Processed meat and red meat are related to cancer

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Introduction

Cancer, which is one of the leading causes of mortality all across the globe, is found to be highly influenced by one’s lifestyle and diet. With more studies that are being conducted by researchers, enough evidence is being accumulated over time that gives us a clear proposition on how the risk of getting a certain type of cancer increases when a particular food item is being consumed frequently. Many experiments and reports have shown that processed meats and red meats are carcinogenic to humans and potentially fall under Group-1 and Group-2A carcinogens respectively. Red meats are nothing but the flesh of animals in which a high proportion of red muscle fiber over white muscle fiber is found like pork, lamb, beef, goat etc. On the other hand, processed meats which are usually prepared from red meats largely, are nothing but meats that have been preserved by smoking, salting, curing, and adding chemical preservatives for a greater lifespan and integrity of the food product like as in ham, bacon, sausages etc. [1]. Several epidemiological surveys and studies conducted by different groups of scientists on a different time, have informed that consumption of processed meat and red meat is positively associated with colorectal cancer (CRC) very often along with some other types of cancer. Many genotoxic effects of processed meats and red meats are hypothesized and scrutinized to find out how the carcinogenic effects are carried out by the nutrient item when consumed frequently. This review will focus and emphasize on the types of cancer which are related to ingestion of these meats, putative carcinogenic ingredients that are present in those foods, and a brief view of how its genotoxic and carcinogenic effects are established on the body. Detailed mechanism of carcinogenesis and their methods of detection, epidemiological survey, statistical analysis, control and prevention will however not be discussed here.

Cancers related to processed meat and red meat consumption

Consumption of both types of meat, processed and red, are found to be a threat of getting cancer especially CRC. In 2007, World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) concluded that there is a positive counterpart between red and processed meat in CRC. Such statements were made upon the basis of the results of 71 case-control studies and 16 cohort studies. The WCRF project in 2011 on CRC gave clearer evidence in favor of a link between red and processed meat [1]. CRC is third most common cancer after lung and breast cancer and also froth common cause of cancer death [2]. Processed meat and red meat intake were positively associated with incident of colorectal adenomas in the PLCO (Prostate, Lung, Colorectal, and Ovarian) trial. Studies revealed that with high intakes of red meat per 100g increase in daily relative risk (RR) for colorectal cancer increased by 17% and increase in daily consumption of per 50g processed meat, the RR increased by 18% [3]. Along with CRCs, one can also elevate the chance of acquiring several other types of cancer like lung, prostate, liver, etc. National Institutes of Health and American Association of Retired Persons (NIH-AARP) study indicated a notable affirmative association between red meat intake and cancers of the lung, liver, kidney, breast, esophagus, pancreas, and prostate. On the other hand, the NIH-AARP study and the PLCO trial suggested that processed meat intake was positively associated with lung and prostate cancer, with the addition of significant associations with chronic liver disease as well (Table 1).

<table>
<thead>
<tr>
<th>Table 1 Meat types with cancer types</th>
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<tbody>
<tr>
<td>Types of Meat</td>
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<tr>
<td>Red Meat</td>
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*Not enough evidences available. Adapted from Abid et al., 2014.

Causative agents related to processed meat and red meat

In 2015, a group of scientists assembled at the International Agency for Research on Cancer (IARC) in France, to determine the carcinogenicity when red meat and processed meat is consumed and their finding reports were published in Lancet Oncology which states that “On the basis of the large amount of data and the consistent associations of colorectal cancer with consumption of processed meat across studies in different populations, which make chance, bias, and confounding unlikely as explanations, a majority of the Working Group concluded that there is sufficient evidence in human beings for the carcinogenicity of the consumption of processed meat.” [4] Right now from all the pieces of evidence and data are being accumulated, processed meat is classified as Group-1 carcinogen and red meat is placed on Group-2A on the list for humans. The genotoxic effects of various processed meat and red meat and their components were studied in rodent models and these were considered as evidence. Many ingredients are used in processing meat or present in red meat, and also serve as a potent genotoxic, carcinogenic agent and also proposed to contribute to cancers like CRC, the most studied one. Curing meat while processing it is an important step and this procedure also involves the production of carcinogenic substances like N-nitroso compounds (NOCs). NOC formation is found to be establishing a connection between red or processed meat consumption to different types of cancers; Smoking of meats produces polycyclic aromatic hydrocarbons (PAHs), a carcinogen. Similarly, heterocyclic aromatic amines (HAAs) are formed when meats are cooked at high temperatures. Plenty of epidemiological studies have indicated that dietary intake of HAAs and PAHs are interlinked with the increase of risk in some particular cancers like colorectal. Another interesting agent is Heme, which does catalyze the NOC formation and nitrosation of secondary amines that are endogenous. They are also responsible for the catalysis of lipid peroxidation in the gastrointestinal (GI) tract and thus forming lipid peroxidation products (LPOs). Among these chemicals, many forms of DNA adducts can induce mutations and promote carcinogenesis. IARC has classified some NOCs and PAHs as Group-1 carcinogens and several HAAs as Group-2A or 2B. [5]

N-Nitroso compounds (NOCs)

NOCs are formed during the curing step of processing meats. The most common examples include N-nitosodimethylamine, N-nitrosodibutylamine, N-nitrosopyrrolidine, N-nitrosodipropylamine. The formation of NOCs can range from less than one part per billion (ppb) up to 130 ppb. Studies have shown that NOCs production endogenously goes high with ingestion of processed meats and red meats in the GI tract. The NOCs are metabolically activated by cytochrome P450 2E1. N-nitrosodimethylamine (NDMA) forms N7-methyl-2’-deoxyguanosine (N7- Mdg), a substance that can
promote DNA strand brakes, abasic site formation as well as cytotoxicity. O6-MeG and O6-carboxymethyl-2′-deoxyguanosine (O6-CmG), which is produced from N-nitrosoglycoeholic acid, is a major element that contributes greatly to carcinogenicity. It can favor G-A transitions and G-T transversions, contributing to mutations in certain genes that are keys for cancer oncoproteins like H-ras, K-ras, and tumor suppressor genes like p53. The level of NOCs produced endogenously is found to be 10 times higher in humans who consume red meat or processed meat when compared to those who are on a vegetarian diet. [5].

Heterocyclic aromatic amines (HAAs) AAAs are produced in cooked red or processed meat. Some abundant AAAs include 2-amino-1-ethyl-6-phenylimidazo[4,5-b]pyridine (PhIP), 2-amino-9H-pyrido[2,3-b]indole (Ac9C) and 2-amino-3,8-dimethylimidazo[4,5-f]quinoline (MeIQx). These AAAs also undergoes metabolism by P450 enzymes and results in the formation of some genotoxic metabolites which can induce the formation of some intermediates that do damage in DNA like – N-acetyltransferases and N-sulfoxtransferases. [5].

Polycyclic aromatic hydrocarbons (PAHS) PAHs are also formed in cooked meats such as [a]pyrene (Ba[a]P) and also follows the activation by human cytochrome P450 enzymes. They also form many genotoxic species and reactive intermediates metabolites. They are found to make DNA damages and oxidative stress production by oxidizing o-quinones. [5].

Heme iron Ingestion of heme iron from either red meat or processed meat leads to lipid peroxidation and induces NOC formation. [6] The feeding of ferrheme can cause DNA damage and protein modification by forming other genotoxic agents. On the other hand, lipid peroxidation results in the production of Malondialdehyde (MDA), which can react with deoxyguanosine(dG) and convert it to cyclic adduct 3′-(2-deoxy-β-D-erythropenta-furanosyl) pyrimido[1,2-α]purin-10(3H)-one 2′-deoxyguanosine (M1- dG). [5].

N-glycolylneuraminic acid (Neu5Gc) N-glycolylneuraminic acid (Neu5Gc) is a non-human variant of sialic acid and is found abundantly in red meats. This act as an antigen for our body and anti-Neu5Gc antibodies were shown to be leading towards chronic inflammation and carcinogenesis in a murine model. It incorporates itself with the cell membrane and also triggers ROS production. [5] (Table 2)

Cancer promoting role

The association of processed meat and red meat consumption with increased risk of cancer are studied by many groups. In vitro findings of many DNA adducts lead to an overall estimation how these meat consumptions are relevant for enhancement of cancer risk and hence perform a pro-tumorigenic role. The formation of NOCs is not only responsible for DNA breakdown and mutation in oncogenes, but also for hampering the DNA repair system. HAAs and PAHS both contribute to DNA damage and this leads to a pro-tumorigenic activity. Oxidative stress production is also observable and associated with processed meat and red meat uptake. A drastic change in the immune system and high inflammatory responses are also believed to be contributing to it. The Presence of sialic acid, N-glycolylneuraminic acid (Neu5Gc) in red meats is very high and thus can trigger a huge inflammatory cascade when incorporated within. Heme is also an important factor to be taken under insight as they are found to be involved in NOC formations and DNA breakdown. They also mediate lipid peroxidation which induces new mutations to form. Apart from that, it’s also observed that they can take part in certain protein modification processes which helps in a carcinogenic event. Reactive oxygen species formation (ROS) is also found to be associated with such meat consumption. All the causative agents can induce mutations in many important regulatory oncogenes and tumor suppressor genes like Kras, p53 etc. Many of these causative agents were formed during the cooking and processing of meat so cooking practices and meat processing also add up to cancer promoting role [7]. Hammerling et al. (2016) [8] demonstrated cancer-promoting mechanisms related to processed meat and red meat consumption with CRC as a reference. The following valid points were made: a. increased N-nitrosation and oxidative pressure which leads to DNA adducts and lipid peroxidation in the GI tract; b. Proliferative stimulation of epithelium through heme or its derivatives acting directly to DNA damage; c. An overall higher inflammatory response due to the presence of many kinds of xenotoxotantigen, triggering many cascades of reactions towards a pro-tumorigenic process. All these findings date to give us enough evidence on how processed meat and red meat consumption promote cancer but still many of these claims are under study and yet to reveal a lot more from a mechanistic perspective. (Figure 1)[9]

Other factors to carcinogenicity

Some other factors should be taken into consideration when discussing processed meat, red meat, and cancers. High intake of salt and salty foods is considered to be a risk factor in cancers like gastric cancers. Foods containing 3 to 5 g salt/100g are adequate but there is some processed meat that goes beyond the range and increases endogenous NOC formation, contributing towards carcinogenicity [10]. Another factor is the high intake of saturated fats was associated with an increased risk in many cases and both processed and red meat contains a large number of saturated fats [7]. While discussing some diet and its effect, gut microbiota should also be involved. Our microbiome is dynamic and its functionality is highly influenced by the diet. Tjalsma et al. (2012) [11] proposed the ‘driver-passerenger model’ to explain the CRC development where it is described that colonization of some Escherichia coli strains, Salmonella, Shigella, Citrobacter, and superoxide-producing strains of Enterococcus faecalis, etc as pro-carcinogenic. Alongside them, some anti-tumorigenic bacteria are also present and make an overall effort to cancer inhibition like certain strains of lactobacillus and Bifidobacterium. The preparation and cooking of red meat and processed meat also make a very distinct impact on its overall nutritional values as well as carcinogenic effects. Barbequing and grilling of red meats are associated with increasing the risk of CRC while oven-baking, boiling, and stewing are found not to be associated with it. NOCs and PAHS were found to be in higher concentration and more bio-accessible in meat which was put under barbeque. So cooking practice of meats is an important aspect modulating the risk of cancer and such practices should be avoided which is related to higher risk [7]. Another thing that should also be noted that red meat is a nutritious food and an important source of protein with all essential amino acids, highly bioavailable iron, zinc, selenium, and B vitamins. WCRF recommended that red meat intake should be limited to <500g/week and lesser than that if that includes processed meat.

Table 2 Substances related to meats and their Carcinogenic effects

<table>
<thead>
<tr>
<th>Substance</th>
<th>Carcinogenic effect</th>
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<tbody>
<tr>
<td>N-Nitroso compounds (NOCs)</td>
<td>DNA breakdown, Mutation in oncogenes</td>
</tr>
<tr>
<td>Heterocyclic aromatic amines (AAAs)</td>
<td>DNA damage, Genotoxicity</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons (PAHS)</td>
<td>DNA damage, Oxidative stress production</td>
</tr>
<tr>
<td>Heme iron</td>
<td>NOCs production, DNA damage, Protein modification</td>
</tr>
<tr>
<td>N-glycolylneuraminic acid (Neu5Gc)</td>
<td>Chronic inflammation, ROS production</td>
</tr>
</tbody>
</table>

Adapted from Rohrmann et al., 2016.
**Figure 1:** Overall cancer promoting role of processed meat and red meat

![Image of Figure 1](https://example.com/figure1.png)

Fig. 1. Showing the overall cancer promoting role associated with processed meat and red meat consumption. Adapted from Cascella et al., 2018.

**Conclusion**

In conclusion, it is again worth mentioning that red meat and processed meat uptake includes a risk of getting cancer, especially colorectal [12]. Things should also be taken into consideration that red meats and processed meats do have some beneficial impact and nutritional values and can be consumed without any such worries in certain quantity over time. The identification of various causative agents of carcinogens that are related to these meats is very important so that a better understanding of diet and cancer can be established with due course of time. Moreover, preventive measures, modification in meat processing, and limited consumption can be very useful to improve the lifestyles and health of people around the globe. More detailed cohort studies among the various human population and a complete understanding of the mechanistic sets of the event underlying the carcinogenicity accomplished by these meats are warranted and expected to be investigated in the future, which may give a lead to new findings contributing towards avoiding such carcinogens.

**References**


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**Competing interests**

The authors declare no conflicts of interest.

**Abbreviations**

CRC: Colorectal cancer; HAAs: Heterocyclic aromatic amines; NOCs: N-nitroso compounds; PAHs: Polycyclic aromatic hydrocarbons; WCRF: World Cancer Research Fund.

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