.<sup>11–13</sup>

The processed meats may also have other carcinogenic compounds such as PAHs present in them which may be formed during smoking of meat (e.g. salami). Processed meats comprising majorly of those food items that contain red meat may also have the presence of heme iron, which has the possibility of increasing the formation of carcinogenic compounds (NOCs) in our body.<sup>14</sup> Unless we know more about the exact mechanisms underlying the relationship between processed meat and cancers, it is best to treat those nitrate-free processed meats as same as any other processed meats and should limit its consumption.<sup>15</sup>

The next question is that “are the processed meat items which are made from the so-called ‘organic’ meats safer”?

This is also the matter of discussion as many companies are promoting these.

Processed meat items which are made from the so-called “organic meats” are usually treated with natural nitrates such as celery juice or smoked as well. At this point there is a lack of concrete information to conclude whether those meats are safer than the “non-organic” meats.<sup>16</sup>

In this review of articles we have included published systematic reviews and meta-analyses that have examined the association between processed meat consumption and cancer risk at different body locations, as well as the overall risk of cancer mortality. In summary, most systematic publications and previously published meta-analyses were taken into consideration and review of literature is done.<sup>13,17–20</sup>

In the (NCBI) study, it was observed that the consumption of processed meat could be involved in the etiology of colorectal cancer, one of the leading causes of death in developed countries. Several hypotheses present in the research paper may explain why eating processed meat is linked to cancer risk.<sup>11,18</sup> Mainly they are

1. High-fat diets might promote carcinogenesis through insulin resistance or faecal bile acids;
2. Cooking meat at high temperatures forms carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons;
3. Carcinogenic N-nitroso compounds are formed in meat when we process them
4. Heme iron from red meat can promote carcinogenesis because it increases cell proliferation in the mucosa, by lipoperoxidation and/or cytotoxicity of faecal waters.

A research paper study (Suril S Mehta) noted that higher daily consumption of processed meats and consumption of grilled/barbecued red meat products were associated with an increased risk of colorectal cancer in American women.<sup>18</sup>

According to the research paper (Wiley Online Library), the theory classified red meat and processed meat as probably carcinogenic and carcinogenic to humans, respectively. These conclusions were primarily based on studies of colorectal cancer, but scientific evidence is still limited for other cancer sites. In this study they investigated possible associations between red and processed meat consumption and overall breast and prostate cancer risk. This prospective study included 61,476 men and women aged  $\geq 35$  years and having made at least three 24-hour dietary records during the first year of follow-up. The risk of developing cancer was compared between sex-specific quintiles of red and processed meat consumption by multivariate Cox models. 1,609 first cases of incident primary cancer were diagnosed during follow-up, including 544 breast cancers and 222 prostate cancers. So it clearly shows relationship between processed meat and CRC.<sup>21,22</sup>

The research paper (British Medical Bulletin) provided evidence that red meat and processed products are positively

associated with CRC risk and appear to be stronger when the two food categories are combined.<sup>11</sup> Considered separately, the evidence is stronger for processed meat than for red meat, and indeed some still argue that the evidence for red meat remains too weak and inconsistent to warrant a conclusion. In the case of processed meat, a positive association with CRC was reported in twelve of the eighteen studies analyzed by the IARC panel. With regard to the effects or consumption of meat on the risk of other types of cancer, although positive associations have emerged from studies, for pancreatic, breast and prostate cancer, but many argue the significance of statistics were inconsistent and most reviews did not find convincing evidence of increased risks at the sites except that in the colon and rectum. A recent ACRF/AICR CUP report, however, concludes that processed meat consumption is now a proven risk factor for non-cardiac gastric cancer. There is also evidence of an increased risk of stomach and pancreatic cancer. But we need more research to know for sure if processed red meat affects the risk of getting these types of cancer. Chemicals (found in meat, added during processing or produced during cooking) can increase the risk of cancer by damaging our cells.<sup>23</sup>

## 2. Lets discuss some Chemicals which might Increase Risk of Chemicals

### 2.1. Heme

This is a red pigment naturally found in red meat and its processed version. It can damage cells and cause bacteria in the body to produce harmful chemicals. This can increase the risk of cancer.<sup>24</sup>

### 2.2. Nitrates and Nitrites

These chemicals can be used to keep processed meats fresh longer. When its consumed by human, nitrites can be converted into carcinogenic chemicals (nitroso compounds or NOCs).<sup>25</sup> These chemicals may be the reason why processed meat increases cancer risk more than fresh red meat.<sup>26</sup>

### 2.3. Heterocyclic Amines (HCA) and Polycyclic Amines (PCA)

These chemicals are produced when meat is cooked at high temperatures, such as when grilling or barbecuing. They can damage the cells of the intestine.<sup>13</sup>

## 3. Discussion

### 3.1. Colorectal cancer (CRC)

We checked more studies to determine at-risk single-nucleotide polymorphism (SNP) alleles for colorectal cancer (CRC) and their relationship. The presence of SNPs

associated with protein metabolism and function may play an important role in the effects of red meat consumption on CC (colon cancer) risk.

Several individual SNPs have been associated with CC risk. It is plausible that a set of SNPs derived from genetic pathways critical in colon carcinogenesis may contribute to cancer risk. Many studies investigated the role of polymorphisms involved in five metabolic pathways relevant to the activation or detoxification of carcinogens formed during red meat processing. The polymorphisms investigated in the present study were primarily functional polymorphisms that alter the expression of genes that participate in metabolic pathways associated with carcinogenesis.<sup>27</sup>

Several hypotheses could explain how processed meat may increase the risk of CRC and accordingly experimental studies have been conducted.

This study states that heme iron from red meat can promote carcinogenesis because it increases cell proliferation in the colonic mucosa, by lipoperoxidation and/or faecal water cytotoxicity.<sup>28</sup> Several hypotheses may explain why the consumption of processed meat is linked to the risk of CRC. Processed meats often differ from red meat in three main ways:

1. They often contain more fat than red meat;
2. They contain specific additives, in particular salt and sodium nitrite.
3. Their long-term storage produces oxidation products of cholesterol. Like red meat, processed meat is high in fat, protein, and heme iron, which may promote carcinogenesis or produce promoters in vivo. Processing and cooking can generate heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs) and nitrous compounds (NOCs). Some HCAs, PAHs and NOCs are animal mutagens and carcinogens. Additionally, people who consume large amounts of processed meat may lack protective phytochemicals and/or be at increased risk for sedentary lifestyles, obesity, and/or insulin resistance.

### 3.2. Fat

Epidemiological studies and laboratory animal models suggest that a high intake of dietary fat promotes CRC. A high fat intake promotes the secretion of bile acids (BA) in the duodenum and activates bacterial 7 $\alpha$ -hydroxylase which produces secondary BAs. These BA acids, deoxycholic and lithocholic, promote colon carcinogenesis in several animal models and are elevated in the feces of cancer-prone populations. Four studies have provided direct evidence that a high-fat diet can increase carcinogen-induced tumors in the colon of rats. Reddy et al. (1976) showed that meat proteins and fats increased the incidence of colon tumors in F344 rats injected with 1,2

dimethylhydrazine (DMH) checks. In contrast, the high-fat diet had no effect when given simultaneously with the carcinogen. Finally, Pence et al. (1995) showed that a 20 t diet significantly increased the number of adenomas in the colon of DMH-initiated rats, regardless of protein and lipid sources (meat, casein, corn oil, or tallow or Beef).<sup>19</sup>

### 3.3. Heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH) when cooking meat

HCA and PAH are formed. HCAs are formed by pyrolysis of creatine with specific amino acids. Since a high temperature is required, only fried, grilled or barbecued meat contains significant amounts of HCA. The main sources of PAHs for humans are cooked and smoked meat and fish, especially grilled meat and tobacco smoke. Furthermore, nitrosation of HCAs such as MeIQx or IQ has been proposed as a mechanism by which well-cooked red meat consumption and inflammation may trigger colon cancer in inflammatory conditions, such as colitis. This mechanism is enhanced by heme.

The association between PAH intake and the risk of adenoma was recently studied in two case-control studies conducted by the same team.<sup>29</sup>

### 3.4. Nitrite and nitrous compounds (NOC)

NOCs, which are alkylating agents that can react with DNA, are produced by the reaction of nitrites and nitrogen oxides with secondary amines and alkylamides. Many NOCs, including nitrosamines and nitrosamides, are carcinogenic in laboratory animals. Humans can be exposed to CNPs exogenously from certain processed meats (eg, grilled bacon), smoked fish, cheeses, or beers. In a large-scale Finnish cohort, intake of N-nitrosodimethylamine from smoked and salted fish and sausages was associated with risk of CRC.<sup>20</sup>

### 3.5. Heme

Heme consists of an iron atom contained in the center of a large heterocyclic organic ring called porphyrin. Heme is included in muscle myoglobin, the hemoglobin of red blood cells and cytochromes. Three mechanisms may explain the promotion of carcinogenesis by heme: (i) heme is metabolized in the intestine to a cytotoxic and promoting factor; (ii) heme induces fat peroxidation in food and intestines and lipoperoxides would promote CRC; (iii) heme catalyzes endogenous nitrosation, which increases NOC formation, as noted above, and HCA activation.<sup>30–32</sup>

## 4. Conclusion

In conclusion, certain genetic polymorphisms may play an important role in the risk of CRC, especially in people who consume more processed meat. A better knowledge

of nutritional genomics can lead to the discovery of new methods to prevent, treat and control CC. The fact that the consumption of processed meat increases the risk of colorectal cancer seems established by published meta-analyses of epidemiological studies.<sup>33</sup> Several hypotheses may explain the association between consumption of processed meat and risk of CRC. From the data reviewed above, it is proposed that the most likely explanations for excess risk in processed meat consumers are

1. Heme-induced promoters.
2. Carcinogenic nitro compounds, nitrite polymerization is likely to increase toxicity: Nitrite binds to heme iron and can produce more toxic lipoperoxides and cytotoxic. Nitrite tanning leads to increased levels of nitrous compounds in food and intestines, so exposed to higher NOC levels than consumers of fresh meat.<sup>34–36</sup>

Further research is needed to probe deep into the cause and relationship.

## 5. Conflict of Interest

None.

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None.

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### Author biography

Surabhi Jain, Chief Nutritionist and Lactation Consultant

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