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Carcinogenicity of consumption of red meat and processed meat: A review of scientific news since the IARC decision

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ABSTRACT

In October 2015, the International Agency for Research on Cancer (IARC) issued a press release on the results of the evaluation of the carcinogenicity of red and processed meat. Based on the accumulated scientific literature, the consumption of red meat was classified as "probably carcinogenic to humans" and processed meat as "carcinogenic to humans". Given the importance of this topic, this review was aimed at revising the current state-of-the-art on the carcinogenicity of red and processed meat, some time after the IARC decision. Some new epidemiological studies and new reviews clearly supporting the IARC decision have been published during these months. However, a number of gaps still exist. It is basic to establish the mechanisms leading to the increased risk of colorectal cancer (CRC) and other cancers arising from red and processed meat consumption. Another important pending issue is to establish the role of known/suspected carcinogens contained in uncooked or unprocessed meats, as well as the influence of cooking. Finally, it would be highly recommended to conduct new epidemiological studies to elucidate whether the consumption of white meat, such as pork and/or poultry, are -positively or inversely- associated with an increased risk of CRC and other types of cancer.

Keywords:

Red meat; processed red meat; carcinogenicity; epidemiological studies; mechanisms; IARC

1. Introduction

In October 26, 2015, the International Agency for Research on Cancer (IARC), an Agency of the World Health Organization (WHO), issued the press release No. 240. (IARC, 2015), which summarized the results of an evaluation by that Agency on the potential carcinogenicity of consumption of red and processed meat. Red meat refers to meat of beef, veal, pork, lamb, horse, goat and mutton. In turn, processed meat is considered as products usually made of red meat that are cured, salted or smoked (e.g., bacon or ham), and often containing high quantities of minced fatty tissues (e.g., sausages). Based on data of the scientific literature, the consumption of red meat was classified as "probably carcinogenic to humans" (Group 2A), while processed meat was classified as "carcinogenic to humans" (Group 1). Details on this decision were published in the Lancet Oncology (Bouvard et al., 2015), as an advance of a monograph of the IARC, whose publication (volume 114) is estimated for summer of 2017.

With respect to the possible mechanisms involved in the potential carcinogenicity of red and processed meat, Bouvard et al. (2015) highlighted the presence of well known/suspected carcinogenic compounds such as N-nitroso-compounds (NOCs), polycyclic aromatic hydrocarbons (PAHs) and heterocyclic aromatic amines (HAAs). These compounds may appear in some meat processing procedures, such as curing and smoking (e.g., NOCs, PAHs), or when meat is heated at high temperatures (e.g., HAAs). After the press release No. 240 of the IARC, we proceeded to carefully revise the scientific literature on the possible mechanisms/reasons of that carcinogenicity, which were not contemplated in the decision of the IARC (Bouvard et al., 2015). Our revision was basically focused on the presence of a number of chemical compounds that are already present in raw or unprocessed meats (Domingo and Nadal, 2016). We concluded

that NOCs, PAHs and HAAs would not the only chemicals potentially responsible of the carcinogenicity of red and processed meat. Taking into account the results of a case-study (Catalonia, Spain) conducted in our laboratory, we noted that environmental pollutants with known carcinogenic potential such as some heavy metals, polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), dioxin-like polychlorinated biphenyls (PCBs), and other persistent organic contaminants, are present -in greater or lesser quantities- in raw/unprocessed meats. We revised the potential role that the presence of arsenic, cadmium, mercury, lead, PCDD/Fs, PCBs, polybrominated diphenyl ethers (PBDEs), hexachlorobenzene (HCB), polychlorinated naphthalenes (PCNs), polychlorinated diphenyl ethers (PCDEs), PAHs and perfluoro alkyl substances (PFASs) in raw/unprocessed meats, could mean for the carcinogenicity of the consumption of red and processed meats. Moreover, the results of our own studies (Aznar-Alemany et al., 2016; Jogsten et al., 2009; Perelló et al., 2008, 2009, 2010), as well as those from other researchers, suggest that certain cooking processes can modify (decreasing or increasing) the levels of environmental pollutants in foods in general, and in meats in particular. However, concentration changes would depend on not only the particular cooking process, but even more their original contents in each specific food item. As most of these environmental pollutants are organic, cooking procedures releasing or removing fat from the meat should tend to reduce the total concentrations of the contaminants in meat (Domingo, 2011, Perelló et al., 2009, 2010). On the other hand, in our studies we also observed that white meats, such as chicken, contained usually less organic contaminants than red meats. This would be an indicator of the importance with respect the potential carcinogenicity of the content of environmental pollutants in meats, before they are cooked or processed (Domingo and Nadal, 2016).

Obviously, the important decision of the IARC reached not only the scientific community and other stakeholders (e.g., governments, food safety agencies, etc.), but also the general population through the mass media. To date, comprehensive and reliable international data on potential changes in the consumption habits of red and processed meats by the general population are not available. It is also not possible to predict if some changes on dietary habits are going to occur when the monograph 114 of the IARC is published. With respect to the social repercussion, for example, it was already published that a single burned steak could be equivalent to smoking 600 cigarettes. In relation to this, concerning cancer risks, Gallus and Bosetti (2016) recently highlighted that obviously "meat consumption is not tobacco smoking". It seems to be currently the perception of the general population with respect to this issue.

The main purpose of the present manuscript was to review the most recent scientific literature specifically focused on the carcinogenicity of the consumption of red meat and processed meat, and whose results have been published after the IARC press release and a few months before the full monograph is published. Therefore, this review covers scientific articles published between October 2015 and February 2017. The scientific literature was reviewed using PubMed (www.ncbi.nlm.nih.gov/pubmed) and Scopus (www.scopus.com/home.url) databases.

2. Recent epidemiological studies and reviews mainly focused on colorectal cancer (CRC)

Lippi et al. (2016) performed a critical review of meta-analyses aimed at establishing whether the consumption of total meat and meat subtypes might be associated with human cancer. A convincing association was found between larger intake

of red meat and cancer, especially with colorectal, lung, esophageal and gastric malignancies. Increased consumption of processed meat was also found to be associated with colorectal, esophageal, gastric and bladder cancers. In contrast, an enhanced intake of white meat or poultry was found to be negatively associated with some types of cancers. Larger beef consumption was also significantly associated with cancer, while the risk was not increased consuming high amounts of pork. The authors concluded by recommending that consumption of red or processed meat should be limited (i.e., < 300 g per week), as already suggested by the World Cancer Research Fund (Demeyer et al., 2008). Lippi et al. (2016) submitted their review in March 2015, but their conclusions are in agreement with the subsequent decision of the IARC (October 2015), as well as with the general recommendations to avoid an increase in the risk of colorectal cancer (CRC) (consumption 50 g per day of processed meat would increase the risk of CRC by approximately 18%). Similarly, Carr et al. (2016a) had already published online (in January 2015, eight months before the press release of the IARC), the results of a systematic review and meta-analysis on meat subtypes and their association with CRC. The main conclusions of the meta-analysis suggested that red meat subtypes differed in their association with risk of CRC and its sub sites, while poultry intake was not associated with risk of CRC or its precursors. Beef and lamb consumption was associated with a moderately increased risk of CRC, while no association was observed with pork consumption. The authors also indicated that additional large scale cohort studies investigating specific meat subtypes were warranted, especially regarding the role of meat pork. In a second study conducted by the same research group (Carr et al., 2016b), the associations of baseline red meat and processed meat with survival outcomes were investigated, and the changes in intake among CRC survivors 5 years after diagnosis were explored. The results suggested that baseline red and processed meat intakes were not

associated with poorer survival among patients with CRC (Carr et al, 2016b). With respect to the association of consumption of red and processed meat and survival among patients with cancer, Miles et al. (2016) examined, through a case control-analysis, the relationship between that consumption and all-cause mortality among patients with cancers of the upper aerodigestive tract (UADT) and lung. An increased consumption of red or processed meat was associated with mortality among UADT cancer cases, but weakly associated with mortality among lung cancer cases. On the other hand, in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, pre-diagnostic consumption of red meat, processed meat, poultry and dietary fiber was examined in relation to CRC-specific mortality and all-cause mortality (Ward et al., 2016). Pre-diagnostic intake of red meat or fiber was not associated with CRC survival in the EPIC cohort. However, there was a suggestive evidence of an association between poultry intake and all-cause mortality among female CRC survivors and between processed meat intake and CRC-specific mortality.

In December 2015, just two months after the press release of the IARC, the content of a conference by Rohrmann and Linseisen (2016) entitled "Processed meat: the real villain?" was published online. The authors reviewed the evidences on the association of processed meat consumption with mortality, as well as some serious chronic diseases including cancer. They found that although the results of meta-analyses showed some degree of heterogeneity between studies, in general terms it must be taken into account that individuals with low red or processed meat consumption tended to have a healthier lifestyle. However, they also noted that substantial residual confounding could not be excluded. De Smet and Vossen (2016) reviewed the contribution of meat consumption to the supply of important micronutrients in the human food chain, and the extent to which this could be improved by primary production strategies, and impacts on human health.

They also discussed the IARC statement on the carcinogenicity of read and processed red meat consumption. It was concluded that more research was required on the mechanisms underlying the harmful effects on meat consumption, and on strategies to reduce these effects by improving the composition, processing and household cooking of meat. The authors also recommended that the interaction of meat with other foods in dietary patterns should be investigated. On the other hand, with respect to the mechanisms linking cancer -mainly CRC- to the consumption of red and processed meat, Demeyer et al. (2016) revised the hypotheses that to date had received most attention. It included the presence of PAHs and HAAs, and the enhancing effect of (nitrosyl)heme on the formation of NOCs and lipid peroxidation. Nevertheless, based on the conclusions of that review, none of these hypotheses would completely explain the link between red meat/processed meat intake and the CRC risk. Therefore, Demeyer and co-workers (2016) highlighted the importance of conducting mechanistic studies to investigate the combined CRC promoting effects of chemicals present in red and processed red meats. The authors indicated that a possible role of NaCl should not be discarded, as well as the combined effects of some PAHs and HAAs.

In another recent review, Jeyakumar et al. (2016) summarized the red and processed meat molecules associated with colorectal carcinogenesis and their relationship with the pathogenesis of CRC. These authors have remarked that there are multiple molecules in red and processed meat, which have been reported to have potential carcinogenic effects on colorectal epithelial tissues. The authors noted that processed meat is more carcinogenic compared to red meat because of the abundance of potent nitrosyl-heme molecules that form NOCs. In agreement with other researchers, they also highlighted that other molecules, such as PAHs and HAAs, have potential mechanisms for the initiation of CRC pathogenesis. The outcome of this review is consistent with the

recent statement of the IARC (2015). Wolk (2017) reviewed the potential health hazards of eating red meat. Since our current review is focused only on the relationship between consumption of red and processed red meat, and the risks of cancer, the rest of his conclusions are not here discussed. Risks from polled analyses and meta-analyses were estimated and presented together with recent findings on this subject. Based on at least six cohorts, Wolk (2016) found that the consumption of unprocessed red meat of 100 g/day increased 17% and 19% the risks for CRC and advanced prostate cancer, respectively. The consumption of 50 g/day of processed red meat significantly increased the risks of total prostate cancer (4%), cancer mortality (8%), breast cancer (9%), CRC (18%) and pancreatic cancer (19%). On the other hand, Grundy et al. (2016) reported that about 12% of CRCs, or 1.5% of all cancers detected in 2012 in Alberta, Canada, were attributable to the consumption of red and processed meat. These results were obtained from men and women participating in Alberta's Tomorrow Project, noting that about one-half of these participants exceeded the World Cancer Research Fund's 500 g/week recommendation for the consumption of red and processed meat. In turn, Boada et al (2016) reviewed recent epidemiological evidences about the impact of red and processed meat consumption on cancer. The main conclusion was that available data confirmed there was enough epidemiological evidence linking processed meat intake and CRC risk, but only limited evidence regarding unprocessed red meat intake and the disease, as well as also limited evidence about the associated between meat intake and other cancers. The revised literature suggested that a dietary intervention (mainly reducing processed meat intake) might be a promising approach for prevention of cancers of the colon, esophagus, liver, stomach and bladder (Boada et al, 2016).

Another issue of interest is the relationship between red meat consumption and healthy aging. Recently, Kouvari et al (2016) reviewed the association between red meat

and its subtypes, with chronic diseases (including cancer), in middle and advanced age subjects. Based on the available scientific information the authors noted that the role of nutrition in older people was still insufficiently investigated, with red meat not being an exception. Therefore, and considering the dramatic raise of older populations, the need of conducting studies targeting these individuals would be evident.

3. Recent studies mainly focused on cancers other than CRC

IARC (2015) indicated that the strongest evidence for an association of cancer with eating red meat was for CRC, while it was noted that there was also evidence of links with pancreatic cancer and prostate cancer (Bouvard et al., 2015). After the IARC press release, some new reviews on cancers –other than CRC- have been published. For example, some authors have investigated the association between various cancers and dietary habits. Butler et al. (2017) examined the relationship between diet and the risk of head-and-neck cancer (HNC) in a Chinese population including also whether smoking status could have any effect on risk. It was found that processed meat intake was associated with an increased risk in HNC. In turn, Bylsma and Alexander (2015) conducted a review and meta-analysis of prospective studies of red and processed meat, meat cooking methods, heme iron, HAAs and prostate cancer. These authors did not find an association between red or processed meat consumption and prostate cancer. However, they observed a weak positive summary estimate for processed meats. Caini et al. (2016) performed a meta-analysis of observational studies that investigated the association between the consumption of foods of animal origin (red, processed and white meat, fish and seafood, dairy products, and eggs) and the risk of non-Hodgkin lymphoma and its major subtypes and multiple myeloma among adults. It was concluded that the

consumption of red meat and dairy products tends to increase the risk, while that of fish tends to decrease it. On the other hand, Crippa and co-workers (2016) conducted a dose-response meta-analysis to quantify the potential association between red and processed meat and bladder cancer risk. The authors suggested that processed meat might be positively associated with bladder cancer risk. A positive association between red meat and risk of bladder cancer was observed only in case-control studies, while no association was noted in prospective studies. In turn, Wang et al. (2016) examined the potential dose-response relationship between red and processed meat consumption and risk of all-cause, cardiovascular and cancer mortality. It was concluded that that higher consumption of total red meat and processed meat was associated with an increased risk of total, cardiovascular and cancer mortality.

Until recently, reports relating meat intake to prostate cancer risk were rather inconsistent. Wu et al. (2016) investigated the associations between dietary factors and prostate cancer in a consortium of 15 cohort studies. The results did not support a substantial effect of total red, unprocessed red and processed meat for all prostate cancer outcomes, except for a modest positive association for tumors identified as advanced stage at diagnosis, while poultry intake was inversely associated with risk of advanced and fatal cancers. In turn, based on the results a prospective study on diet and prostate cancer progression, Wilson et al. (2016) reported that lower intakes of red meat and well-done red meat and higher intakes of poultry and fish, were associated with lower risk of high grade and advanced prostate cancer and reduced recurrence risk.

Zhao et al. (2016) recently conducted a systematic review and meta-analysis to analyze the relationship between consumption of red and processed meat and pancreatic cancer risk. The authors found sufficient evidence that red and processed meat consumption was positively associated with pancreatic cancer risk in case-control studies,

while no overall association was observed in cohort studies. Interestingly, red and processed meat consumption might increase pancreatic cancer risk in men, but not in women. In turn, Johnson (2016) reviewed published reports and systematic reviews published both before and after the IARC decision. This author identified areas of agreement and areas of controversy related with that decision. Among the first, epidemiology indicated that processed meat products were associated with increased risk of CRC, while evidence for red meat and for other cancers remained tentative. With respect to the areas of controversy, it was observed that several mechanisms for mutagenic effects of meat consumption had been identified, remaining unclear which ones cause cancer in humans. The extent to which complete abstention from meat protects against cancer would be also uncertain.

4. Mechanisms of cancer promotion associated with the consumption of red meat and processed meat

With respect to the possible mechanisms involved in the promotion of cancer by the consumption of red and processed meat, Hemeryck and co-workers (2016) conducted a study focused on the detection of diet-related DNA adducts in meat digests. Different identified DNA adducts were detected *in vitro*, while various DNA adduct types were found to be more prevalent upon digestion of a particular meat (e.g. concentrations of O^6-caboxymethylguanine (CMG) and the putatively identified carboxyethyl-C were higher in beef vs. chicken digests). The lipid peroxidation product malondialdehyde also increased upon digestion of beef compared to chicken. The impact of DNA repair on the dose-response relationship in CRCs was recently reviewed by Fahrer and Kaina (2016), demonstrating the existence of 'no effect' point of departures (PoDs) (i.e. thresholds for

genotoxicity and carcinogenicity). The available data supported the threshold concept for NOCs with DNA repair being causally involved. In turn, Hammerling et al. (2016) summarized possible mechanisms underlying the significant association between consumption or red/processed meat and CRC. The following three mechanisms, which could be partly overlapped, were particularly discussed: a) increased N-nitrosation/oxidative load leading to DNA adducts and lipid peroxidation in the intestinal epithelium, b) proliferative stimulation of the epithelium through haem, or food-derived metabolites, which could act either directly or subsequently to conversion, and c) higher inflammatory response, which might trigger a wide cascade of pro-malignant processes. According to Samraj et al. (2015), a red meat-derived glycan could also promote inflammation and cancer progression. These authors used an improved method to survey common foods for free and glycosidically bound forms of the nonhuman sialic acid *N*-glycolylneuraminic acid (Neu5Gc), showing that it was highly and selectively enriched in red meat. On the other hand, Inoue-Choi et al. (2016) reported that high consumption of red meat and processed meat might increase risk of postmenopausal breast cancer. They highlighted that added nitrite and heme iron might partly contribute to these observed associations. Recently, Alisson-Silva et al. (2016) described another mechanistic explanation for the human propensity for risk of red-meat associated diseases –including CRC- that is consistent with most observations: metabolic incorporation of a non-human sialic acid N-glycolylneuraminic acid (Neu5Gc) into the tissues of red meat consumers, and the subsequent interaction with inflammation-provoking antibodies against this *xenoautoantigen*. These authors also questioned that carcinogenic substances generated during cooking could be the main responsible of CRC and other types of cancer. They raised this interesting question: if the PAHs arising from high temperature cooking methods, which are not red meat-specific as they are also generated when grilling poultry

or fish (as well as by other forms of cooking), are the main responsible of CRC, why consumption of cooked poultry or fish is not considered as carcinogenic? We absolutely agree with this observation (Domingo and Nadal, 2016), being a key question which deserves further investigation by the scientific community.

5. Influence of cooking procedures

De Batlle and co-workers (2016) investigated the association between meat consumption and cooking practices and the risk of CRC in a population-based case-control study. The results supported an association of red, processed/cured/organ and total meat intake with an increased risk of CRC. Interestingly, and in contrast to the statement of the IARC, as well as the results of other previous studies, white meat showed also an increased risk of CRC. It was found that red and total meat rare-cooked preference was associated with lower risk of CRC for meat consumers. In turn, griddle-grilling and barbequing meat could be associated with increased CRC risk. However, stewing and oven-baking could increase the risk of white, but not red meat. In summary, cooking practices could modulate the risk of CRC. On the other hand, van Hecke et al. (2015) reported that increased oxidative and nitrosative reactions during digestion, could contribute to the association between well-done red meat consumption and CRC. These authors indicated that the hypothesis of the increased CRC risk caused by consumption of well-done red meat, which is usually explained by the formation of HAAs and PAHs, was not consistent with epidemiological findings. They suggested that the formation of NOCs and oxidation products might be more relevant. With respect to PAHs, the risks associated with consumption of barbecued meat may increase, if consumers use cooking practices that enhance the concentrations of these contaminants and their bioaccessibility.

In this sense, Hamidi et al. (2016), in a recent review on PAHs and their bioaccessibility in meats, found that there is a lack of studies on the bioaccessibility of these contaminants in foods, including meat. These studies are essential to estimate the bioaccessibility of PAHs, which is in turn critical for human absorption.

6. Discussion and conclusions

The intake of meat as a component of a healthy diet is being a controversial issue, as it has been noted in various reviews published in recent years (Biesalski, 2005; Celada et al., 2016; Corpet, 2011; McAfee et al., 2010; McNeill and van Elswyk, 2012). Lifestyle factors, including diet, have been vastly recognized as potentially important determinants of cancer risk. With regard to this, the 4th edition of the European Code against Cancer recently recommended that to reduce the risk of cancer, people following a healthy diet should avoid sugary drinks and processed meat, while they should also limit red meat and foods high in salt (Norat et al., 2015). These recommendations go along the same lines with the recent decision of the IARC (2015).

The main goal of the present review was to conduct an exhaustive revision of the scientific literature published after the IARC decision on the carcinogenicity of the consumption of red meat and processed meat (IARC, 2015). We have noted that the results and conclusions of both, the new epidemiological studies and reviews on the topic, agree with the IARC decision. This is especially evident for CRC (Boada et al., 2016; Carr et al., 2016 a,b; Demeyer et al., 2016; Jeyakumar et al., 2016; Kassier, 2016; Ward et al., 2016; Wolk, 2017), while associations between red/processed meat consumption and the incidence of other types of cancer, have been also reported (Butler et al., 2017;

Caini et al., 2016; Lippi et al., 2016; Grundy et al., 2016; Miles et al., 2016; Wolk, 2017; Wu et al., 2016).

However, there are still important gaps in the knowledge of the mechanisms of promotion of cancer associated with the consumption of red and processed meat. IARC focused the risks mainly on three groups of carcinogenic compounds: NOCs, PAHs and HAAs. These compounds are mainly generated during processing or cooking at high temperatures of red meats. However, other hypotheses remain open. While some possible mechanisms have been recently suggested (Fahrer and Kaina, 2016; Hemeryck et al., 2016; Samraj et al., 201), we would like to rise an important question, for which there is not yet a clear response: what happens with the known/suspected carcinogenic substances, which can be already present in red meats, before being cooked or processed? A number of studies have analyzed the concentrations of carcinogenic compounds such as PCDD/Fs, dioxin-like PCBs or the own PAHs –among others- in raw red meats, showing more or less notable levels of these compounds (Domingo and Nadal, 2016), depending on the kind of red meat and its origin. This would denote that the consumption of these meats, either unprocessed or uncooked, should also mean certain risks for the consumers. Cooking or processing simply would add new carcinogens, or it would increase the amounts (e.g., PAHs) that are already present in the same raw/uncooked meat. Another important question is what happens during the cooking or processing of white meat and poultry. The consumption of this kind of meats has not shown any positive association with CRC or other types of cancer (Carr et al., 2016a; Lippi et al., 2016; Wilson et al., 2016). However, recently De Batlle et al. (2017) showed an increased risk of CRC related with the consumption of white meat. Interestingly, white meats contain -in raw- lower concentrations of the examined organic pollutants with carcinogenic potential, than those found in red meats (Domingo and Nadal, 2016). However, an

association between poultry intake and all-cause mortality among female CRC survivors was recently found by Ward et al. (2016), while Wu et al.(2016) and Wilson et al. (2016) reported that poultry intake was not associated, or even inversely associated with prostate cancers. On the other hand, there are also doubts regarding pork consumption, since some authors have not found an increased risk of CRC associated with pork intake (Carr et al., 2016a; Lippi et al., 2016).

In summary, after 18 months of the press release of the IARC (2015) on the carcinogenicity of consumption of red meat and processed meat, most new publications clearly support that decision. Notwithstanding, there are still a number of gaps that need to be investigated. Thus, it is basic to establish the mechanisms that lead to an increased risk of CRC -and other cancers- for the consumers of red and processed meat. Another pending question is to elucidate the role of known/suspected carcinogens contained in uncooked or unprocessed meats, as well as the influence of cooking and its characteristics. Finally, it is important to conduct new epidemiological studies that allow clearly establish if the consumption of pork and/or poultry are associated or not with an increased risk of CRC and other types of cancer.

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