REVIEW ARTICLE

Diet and cancer: The case of red and processed meat

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RESUMEN

Algunos alimentos de consumo cotidiano pueden ser carcinogénicos; recientemente la Organización Mundial de la Salud (OMS) incluyó en este grupo a las carnes procesadas y carnes rojas. Los mecanismos por los cuales estos alimentos son cancerígenos, principalmente a nivel de tracto gastrointestinal, han sido bien estudiados y se relacionan tanto con compuestos presentes *per se* en la carne como algunos añadidos (en el caso de la carne procesada), o bien, formados durante su preparación. Es importante, a nivel de políticas de salud pública, informar a los pacientes sobre las mejores opciones de elección, cocción y almacenamiento de estos alimentos para reducir el riesgo carcinogénico, así como enfatizar en un estilo de vida que incluya el consumo de frutas, fibra y verduras. El propósito de este artículo es revisar dichos mecanismos y las recomendaciones para contrarrestar su efecto deletéreo a la salud.

Palabras clave. Carcinogénesis. Epigenética. Embutidos.

ABSTRACT

Some daily consumed foods can be carcinogenic; recently, the World Health Organization (WHO) included processed meats and red meats within this group of foods. The mechanisms by which these foods act as carcinogens, mainly at the gastrointestinal tract, have been well studied, and are related both to compounds natively present in meats as well as additives (as with processed meats) or compounds formed during its preparation. For public health reasons, it is important to inform patients about better options for selecting, cooking and storing these foods in order to reduce their carcinogenic risk, as well as emphasize a healthy lifestyle with fruit, fibre and vegetables intake. The purpose of this article is to review these mechanisms as well as recommendations to counteract their deleterious effects.

Key words. *Carcinogenesis. Epigenetics. Cold meats.*

INTRODUCTION

On October 26, 2015 the World Health Organization (WHO) published a statement in which red meat had been classified within group 2A as probably carcinogenic (based on limited evidence), and processed meat was classifies as carcinogenic within group 1 (based in sufficient evidence), a group in which well-known carcinogenic substances, such as asbestos and alcohol, are also included. It's worth mentioning that even though the role of carcinogenicity has been well demonstrated, their carcinogenicity degree is not the same.[1] This document was done by the International Agency for Cancer Research (IARC), which is formed by a group of 22 field experts from 10 different countries. The report was issued after having reviewed more than 800 articles where red meats were linked to cancer,[2] and it uses the following definitions:

- **Red meat.** Muscular meat that comes from bovine cattle, sheep, pigs and goats. It does not include poultry or fish.
- **Processed meat.** Any kind of meat including poultry, that has been salted, cured, fermented, treated with additives or smoked, in order to better its flavor or for storage purposes. Preparations such as bacon, sausages, ham, and salami are included in this group.[3]

These statements were controversial, and so it was later emphasized that, although the risk is small in individual form, recommendations are made because the huge

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impact they have both at population level as well as public health level. Specifically, in the case of processed meat, it is estimated that its intake causes 34,000 deaths each year worldwide.[1]

The WHO considers an *average* red meat intake for an individual of 50-100 grams per day, and a *high* intake is defined as more than 200 grams per day.[1] It is estimated that for every 50 g of processed meat consumed daily, the risk of colorectal carcinoma (CRC) increases in 18%, and for every 100 g of red meat consumed daily, the risk is 17% higher.[1,3] In Mexico, as of April, 2016, the average intake of bovine cattle derived meat was 38 g per person per day, which represents 22% less than the numbers reported in 2008.[4] Bovine and porcine meat intake in Mexico in 2012 per person per year was approximately 92 g[5] and 86 g in 2013.[6]

Both types of meat (red meat and processed meat) are linked mainly to the development of CRC, and to a lesser extent, prostate and pancreas cancer (red meat) and stomach cancer (processed meat).[1] Carcinogenic substances identified in red and processed meat (potentially responsible for such an increment in risk) are polycyclic aromatic hydrocarbons (PAHs), heterocyclic amines (HCAs) and N-nitrous compounds (NNCs), amongst others.[7] These substances conform large families of compounds with different carcinogenicity degrees,[8] that will be later addressed. The main goal of this paper is to communicate the evidence regarding the effect of red and processed meat intake in cancer development.

MATERIAL AND METHODS

We used the terms *Carcinogenesis*, *Epigenetics* and *Cold meats* to search in the MEDLINE databases for publications that included meta-analyses, systematic reviews, clinical trials and review articles. We reviewed the published information.

WHY ARE RED MEATS PROBABLY CARCINOGENIC?

The following are compounds potentially responsible for cancer, and their mechanisms of carcinogenicity are also mentioned. Some theories include compounds present in meats additives used during its preparation, or during cooking processes.

Hem iron

Iron has an important role in many bodily functions, many of which depend on iron's ability to take part in oxidation and reduction reactions (redox), changing from $Fe2^{+}$ (ferrous) to $Fe3^{+}$ (ferric) and *vice versa*. Even though iron's ability to change between both forms is vital, this reactivity may be deleterious because gives rise to the formation of free radicals which damage cell membranes and deoxyribonucleic acid (DNA). Iron within animal meat (cows, pork, poultry and fish) is part of haemoglobin and myoglobin, and it's referred to as hem iron; conversely, iron in vegetables, grain and supplements is termed Non-hem iron. It is known that hem iron is cytotoxic by means of oxidative stress,[9] free radical production and lipid peroxidation. This translates into hyper-proliferative effects in the colon of lab rats.[10] Hem iron is usually found in a standard diet between 10% and 20%, and its absorption is higher than 50%.[11]

Nitrites and N-nitrosamines

These are amongst the most commonly used additives in cold meats, as well as phosphates, sodium chloride, soy and milk proteins, caseinates, nitrates and thickener agents.[12] Nitrites are necessary to obtain the rosy color, as well as the characteristic smells, and are also used because of their antimicrobial properties. These can form N-nitrosamines when the exceed the necessary content, or during the digestion process itself because of contact of sodium nitrite with hydrochloric acid. When metabolized, N-nitrosamines form unstable nitrogenous cations and alkylating agents that interact with DNA causing mutations.[13]

The higher levels of nitrosamines are found in smoked foods using the traditional method, that is, wood combustion.[12] Roasting and frying heighten nitrosamine production derived from methylamines, and may give rise to the generation of new compounds such as diethylnitrosamine, that are not found in the raw state.[13] It is important to note that formation of NNCs may be blocked with the concomitant intake of vitamin C.[7]

FOOD PROCESSING TECHNIQUES ASSOCIATED WITH CARCINOGENESIS

Food preparation processes to which red and processed meats are subjected may also contribute to the additional formation of carcinogens.

Cooking

Most of the time, meat is cooked before being eaten, a process that not only destroys potential pathogens, but

also eases digestion, and modifies the taste, texture and color of foods.[8]

High temperature processes (> 160-200 °C) are responsible for the formation of carcinogenic compounds,[1] specially when cooking with an open flame; these temperatures are achieved when cooking barbecue (roast/grill) or when using a frying pan. It is worth mentioning that some carcinogenic compounds (such as PAHs y HCAs) are present *per se* in materials used for cooking, such as coal and wood, and may be transferred to foods by contact o by generation of volatile PAHs after pyro-lysis of (mainly) fats or proteins.[7]

When inhaled carcinogens are formed, the airway becomes another source of exposition, although to a lesser extent. Once formed, these compounds mat enter the human body by inhaling, skin contact o bay ingestion of contaminated foods. The latter path represents about 88-98% of the compounds that enter the organism.[14] The surface of meats is where the majority of these compounds are formed. Another important source of PAHs are meat juices, rich in free amino acids.[8]

A major factor for carcinogen formation is cooking time, which is influenced by the number of times meat is turned, and determines time of contact with high temperatures (the fewer the times the meat is turned, the higher the formation of PAHs).[8]

Additives

These refer to substances added to foods in order to better their taste (for example, to give a smoked flavor), such as protective or glazing covers.

Adding monosodic glutamate to spice food may increase PAHs content,[8] but there are also some condiments that, when applied to meats before cooking, actually reduce carcinogen formation, such as onion, rosemary, garlic and sage.[8]

Storage

Even though the higher concentration of carcinogen substances are formed during the process of cooking, they may also diffuse during storage processes; this happens after preparation, and diminishes as time passes,[8] and just as with cooking processes, the maximum concentrations are located at the food's peripheral zones.

Although the aforementioned cooking processes are shared with other types of meat, there's another series of factors (myoglobin content, fat content, necessary cooking times, etc.) that determine a higher carcinogenicity of red meat when compared with white meat.[7,8] This has been demonstrated in colon cancer patients when compared with controls.[14]

Once formed, the properties of these compounds vary, such as lipo-solubility and molecular weight, and these are mayor determinants of their absorption and bioavailability. It is known that concurrent intake of fibre-rich foods reduces PAHs bioavailability.[15]

PREVENTION

Epigenetics

Recent studies show that diet components may have an effect on carcinogenesis process by epigenetic mechanisms, that is, changes in gene expression that do not require changes in DNA sequence.[16] These mechanisms are produced by nutrients and bioactive components of foods. Bioactive components is the term used to refer to substances that directly affect enzymes that take part in epigenetic mechanisms; examples are genistein and tea catechins (they affect DNA methyltransferases), resveratrol (inhibits histone deacetylase) and curcumine (inhibits histone acetyltransferases).[17]

Effects of food components in DNA methylation

Certain bioactive food components, such as tea polyphenol and soy bean genistein, may inhibit cancer development by reducing the hyper methylation state of DNA in critical genes associated with cancer, such as the p16 gene or the retinoic acid receptor beta.[17]

To date, 40 dietary compounds with preventive cancer effects have been identified, such as green tea, red wine, ginger, soy bean, cauliflower and broccoli.[18] For example, indol found in cuciferous vegetables is associated with a reduction in colon, lung and breast cancer, the specific compound being indol-3-carbinol. The acid environment of the gut turns indol into a dimer known as 3,3'-diindolylmethane. These indolic compounds are considered chemopreventive supplements because they create an antiproliferative effect in cancerous cells.[19]

Apoptosis

Blueberries has the ability to induce apoptosis by means of loss of mitochondrial membrane potential, cytochrome C release and caspase-3 and DNA fragmentation factor (DFF-45) activation, as well as fragmentation of poly (ADP-ribose) polymerase in human gastric cancer cells. A com-

ponent of garlic, dyallil sulfur, induces apoptosis by means of reactive oxygen species generation regulated by the Bax/Bak complex, although independent of Bcl-2 or Bcl-KL. Table 1 shows the food source of the main dietary components with pro apoptotic properties.[20]

Phytochemicals

Many studies have demonstrated that a high phytochemical intake may prevent cancer in humans.[19] The following are some examples with their protective mechanisms.

Carotenoids

Present in dark green leaves and carrots, these have been linked to a diminished risk of breast, ovarian and pancreatic cancer.[20]

Vitamin E

Acts by reducing lipid peroxidation of poly-unsaturated fatty acids by means of oxidative stress. Nevertheless, if this peroxidation is not controlled, it may give rise to free radicals that will act as carcinogenesis inductors.[16,19]

Vitamin B6

Epidemiological research in colorectal cancer has shown an influence over DNA synthesis and methylation. It has been observed, in animal models, that it reduces the number of colon tumors, inhibits angiogenesis and reduces oxidative stress.[16] Amongst vitamin B6 sources, we have avocados, leguminous plants, bananas and nuts.

Table 1. Food source of the main dietary components with pro apoptotic properties.

Agent	Food source
Curcumin	Curcuma
Resveratrol	Grapes
Pterostilbene	Blueberries
Epigallocatechin galate (GECG)	Tea
Acacetin	Chrysanthemum flower
[6]-Gingero	Jengibre
[6]-Shogaol	Ginger
Luteolin	Celery
Capsaicin	Pepper
Indole-3-carbinol	Cabbage
Phenethyl isothiocyanate	Broccoli
sulforaphane	
Diallul sulfure	Garlic
Allicin	
Lycopene	Tomato
Caffeic acid phenethyl ester	Honey

Source: Flores-Balcázar, 2015.[18]

Fibre

High-fibre diets are related to a lower incidence of cancer.[21] Wheat fibre modifies absorption and excretion of carcinogens such as HCAs; it also modulates enzymatic activity.[7]

RECOMMENDATIONS

Given that the main way in which carcinogenic compounds produced during cooking adhere themselves to foods is by direct contact with hot surfaces, and that their production is proportional to the fat content of meat and pyro-lysis said fat, it is recommended to eliminate as much as possible portions with a burnt aspect, and to choose meat cuts with little fat.[22] A simple way to reduce formation of carcinogenic substances is to first marinate the meat in order to form a protective layer, but with the added benefit of a better flavor,[9] or to pre-cook in a microwave oven.

Guidelines from the American Society of Cancer regarding nutrition to prevent cancer[3] make the following recommendations:

- To eat five or more portions of fruits and vegetables a day, because high-fibre diets reduce carcinogen bioavailability.
- To choose whole grains instead of processed (refined) grains and sugars.
- To limit red and processed meat intake. For protein intake, choose fish, poultry or leguminous plants instead of red meat. When eating red meats, choose meat cuts with little or no fat. Instead of frying or grilling the meat, use other cooking methods, such as cooking in an oven o simmering.

It is worth mentioning that even though some of the meat cooking processes contribute to its carcinogenicity, this does not mean that meat must be eaten raw because this carries important health risks.[1]

AREAS OF OPPORTUNITY AND LIMITATIONS

It is necessary to define risk degrees within the same meat category (red versus processed), as well as establishing specific recommendations for high risk groups, such

as patients with a history of cancer, patients with a higher risk for CRC, or carriers of susceptibility genes, amongst others. Underage patients are of critical importance in our country because the Procuraduría Federal del Consumidor (Profeco) estimates that one in three Mexicans eats sausages at least three times a week, including 70% of children and adolescents.[23]

Knowing that the pathways that lead to cancer are rarely simple, it is difficult to study meat intake, in an isolated form, as a cause of cancer, because there are multiple external factors, such as genetic susceptibility, exposition to other carcinogens from sources other than oral intake (occupational, for example), and even inflammation caused from eating habits in people who consume higher quantities of meat and/or fat, with or without obesity. Within the field of food carcinogenicity, the existence of carcinogenic, co-carcinogenic and anti-carcinogenic substances, that may be present in the same foods, must be recognized.[7] There are also other factors native to the animal that determine the amount of fat and the proportion of saturated fat versus poly-unsaturated fatty acids, such as in the case of pigs raised in farms versus wild sow.[8]

It must also be underscored that red meat also contains other substances with anti-carcinogenic effect (zinc, selenium, folate, vitamins B6, B12 and D); however, the evidence seems to suggest that these have only a small role.[7]

CONCLUSIONS

As stated by Crowe,[9] there is no single *super food* that can prevent cancer; it is more of a combination of healthy eating habits and the variety of foods that achieves the desired effect. It is important to promote a healthy lifestyle in the patient, including a higher intake and variety of fruits and vegetables, as well as making better choices regarding meat intake. In individuals older than 20 years, digestive organ cancer is the main cause of hospital morbidity in men, and the third in frequency in women; it was also the one with the higher mortality for both genders in Mexico in 2013, according to data from the Instituto Nacional de Estadística y Geografía (INEGI).[6] For this reason, modifications that can reduce the incidence of these types of cancer may have a higher impact in our particular population.

Lets not forget that meats provide proteins of high nutritional value, as well as other nutrients (vitamin B6, vitamin B12, vitamin D, calcium, folate and selenium, amongst others). Current recommendations emphasize the message of moderating meat intake, instead of avoiding it altogether, by means of daily evidence-based decision making.

HIGHLIGHTS

- In Mexico, cold meats intake is high, so it is important to develop diets without these products.
- It is necessary to teach the people the group of foods to which cold meats belong, so that they may appropriately substitute these foods in order to achieve healthy diets.
- Given the evidence linking cancer and red meats, it is important to encourage fish and sea food intake.
- The individual's history of cancer must be considered when giving recommendations about red meat intake.

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