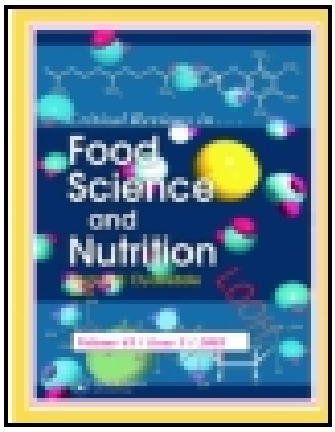

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Vic Shao-Chih Chiang[a] & Siew-Young Quek[b]
[a] Liggins Institute, The University of Auckland, New Zealand
[b] Department of Food Sciences, School of Chemistry Sciences, The University of Auckland, New Zealand
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The Relationship of Red Meat with Cancer: Effects of Thermal Processing and Related Physiological Mechanisms

Vic Shao-Chih CHIANG [1]; Siew-Young QUEK [2]

[1] Liggins Institute, The University of Auckland, New Zealand

[2] Department of Food Sciences, School of Chemistry Sciences, The University of Auckland, New Zealand

Corresponding Author

Associate Professor Siew-Young Quek

E-mail: sy.quek@auckland.ac.nz

Physical address: Level 5, Science Building, School of Chemical Sciences, The University of Auckland, 23 Symonds Street, Auckland 1142, New Zealand

Phone: +64 9 373 7599 Ext 85852

Fax: +64 9 373 7422

Abstract

Red meat is consumed globally and plays an important role in the Western diet. Its consumption is however linked with various types of diseases. This review focuses on the relationship of red meat with cancer, its dependency on the thermal processing methodology and the subsequent physiological effects. The epidemiological evidence is discussed, followed by introduction of the

species that were hypothesized to contribute to these carcinogenic effects including polycyclic aromatic hydrocarbons (PAHs), heterocyclic amines (HCAs), N-nitroso compounds (NOCs), heme iron and macromolecular oxidation products. Their carcinogenic mechanisms were then addressed with further emphasis on the involvement of inflammation and oxidative stress. The thermal processing dependency of the carcinogen generation and the partially elucidated carcinogenic mechanism both represent doorways of opportunities available for the scientific manipulation of their impact after human consumption, to minimize the cancer risks associated with red meat.

Keywords

Polycyclic aromatic hydrocarbons; heterocyclic amines; heme iron; oxidation products; inflammation; oxidative stress; N-nitroso compounds; carcinogenic

Introduction

Red meat is a generic term that refers to the skeletal muscle which is red when raw and generally refers to beef, veal, lamb, mutton and goat meat and does not include pig, kangaroo meat or game meats (RW.ERROR - Unable to find reference:676). The use of the red meat definition can vary between researchers where in some studies, pork has also been considered as red meat (Wie et al. 2014, Ley et al. 2014, Fretts et al. 2012). However, since pork displays minimal redness and possesses inferior levels of heme iron to other red meats (Lombardi-Boccia et al. 2002), it is disregarded in the current review as red meat. It will be discussed through the review why this discrimination is important. The average consumption of total meat globally is currently estimated to be 41.90 kg per person per year, with North America, South America, Australia, New Zealand, Europe, East Asia and Russia consuming more than 55 kg per person (FAO. 2012). Even though no up-to-date global statistics exist for red meat consumption, in the US, 50% of all meat consumption in 2013 was deemed to be red meat (USDA. 2014). Around the world in general, there has been increasing trends in the greater intake of meat in developed countries, therefore red meat can be expected to remain a major component in the Western diet (Daniel et al. 2011). From consumer perception research, red meat is appraised as a highly valued culinary ingredient and consumer product (Troy and Kerry. 2010). Red meat also acts as a rich source of high quality protein and provides other health benefits from their composition including conjugated linolenic acid, omega-3 polyunsaturated fatty acid, alpha-linolenic acid, retinol, a range of B vitamins and minerals including iron, zinc and selenium (McAfee et al. 2010). However, despite its importance in the Western diet and potential health benefits, the consumption of red meat had been associated epidemiologically with an increased prevalence of various diseases including cardiovascular disease (McAfee et al. 2010), type II diabetes (Song et

al. 2004) and cancer (Ferguson. 2010). This review focused on the association of red meat with cancer, the thermal processing dependency of the associated carcinogen formation and the physiological responses to these agents.

Epidemiology

From 17 cohort studies between 1990 to 2010, the World Cancer Research fund conducted a meta-analysis on the association between red meat intake with the colorectal cancer risk, involving approximately 2.6 million people *(WCRF. 2010)*. After controlling for various confounders, they found a 17% increase in colorectal cancer risk for each additional 100g of red meat consumed per day. Moreover, this positive association was observed in various other studies including different populations from Shanghai, US and Sweden as well as a 2011 meta-analysis that included the relevant PubMed publications from 1966 to 2011 (Chiu et al. 2003, Sinha et al. 2005, Larsson et al. 2005, Chan et al. 2011). This effect is not limited to the colorectal region, but increases in cancer risks for the bladder and endometrial has also been repeatedly reported (de Stefani et al. 2009, Lin and Sun. 2010, Ferguson. 2010) in addition to the 2014 systematic review that reported increases in esophageal cancer risk (Zhu et al. 2014).

Some researchers had further characterised the category of red meat and some studies has found a processing-type dependent relationship to exist with the associated cancer risks (Ferguson. 2010). These processing methods refers to both chemical processing including addition of nitrites, curing, salting, smoking and thermal processing that involves heat (Ferguson. 2010). This relationship is not exclusive for red meat as a Shanghai Women's health study and an Iran case-control study found that a wide variety of food types also exhibited this relationship (Lee et al. 2009, Hakami et al. 2013).

Chemically processed meats are frequently reported to augment the cancer risk in comparison to the non-chemically processed counterparts, including the two meta-analyses mentioned earlier as well as a recent Norwegian Women cohort study involving 85,000 women (WCRF. 2010, Chan et al. 2011, Parr et al. 2013, Catsburg et al. 2014).

Thermal processing can differ drastically from each other in aspect of their methods and the additional parameters involved such as the processing temperature and duration. Multiple studies including a Danish prospective study, a multi-ethnic cohort study, a California case-control study and a literature analysis on cancer burden demonstrated that longer processing duration and higher temperature in general, attributes to a higher cancer risk (Sinha et al. 2005, Joshi et al. 2012, Nothlings et al. 2009, Berjia et al. 2014, Sorensen et al. 2008). Interestingly, one study found this thermal processing dependency to disappear when white meat consumption was analysed and therefore suggest that red meat may potentially possess unique features that contributes to their associated cancer risks (John et al. 2011).

On the other hand, some studies had failed to observe the thermal processing dependent cancer relationship with red meat, despite the presence of an increased risk for total red meat consumption (di Maso et al. 2013, Parr et al. 2013). It is likely that this disagreement exist at least in part due to the inaccuracies in dietary reporting, inherent differences in the study conduct and the duration of the study. In addition, the use of a European based population for these two studies may have contributed to the null-reporting as a recent study found racial disparities in the red meat associated breast cancer risk between African American and Caucasian women (Chandran et al. 2013). Furthermore, a study that found higher colon cancer risks with lamb in comparison to other red meat, implicate that individual red meat subtypes can also influence the resulting cancer outcome (Egeberg et al. 2013). It is also imperative to note that some of these

epidemiological studies has taken pork into account as red meat. Pork has been disregarded as red meat in this review due to its low heme iron content (Lombardi-Boccia et al. 2002), which is known to influence the cancer risk (Kuhnle et al. 2007, Bingham et al. 1996,Lunn et al. 2007). A consensus should be reached among scientists on the definition of red meat, in order to make future studies more comparable to each other. Clinical intervention studies should also be conducted to directly measure the physiological effects of red meat consumption, both acutely and chronically, to provide a broader insight to the story in addition to the epidemiological results.

Carcinogenic Mechanisms

Several mechanisms were proposed for the processing dependent cancer associations. This includes the thermal formation of different carcinogens, polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs), the nitrite derived carcinogen, N-nitroso compounds (NOCs), endogenous NOC formation from inherent heme iron and the generation of lipid and protein oxidation products that initiate carcinogenic responses (Hui. 2012,Cross and Sinha. 2008,Corpet. 2011,Hedlund et al. 2008,Negre-Salvayre et al. 2010,Yeh, C.C., Lai, C.Y. et al. 2010).

Polycyclic Aromatic Hydrocarbons

PAHs constitute of fused aromatic rings that do not contain heteroatoms or substituents and the most commonly generated PAH in red meat is the benzo[a]pyrene (BaP) (Fetzer. 2000). It is generally accepted that PAH formation undergoes the hydrogen subtraction – C_2H_2 reaction route due to the low reaction barriers, high exothermicities and high abundance of acetylene and benzene/phenyl in the combustion flame (Kislov et al. 2013). In red meat, PAHs can be

generated through organic matter combustion that can occur under intense and direct heating conditions in addition to smoking processes that deposits PAHs from incomplete combustion with the heating source (Farhadian et al. 2012). In agreement with the hypothetical link of PAH with meat thermal processing and cancer risks, the amount of PAH generated is dependent on multiple parameters associated with the thermal treatment *(Table 1).*There has been reviews on the PAH content in various food types but these are not recent and they do not focus on red meat (Howard and Fazio. 1969, Dennis et al. 1983, Fretheim. 1983, Phillips. 1999). *Table 1* provides a summary of the studies conducted in the past decade that gave PAHs in red meat together with the thermal treatment parameters and the contents of the five key PAHs including benzo[a]anthracene (BaA), benzo[b]fluoranthene (BbF), BaP, indeno [1,2,3-cd]pyrene (InP) and benzo[g,h,i]perylene (BghiP). Generally, with longer duration of treatment times, there were higher amounts of PAHs generated as seen in infrared and smoking studies (Kendirci et al. 2014, Djinovic et al. 2008). This phenomenon was as expected because this would allow higher level of pyrolysis as well as higher smoke deposition and penetration into the meat matrix (Rey-Salgueiro et al. 2008). In contrast, indirect heat transfer such as convection was observed to reduce the amount of PAHs formed (Farhadian et al. 2011,Olatunji et al. 2014). This would be in part due to the reduction of pyrolysate deposition through the medium, as well as the medium acting as a barrier to the combustion taking place (Phillips. 1999).

PAHs can initiate carcinogenesis through their metabolically activated intermediates through covalent bonding to DNA, leading to the formation of protein adducts (Gurjar et al. 2010). This occurs through a dysregulated detoxification system that begins in the liver which up-regulates the cytochrome P450 enzymes (CYPs), CYP1A1 and CYP1B1, in response to PAH exposure, which then acts on the aryl hydrocarbon receptor to initiate detoxification (Baird et al. 2005).

The mono-oxygenase enzymes, CYP1A1 and CYP1B1 adds an epoxide group to the inert lipophilic PAH, that is then reacted into dihydrodiol by enzyme epoxide hydrolase, resulting in the formation of a reactive electrophile, the PAH diol epoxide (Baird et al. 2005). This diol expoxide could then bind to DNA to form DNA adducts that can induce mutations and subsequently intercalate within the DNA helix (Baird et al. 2005). There is also evidence that the carcinogenicity of PAHs can mediate through action of microRNAs, as reviewed very recently by (Izotti and Pulliero. 2014). In 2013, a study demonstrated that PAH treated hepatocellular carcinoma cell line could promote cancer cell migration through the up-regulation of microRNA-181 (Song et al. 2013a).

PAHs have been found in biological fluids including in the blood samples of Indian children, semen of Chinese infertile men, urine samples of Shanghainese men as well as urine samples of Korean adults and children (Song et al. 2013b, Yuan et al. 2014, Yoon et al. 2012, Singh et al. 2008). The presence of PAHs in the above mentioned biological fluids suggest that their carcinogenic effects may not be isolated to particular organs or tissue but it could exert systemic influence on the whole body.

Heterocyclic Amines

HCAs are made up of at least one bi-element heterocyclic ring in presence of at least one amine group (Cheng et al. 2006). The most abundant HCAs associated with red meat are the 2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenylimidazo(4,5 b)pyridine (PhIP) (Malejka-Giganti et al. 2005). The HCA contents in food have been reviewed multiple times in the past including a recent review that focused on meat (Shabbir et al. 2013). However, this review was not specific to red meat and studies before 2004 were not included. Similar to PAHs, it is evident that thermal processing parameters are highly responsible to the

generation of these species (Vitaglione and Fogliano. 2004, Sugimura et al. 2004, Eisenbrand and Tang. 1993, Skog et al. 1998, Shabbir et al. 2013). *Table 2* summarises the studies that investigated HCA content in red meat with focus on thermal treatment procedures and the contents of five key HCAs commonly measured, including MeIQx, PhIP, 2-Amino-3,4,8-trimethylimidazo 4,5-f quinoxaline (4,8-DiMeIQx), 1-methyl-9H-pyrido[3,4-b]indole (Harman) and 9H-pyrido[3,4-b]indole (Norhaman).

HCAs with a N-methyl 1-2-aminoimidazole moiety can be generated from Maillard reaction between carbohydrates and amino acids in the meat matrix to give rise to Schiff bases and the subsequent imine from aldol reaction (Vitaglione and Fogliano. 2004, Turesky. 2007). This imine then undergoes further heat catalytic events to generate dialkyl-pyrazine radical or pyridine radical from condensation of glyoxal and another imine (Vitaglione and Fogliano. 2004,Turesky. 2007). The radicals produced can then react with creatinine in the meat, and depending on the aldehyde added, a specific type of HCA is formed (Vitaglione and Fogliano. 2004,Turesky. 2007). A separate HCA class including 2-amino-9H-pyridole[2,3-b]indole (AαC) and 2-amino-3-methyl-9H-pyridole[2,3-b]indole (MeAαC) can be formed as a result of direct pyrolysis of glutamic acid and tryptophan pyrolysate (Turesky. 2007). As observed in *Table 2*, reductions in the formation of HCAs have been demonstrated using a variety of strategies that exploited their reaction mechanism. One example is to use the physiochemical properties of carbohydrates to induce food macromolecule interactions through polymerisation, branching and solubility to reduce the interactions responsible for HCA formation (Persson et al. 2004). Additionally, antioxidants have also been observed to reduce HCA formation and this was hypothesized in many studies to mediate through the scavenging activity of free radicals that were generated during HCA formation (Quelhas et al. 2010, Melo et al. 2008, Tsen et al. 2006,

Ruan et al. 2014). However, mechanistic studies conducted by (Wong et al. 2012) disproved this hypothesis and suggest the reduction effect mediates through trapping of phenylacetaldehyde. Furthermore, these studies also found that the HCA reduction does not act in a positive linear manner because under some of conditions tested, certain antioxidant concentrations were actually found to exert pro-oxidative effects (Melo et al. 2008, Quelhas et al. 2010, Ruan et al. 2014, Tsen et al. 2006, Wong et al. 2012).

Similar to PAHs, the carcinogenic property of HCAs inflicts at least in part through DNA adduct formation, but with different underpinning mechanism (Turesky. 2007). In the liver metabolism of these HCAs, CYP1A2 oxidation can occur to generate N-hydroxy-HCA species that is further acetylated and sulphated by acetyltransferases and sulphotransferases, respectively (Turesky. 2007). Then the esterified N-hydroxy-HCA can react with deoxy-guanosine of the DNA via its reactive intermediate, the nitrenium ion, to form HCA-DNA adducts (Turesky. 2007). It can also induce direct genotoxic effects as explored by recent studies using the HepG2 cell and mice (Pezdirc et al. 2013,Totsuka et al. 2014) and they were found to perturb the microRNA network in rat and mice models (Parasramka et al. 2012,Yamakawa et al. 2010).

In addition to the epidemiological evidence of red meat with cancer, a case-control study that focused on the levels of HCA consumption demonstrated a positive relationship with the risk of colon cancer (Helmus et al. 2013). Interestingly, this effect was found only for red meat derived- but not white meat derived- HCAs, which is in concordance with the observations found in another study discussed earlier (John et al. 2011). Genoptype polymorphisms in the HCA metabolizing genes, N-acetyltransferase and CYP1A2 were investigated in a nested case-control study in relation with red meat consumption and breast cancer risk (Lee et al. 2013). Despite the above study did not find a genotype dependent effect, it remains to be elucidated whether an

interaction exist for other cancer types. In combination, these two studies provide a taste of the complexity on the HCA associated toxicology where the adverse effect can be dependent on the food matrix as well as the genotype of the consumer.

Corresponding to PAHs, a systemic carcinogenic effect can be exerted by HCAs as PhIP DNA adducts has been found in human albumin and haemoglobin in participants taking a PhIP containing gelatin capsule and the native form of PhIP has been found in human hair (Dingley et al. 1999,Turesky et al. 2013). Moreover, after the consumption of a single meal of chicken, cooked at 180 °C for 6 min (estimated to result in 6 μg of HCAs) by non-smoking healthy adults, the PhIP levels in the urine rose postprandially from urine samples collected regularly over 12 hours (Busquets et al. 2013).

N-Nitroso Compounds

The use of nitrites are frequent in the industry for meat preservation against pathogenic bacteria including *Clostridium botulinum* and inhibiting the rancidity development, which gives the characteristic pink colour derived from the myoglobin reaction into mononitrosylhaemochrome (Cammack et al. 1999). This chemical processing could favour the formation of NOCs under high temperature conditions, through the nitrite and nitrogen oxide reaction pathway with secondary amines and N-alkylamides – which are components that are all present in the chemically processed meat (Cammack et al. 1999). The exposure to NOCs do not limit to chemically processed meat but endogenous nitrosation pathways, such as mediated by heme iron, can also contribute to NOC exposure and these were found to account for 45 – 75% total NOC exposure (Cammack et al. 1999, Dubrow et al. 2010).

It has been demonstrated that endogenous NOC production could be enhanced through the consumption of hemin (chloroprotoporphyrin IX iron (III)) (heme iron), via the reaction of nitric oxide to generate nitrosyl hemes, which can then react with secondary amines to form NOCs (Lakshmi et al. 2005b,Lakshmi et al. 2005a,Mirvish et al. 2008). Red meat harbours a rich source of heme iron and it was therefore hypothesized that NOC production could increase with increment in red meat intake, and this was indeed proven in several studies (Kuhnle et al. 2007,Bingham et al. 1996,Lunn et al. 2007). It was further demonstrated that white meat, which possesses much lower heme iron, is less capable in generating endogenous NOCs (Kuhnle et al. 2007,Bingham et al. 1996,Lunn et al. 2007). Since NOCs are an established carcinogen, this could in part explain the comparatively lower cancer risks for white meat than red meat, as described earlier (Helmus et al. 2013,John et al. 2011,Lunn et al. 2006). This cancer risk dependent on heme iron content is the reason why pork has been disregarded as red meat in the present review. Other meats that are high in heme iron including anchovy (Turhan et al. 2004) and ostrich (Lombardi-Boccia et al. 2002) are also generally disregarded as red meat because red meat conventionally refers to meat from mammal origin and therefore seafood and bird-derived meats are not considered as red meat (Williams. 2007).

Heat is known to degrade heme iron content in meat matrix and this effect was proposed to involve oxidative cleavage of porphyrin ring that result in transformation of heme iron into its non-heme counterpart (Garcia et al. 1996,Buchowski et al. 2006). The amount of heme iron retained in the meat matrix is dependent on the types and parameters of thermal processing (*Table 3*), and will therefore influence the subsequent physiological formation of carcinogenic NOCs. No review on the heme iron content of meat has been reported previously. Here, in *Table 3*, we provide a summary of all of the studies conducted to date (1988 – 2014) that determined

the content of red meat heme iron in relation to thermal processing. While heat does degrade heme iron, it was observed that at certain high temperatures, the denaturing of meat sarcoplasmic proteins prevented leaching of the heme iron associated proteins from the meat matrix but this effect was observed to be overrode with longer treatment times (Buchowski et al. 2006, Han et al. 1993, Pourkhalili et al. 2013).

A key NOC, N-nitrosodimethylamine (NDMA) can initiate carcinogenic response through CYP oxidation into alpha hydroxyl NDMA and further conversion into methyl diazonium ion (Chikan et al. 2012). This methyl diazonium ion had been found in *in vivo* studies to alter DNA methylation, leading to subsequent mutation and cancer progression (Chikan et al. 2012). Supplementary to the heme iron discussion, they have been directly linked with colorectal cancer risks in a 7.3 years follow-up Netherlands Cohort study (Gilsing et al. 2013). Higher red meat consumption in human lung tumour tissues has a differential gene profile with those that consumed lower amounts of red meat and 28% of these differentially expressed genes were directly or indirectly involved with heme iron metabolism (Lam et al. 2013).

Oxidation Products

Thermal processing of meat is well-known to generate lipid and protein oxidation products in relation with the production of free oxygenated radicals and the depleted antioxidant defence system within the food matrix (Sante-L'Houtellier et al. 2007, Gatellier et al. 2010, Traore et al. 2012, Ladikos and Lougovois. 1990). Reheating of meat subjects the meat to further thermal treatments and can therefore result in higher oxidation products (Pikul et al. 1984). Reheating was found to result in as high as 70% increase in the lipid oxidation product called malondialdehyde, during microwave and oven-reheating of chicken breast and 60% in chicken legs (Pikul et al. 1984).

Lipid oxidation can be initiated through the abstraction of a hydrogen atom from the lipid molecule and when this radical reacts with oxygen molecules, a lipid oxidative radical can be formed (Min and Ahn. 2005). This radical can propagate lipid oxidation by further abstracting hydrogen from other lipid molecules and termination can be achieved when these radicals react with each other (Min and Ahn. 2005). However, this terminated product can further decompose to generate secondary lipid oxidation products (Min and Ahn. 2005). Protein radicals can be formed through the same mechanism and the propagation step can lead to oxidation products to occur through cross-linking, side-chain modification and fragmentation to form carbonyl derivatives, free thiol groups, dityrosine species and Schiff bases (Lund et al. 2011).

Lipid oxidation in meat products was reviewed by (Love and Pearson. 1971, Ladikos and Lougovois. 1990) which were more than one quarter of a century old. Comparatively, for protein oxidation, a much more recent review was written by (Estevez. 2011), which very much focused on protein carbonyls in meat. *Table 4* summarises the literature in the area of lipid oxidation for the past decade. For protein oxidation, since a recent review is present, only studies conducted later than 2011 were included. While many studies have been concentrating on the oxidation during meat storage, *Table 4* emphasises on the thermal treatment effects and the associated oxidation products produced in red meat, as specified by the key markers used including acid value, peroxide value, p-anisidine value, malondialdehyde content and protein carbonyl content. Generally, higher temperature and longer duration treatment times corresponds to higher total oxidation but in some reported studies, they have observed a reduction in some oxidation markers with increase in these parameters (Gatellier et al. 2010, Roldan et al. 2014). This was explained to be due to further oxidative reactions of these products at more intense treatment

conditions, leading to new oxidation products (Gatellier et al. 2010, Roldan et al. 2014) which were measured in some studies, but not reported here.

Lipid oxidation can produce DNA-reactive aldehydes that yield DNA damage which progressively lead to cancer (Nair et al. 2012,Negre-Salvayre et al. 2010). Additionally, they also exhibit carcinogenicity through their adverse effects on signalling molecules or growth regulating factors that influences the cancer cell proliferation, differentiation and apoptosis (Nair et al. 2012,Negre-Salvayre et al. 2010). Not only can endogenously produced lipid oxidation products exert detrimental physiological effects, diet derived lipid oxidation products has also been shown to demonstrate adversities in aspects of cytotoxicy, genotoxicy and mutagenicity, which all have implications in carcinogenesis (Kubow. 1990, Biasi et al. 2013, Esterbauer. 1993). Oxidation products demonstrate potential to affect organisms systemically as reported in a Wistar albino rat study that after consumption of trans-2-alkenal, a polyunsaturated fatty acid oxidized derivative, the product subsequently appeared in the circulation of these rats (Grootveld et al. 1998).

Most of the studies on dietary lipid oxidation products are out of date except the Caco-2 cell study by (Biasi et al. 2013). Therefore, more recent studies are needed to further evaluate the effects of dietary oxidation products, especially for protein oxidation products as none exist to date. While some properties may be shared between lipid and protein oxidation products, there are undoubtedly differences that exist which are important to be elucidated. It is likely that protein oxidation products would also exhibit carcinogenic properties, as their levels has been found to be elevated in breast cancer, colorectal cancer and brain tumour (Mannello et al. 2009, Yeh, C.C., Lai, C.Y. et al. 2010, Amareshwara et al. 2011).

Carcinogenesis through Oxidative Stress and Inflammation

Red meat can also contribute to cancer through oxidative stress and inflammatory pathways and this was found to potentiate acutely in a study that investigated the consumption of 100 g wagyu beef on the postprandial inflammatory response in a randomized cross-over clinical trial involving ten healthy subjects (average 26.5 years) (Arya et al. 2010). Serum levels of the inflammatory markers, C-reactive protein, interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNFα) were significantly increased at 1 hour postprandial time point after consumption (Arya et al. 2010). Despite a postprandial increase in these inflammatory markers, a longer term intervention involving 60 participants to consume 215 g red meat per day for eight weeks did not increase the measured inflammatory markers including white cell counts, C-reactive protein, serum amyloid A and fibrinogen (Hodgson et al. 2007). In a cross-sectional study involving Tehrani female teachers however, higher quintiles in red meat intake association with higher plasma C-reactive protein concentration was observed (Azadbakht and Esmaillzadeh. 2009). This association was repeated in a more recent study that involved cross-sectional analysis on Europeans (Montonen et al. 2013) and American women (Ley et al. 2014). These long term studies can be confounded by other dietary contributions that were not controlled and therefore the evidence presented are less persuasive. In saying that, the red meat intervention of the (Hodgson et al. 2007) study was conducted in lieu of carbohydrate content and therefore any inflammation relationship with red meat may be obscured. The study by (Arya et al. 2010) provided support for the immediate inflammatory response of red meat but this is the only study of this nature that has been published to date, so further comparisons are therefore not yet possible.

Relationship of cancer with oxidative stress and inflammation

Chronic inflammation underlies multiple cancer related events have been demonstrated with leukocyte and lymphoreticular infiltration as well as a pro-inflammatory gene profile in various tumours (Rakoff-Nahoum. 2007). Furthermore, the involvement of microbe-induced inflammation in cervical and hepatocellular carcinoma, the increased colorectal cancer risk in inflammatory bowel disease patients, the relationship of IKKβ and JNK1 mediated inflammation with tobacco-smoking induced tumour and the enhanced IL-6 and TNFα levels in obesity related liver tumorigenesis, together supports the inflammation underpinnings in cancer (Triantafillidis et al. 2009, Takahashi et al. 2010, Park et al. 2010,Rakoff-Nahoum. 2007). The detailed discussion on inflammation and colorectal cancer, which is an important red meat related cancer as described earlier, can be found in the review by (Grivennikov et al. 2010).

The mechanisms of how inflammation can initiate carcinogenesis remains to be further characterised and the summary of current evidence in this area can be a separate review in itself. Various mechanistic studies have been previously reviewed and major highlights given include the inflammatory cytokine up-regulation of activation-induced cytidine deaminase to generate instability in various cancer genes and the pro-inflammatory macrophage microenvironment to generate mutagens in proliferating epithelial and stroma cells (Grivennikov et al. 2010, Lu et al. 2006). Recently, microRNAs has been found to contribute to this mechanism where multiple overexpressed microRNAs (miR) in cancer including miR-21, miR-125b, miR-155, miR-196 and miR-210 have been found to function in a network to regulate inflammation-related genes including nuclear factor kB (NF-KB), activator protein-1 (AP-1), signal transduction and activators of transcription (STAT), AKT and transforming growth factor-beta (TGFβ) (Tili et al. 2013).

An outstanding link between cancer and inflammation relationship is oxidative stress, which is the equilibrium loss between the antioxidant and reactive oxygen species (ROS) balance, and this is well known to promote carcinogenesis (Hemnani and Parihar. 1998, Scandalios. 2002, Fiaschi and Chiarugi. 2012, Sosa et al. 2013). This notion is supported by various studies including the participation of ROS in activating the stress kinases to promote inflammation (Rahman and Adcock. 2006), the finding that mitochondria derived ROS can promote secretion of the pro-inflammatory cytokine, TNFα (Ambade and Mandrekar. 2012) and in a recent study that found chronic oxidative stress to increase growth and tumorigenic potential of breast cancer cells (Mahalingaiah and Singh. 2014). This positive relationship between oxidative stress and inflammation can exhibit a positive regulatory feedback loop and therefore creates a self-perpetuating cycle that is devastating for the biological system (Vaziri. 2008).

Relationship of Carcinogens with Oxidative Stress and Inflammation

In response to PAH treatment, human promonocytic THP-1 cell lines expressed higher levels of pro-inflammatory cytokines, IL-1β, IL-8 and IL-12 (Goulaouic et al. 2008). The PAHs, BaP and Benzo[e]pyrene can increase the CD45 positive inflammatory cells to promote an inflammatory atherosclerotic plaque phenotype in apolipoprotein E knockout mice (Curfs et al. 2005). Furthermore, BaP can also exacerbate the high-fat diet induced expression of IL-1 β and TNFα in a mice model (Khalil et al. 2010). In humans, a population based cross-sectional study involving coke oven workers, which are at high risk of environmental PAH exposure, has elevated serum levels of the inflammatory markers, IgA and TNFα in comparison to steel-rolling workers (classified as low risk to environmental PAH exposure) (Jeng et al. 2011). This pro-inflammatory property of PAH is continuously demonstrated in recent studies using murine C10

lung cells and human bronchial epithelial cells (BEAS-2B) (Osgood et al. 2013, Ovrevik et al. 2013).

HCAs can generate free radicals *in vitro* via cytochrome P450 reductase and cytochrome b5 reductase and this free radical generation by the HCA, 3-amino-1,4-dimethyl 1-5*H*-pyrido[4,3-*b*]indole (Trp-P-1), can mediate the pro-inflammatory NFκB activity (Maeda et al. 1999,Yun et al. 2006). During incubation under pro-inflammatory conditions using acidic pH, HOCl and myeloperoxidase, DNA adduct formation from the HCA, 2-methylimidazo[4,5-*f*]quinoline (IQ) was promoted (Lakshmi et al. 2005b). Furthermore, two animal studies that investigated the effect of PhIP, one looking at the mice ventral prostate and the other in rat colons, found elevations in inflammation and oxidative stress, respectively, in response to PhIP (Nakai and Nonomura. 2012, Li et al. 2014).

No studies could be identified to relate inflammation with NOCs but heme iron, described earlier as a promoter for endogenous NOC production, was found to induce inflammation in mice (Wagener et al. 2001), though this was the only study identified to date. Studies involving heme oxygenase are comparatively more abundant and may provide insights to this story because of its primary function to degrade heme. It exhibited anti-inflammatory properties in mice, Zucker diabetic fatty rats and macrophages (Jadhav et al. 2013, Ndisang et al. 2014, Lee and Chau. 2002, Wagener et al. 2001). Even though the underlying mechanisms that were described in these studies did not discuss about heme, its primary function to degrade heme should not be disregarded in these experimental models.

Although there is very exiguous information on the effects of dietary lipid and protein oxidation products on biological inflammation and oxidative stress, it is feasible to hypothesize that a positive relationship exist because of the intimacy of lipid and protein oxidation with oxidative

stress ((Dalle-Donne et al. 2003, Menazza et al. 2014, Seet et al. 2011, Jialal et al. 2012). There is also evidence that demonstrate the endogenous lipid and protein oxidation processes are inflammatory as seen in studies that showed inflammation-related epigenetic changes to lipid peroxidation in the intestinal epithelial cells (Yara et al. 2013) and advanced protein oxidation products to mediate inflammation in chronic renal failure patients (Witko-Sarsat et al. 1998).

Insight for Future Work

From the discussion presented in this review, a number of major gaps can be identified. In order to further understand the relationships between red meat and cancer, these gaps needs to be addressed in future studies.

Epidemiology studies are continuingly important but new studies should critically assess the current methodologies used for these studies and explore newer technologies and solutions that address the weaknesses in these methodologies. For example, there are new studies (Adamson and Baranowski. 2014, Freese et al. 2014, Kirkpatrick et al. 2014) that applied methods that can increase the accuracy and efficiency of dietary assessments, which are fundamental to the success of epidemiological studies. In this context, for example, more specific dietary groupings for red meat can be achieved in aspects of red meat subtypes, thermal treatment methods and their specific parameters.

Though there has been a number of research that studied the carcinogen production mechanisms (Zamora et al. 2013, Kislov et al. 2013), deeper insight needs to be attained to complement the observed differences in the content of these species with varying thermal processing parameters. With the development of various novel food processing technologies including dielectric heating, ohmic heating, pulsed electric fields and high hydrostatic pressure (Pereira and Vicente. 2010),

it is also important to determine how these methods can affect the generation of carcinogenic species. It is equally essential to consider other factors that play a role in the carcinogen generation in addition to the thermal processing parameters, including the storage time, food packaging, age, sex and feed of the animal as demonstrated in various studies (Szterk and Waszkiewicz-Robak. 2014, Johnston et al. 2005, Kim et al. 2012). It may be useful to develop mathematic models that allow *in silico* calculation of the carcinogen formation that takes into account these different factors. The understanding of carcinogen formation in the food matrix will enable better strategies to be developed that counteract their final concentrations. As shown in the summarised tables, several studies has already been published to endeavour this objective through manipulating the animal feed and by studying the effects of antioxidants, carbohydrates, oils, acid, alcohol and other food matrices.

In addition to the effects of extra dietary components to the red meat in influencing the *ex vivo* carcinogen formation, they may also exert impact on the *in vivo* digestion and metabolism of red meat that contributes to the carcinogenicity. The feeding of turkey meat supplemented with antioxidants, grape seed extract or butylated hydroxytoluene to swines for seven days resulted in lower oxidation products, conjugated dienes, compared to those without supplements (Kuffa et al. 2009). Turkey meat feeding in healthy humans resulted in postprandial reduction in plasma and urinary malondialdehyde levels when the meat was soaked with red wine before or after thermal processing (Gorelik et al. 2008). Postprandial plasma and urinary malondialdehyde levels was also found to be reduced when healthy participants consumed a burger with beef patty blended with rosmarinic acid (Li et al. 2010). These types of studies addressing food molecule interaction and physiological response were not identified for other red meat carcinogens and therefore highlight key voids to be fulfilled.

Emphasis also needs to be given to investigate how these carcinogens can affect the biological system in term of effect and mechanism. In order to truly understand this, the consideration of potential contributing factors needs to be taken including demographics, genotype, microbiota and clinical factors. While there are studies that have been conducted in cell culture and animal models to elucidate this relationship, there is a need to translate these into clinical studies that controls dietary intervention critically. At the same time, the different concentrations of carcinogens in the meat matrix also need to be translated physiologically as it is unlikely that these carcinogens will act in a linear concentration-dependent relationship physiologically. At the moment, a randomized clinical trial is being conducted by us and co-workers to investigate the effects of contrasting thermal processing on the postprandial inflammatory response in healthy young males (Chiang et al. 2014). The understanding of the physiology mechanism can facilitate development of solutions that goes beyond reductions in the carcinogen formation. Reducing carcinogen formation is a key strategy but understanding how these differing concentrations affect our physiology will enable the monitoring of optimal efficacy and paves way for better meat matrix studies in the future.

Conclusion

From multiple epidemiological studies, the consumption of red meat has been linked with cancer risks and this effect was found in some studies as dependent on the processing methods used for the red meat. This observation is in line with the thermal processing dependency of the key cancer associated agents related to red meat including PAHs, HCAs, heme iron and oxidation products. The parameters of thermal processing incorporates a wide range of factors including duration, temperature, ingredients or food additives present, dimension, heat transfer method and heating source as well as profound impact from pre- and post- processing parameters. These

cancer associated agents can direct or facilitate DNA damage at both local metabolic sites and systemically. They can also potentiate their carcinogenesis effects through dysregulation of the oxidative balance and inflammation homeostasis. In order to minimize the cancer risks associated with red meat consumption, it is essential to obtain further understanding in the associated areas including epidemiology, food chemistry and physiology. Future epidemiological studies needs to be conducted with improved accuracy and higher specificity. The effect of multiple parameters and their mechanism associated with thermal processing formation needs to be further understood including those from novel processing methods. The physiological effects and mechanisms of carcinogenesis as well as the effects of the resulting reductions in carcinogen concentrations and food molecule interactions on the physiology need to be elucidated.

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Table 1. Effects of thermal processing and associated parameters on the PAH content in red meat

Red Meat[1]	Thermal Treatment	Treatment Parameters[2]	Total Sample Size [7]	BaA	BbF	BaP	InP	Bghi P	TP	Reference[3]
Beef;Australia ;150 g (3 x 4)	Grilling - Methane fuelled home cooker	Medium Heat(3)	10	0.037	0.064	0.027	0.032	0.09	1.5	(Saito et al. 2014)
Lamb mandi; Kuwait;	Charcoal-grilling (Indirect heat)	-	4			0.05			76.3	(Alomirah et al. 2011)
Lamb kabab (minced); Kuwait;	Charcoal-grilling (direct heat)	-	6			1.37			241	
Lamb tikka	Charcoa	-	4			2.4			648	

(cubes); Kuwait;	l-grilling (direct heat)			8		
Lamb shawerma (slices); Kuwait;	Gas-grilled (indirect heat)	Marinated	6	1.33	27	
Lamb burger; Kuwait;	Electric-grilled (indirect heat)	-	3	1.93	110	
Smoked lamb; Kuwait;	Electric-smoked (indirect heat)	-	2	1.09	92.2	
Lamb arrayes; Kuwait;	Charcoal-grilling (direct heat)	With pita bread, onion, parsley and spices	3	0.87	60.5	
Beef strip	Barbecu	End	10	6.3	229	(Aaslyn

loins; Denmark; 2 cm	ed	internal temperature (40 - 80)								g et al. 2013)
Beef satay; Malaysia; 4 - 5 small pieces	Charcoal-grilled	Well done	18		9.67	7.35				(Farhadian et al. 2010) [5]
Beef kebab; Malaysia; Sliced	Gas-grilled	Well done			0.32	0.37				
Longissimus dorsi of beef ; Portugal; 399.4 g (2.5 cm thick)	Charcoal-grilled (Wood)	200(18)	18	0.39	1.03	0.41	nd	0.64		(Viegas et al. 2012)[5]
	Charcoal-grilled (Coconut)	200(18)		1.38	0.81	0.51	nd	0.63		
Beef loin; Korea; 0.5 cm cubes	Gas-Roasted	200(30)	30			0.003			0.025	(Chung et al. 2011) [5]
	Charcoal-Roasted	200(30)				nd			0.007	
	Charcoa	(30)				0.0			0.7	

	l-Grilled			55			53	
Beef	Charcoa	200(30)		0.0			0.0	
ribs;Korea;0.5	l-			32			5	
cm cubes	Roasted							
	Charcoa	(30)		0.1			0.7	
	l-Grilled			99			87	
Beef ribs with	Charcoa	200(30)		0.0			0.0	
sauces;Korea;	l-			05			21	
0.5 cm cubes	Roasted							
	Charcoa	(30)		0.2			0.7	
	l-Grilled			02			97	
Lean beef	infrared	370.62		3.1		nd	0.25	50.	(Kendir
meatball;	processi	(4);		7				2	ci et al.
Turkey; 5cm	ng (10.5	Meatball							2014) [4,5]
x 2.5cm	cm)	filling							
				3.2		nd	0.24	64.	
		370.62(8	3	3				06	
		);							
		Meatball							
		filling							
				2.5		nd	0.14	24.	
		370.62(1		1				31	
		2);							

	Meatball filling				
infrared processing (13.5 cm)	370.62(4); Meatball filling	0.24	nd	0.31	13.02
	370.62(8); Meatball filling	0.28	nd	0.3	8.98
	370.62(12); Meatball filling	0.52	nd	0.37	14.21
infrared processing (16.5 cm)	370.62(4); Meatball filling	0.18	nd	0.17	11.12
		2.5	nd	0.33	32.

	370.62(8); Meatball filling	8			08
	370.62(12); Meatball filling	2.56	nd	0.27	46.66
infrared processing (10.5 cm)	567.83(4); Meatball filling	1.95	nd	0.16	13.93
	567.83(8); Meatball filling	2.01	nd	0.22	21.32
	567.83(12); Meatball	1.39	nd	0.24	19.17

	filling				
infrared processing (13.5 cm)	567.83(4); Meatball filling	1.95	nd	0.07	33
	567.83(8); Meatball filling	1.93	nd	0.09	32.93
	567.83(12); Meatball filling	1.89	nd	0.23	25.48
infrared processing (16.5 cm)	567.83(4); Meatball filling	2.12	nd	0.25	23.65
	567.83(8	2.33	nd	0.28	30.58

	); Meatball filling				
	567.83(12); Meatball filling	2.22	nd	0.23	38.52
infrared processing (10.5 cm)	847.55(4); Meatball filling	0.41	nd	0.19	7.86
	847.55(8); Meatball filling	0.38	nd	0.08	7.55
	847.55(12); Meatball filling	0.48	nd	0.22	7.19

infrared processing (13.5 cm)	847.55(4); Meatball filling	0.36	nd	nd	8.69
	847.55(8); Meatball filling	0.22	nd	0.09	10.9
	847.55(12); Meatball filling	0.24	nd	0.24	9.9
infrared processing (16.5 cm)	847.55(4); Meatball filling	0.2	nd	0.19	5.63
	847.55(8);	0.25	nd	0.08	6.41

		Meatball filling						
			0.3		nd	nd	4.47	
		847.55(12); Meatball filling						
Beef filet; Malaysia; 0.5 cm cubes	Steam preheating, Charcoal-Grilling Microwave preheating, Charcoal-grilling Charcoal-grilling	(4 for steam; 2 charcoal-grilling); Satay mrinade (60s microwave; 4 charcoal-grilling); (10); Satay mrinade,	3	nd	nd		77.6	(Farhadian et al. 2011) [5]
				nd	nd		86.3	
				nd	nd		83.3	

		Aluminium Wrapping (5); Satay mrinade, Banana Wrapping (8); Satay mrinade								
	Charcoal-grilling			1.19	0.49				92.2	
	Charcoal-grilling			6.54	3.16				153	
Frankfurter-type sausage (19.8% beef); Germany	Smoked, beech Smoked, oak Smoked, spruce Smoked, poplar Smoked, alder Smoked, hickory	reddened 52 (10), dried 56 (12), smoked 58 (12), scalded 75 (25), other sausage filling	29	1.61 1.07 1.17 0.92 1.69 0.98	0.61 0.43 0.46 0.44 0.65 0.36	0.71 0.47 0.57 0.44 0.84 0.46	0.4 0.27 0.3 0.26 0.44 0.23	0.33 0.23 0.26 0.23 0.39 0.19	10.4 7.33 7.44 6.23 10.9 6.29	(Hitzel et al. 2013)

Smoked, spiced beech wood chips with apple smoking spice mix	0.82	0.27	0.32	0.17	0.12	5.1
Smoked, spiced beech wood chips with cherry smoking spice mix	1.64	0.58	0.73	0.38	0.41	10.7
Smoked, spiced beech	1.11	0.38	0.55	0.25	0.19	6.86

	wood chips with juniper berries and bay leaves									
	Smoked, fir			1.02	0.37	0.58	0.26	0.73	6.97	
Beef ham; Serbia;	Smoked	(0 day)	1	0.05	0.03	0.02	0.02	0.03	0.4	(Djinovic et al. 2008)
		(3 day)		0.20	0.08	0.07	0.03	0.04	1.5	
		(6 day)		1.04	0.34	0.4	0.23	0.21	7.7	
		(9 day)		1.36	0.45	0.48	0.28	0.25	8.8	
		(12 day)		1.68	0.51	0.63	0.3	0.29	12.4	
		(15 days)		1.98	0.63	0.69	0.35	0.34	15.2	
		(18 days)		2.94	0.91	1.09	0.56	0.51	21.3	

Beef stripe; South Africa; 50g	Smoked	-		5.34	5.1	1.42	(Olatunji et al. 2014) [6]
	Grilled	-	1	2.74	0.62	1.5	
	Boiled	-		0.87	0.54	0.82	

Abbreviations: TP (total PAH content measured); nd (not detected); benzo[*a*]anthracene (BaA); benzo[f]fluoranthene (BbF); benzo[a]pyrene (BaP); indeno[1,2,3-cd]pyrene (InP); benzo[g,h,i]perylene (BghiP).

[1]The type of red meat, the source of purchase and the sample dimension used for thermal treatment is listed.

[2]The parameters of the thermal treatment – temperature (^{o}C) (time – minutes); other parameters.

[3]All PAH contents are reported as ng per g of meat matrix

[4]Infrared processing – instead of temperature the unit is in voltage (kW/m^2) and all samples were ohmic preheated for 92 seconds at 15.25 V/cm.

PAH contents were measured using GC-MS unless superscripted [5]HPLC & [6]GC-FID

[7]Total sample size is calculated from the thermal processing and the final analytical sample size; the sample size is delegated as 1 if it was not specified in the publication

Table 2. Effects of thermal processing and associated parameters on the HCA content in red meat

Meat [1]	Thermal Treatment	Treatment Parameters [2]	Total Sample Size [5]	MeIQx	4,8-DiMeIQx	Norharman	Harman	PhIP	TH	Reference [3]
Longissimus dorsi of Beef; Portugal; 90 - 100 g (0.8 - 1.0 cm thick)	Grilled	180-200(8);	4	4.1	1.3			3 3.8		(Quelhas et al. 2010)
		180-200(8); Green tea marinade - 1 h		4.1	1.7			2 0.9		
		180-200(8); Green tea marinade - 2 h		3.6	1.3			2 4.1		
		180-200(8); Green tea marinade - 14h		3.7	2.4			1 6.9		

		180-200(8); Green tea marinade - 6 h	4.9	2.01		8.8	
Beef;Australia; 250g	Pan fried	(10);			2.69	6.29	(Raza et al. 2014)
	Deep fried				5.51	20.94	
	Grilled	(20);			17.21	27.51	
	Roasted				1.52	4.01	
Mutton;Australia; 250g	Pan fried	(10);			3.46	8.12	
	Deep fried				6.44	24.13	
	Grilled	(20);			19.06	30.26	
	Roasted				1.6	4.51	

Beef; Malaysia;1 kg (1cm x 1cm cubes)	Char coal-grilled	270 - 300(7); Marinade		1 5.6	nd		n d	81 .68	(Jinap et al. 2013)
	Microwave-charcoal grilled	270 - 300(30s microwave, 3min fry); Marinade		9.99	nd		n d	65 .52	
	Microwave-deep fried	160(30s microwave, 3min grill); Marinade	3	nd	nd		n d	nd	
	Char coal-grilled	270 - 300(8); Marinade		1 5.12	nd		1 1.3	14 0.68	
	Microwave-e-	270 - 300(40s microwave, 4 min grill);		1 1.9	nd		n d	81 .31	

	charcoal grilled	Marinade	2					
	Microwave-deep fried	160(40s microwave, 4 min fry); Marinade	nd	nd		nd	2.51	
Minced Beef; Sweden;100 g	Pan-fried	200(5);	0.6	15.3		44.2	60.1	(Persson et al. 2004)
		200(5); TPP, NaCl	0.1	5.1		11	16.2	
		200(5); Guar gum, TPP, NaCl	1.1	7.8		8.7	17.6	
		200(5); Pectin, TPP, NaCl	10.5	16.8		17.1	34.4	
		200(5); Methylcellulose, TPP, NaCl	1.4	5.6		7.7	14.7	
		200(5); Hi-	0.	13.		1	24	

		Maize, TPP, NaCl 200(5); Potato starch, TPP, NaCl 200(5); Potato fiber, TPP, NaCl 200(5); Wheat, TPP, NaCl	4 0.2 0.1 0.3	9 2.3 4.1 5.6	0.1 3 6 7.4	.4 5.5 10.2 13.3	
Longissimus dorsi of beef; Portugal; 90 - 100 g (0.8 - 1.0 cm thick)	Pan-fried	180 - 200(8); 180 - 200(8); Pilsner Beer marinade - 1h 180 - 200(8); Pilsner Beer marinade - 2h 180 - 200(8); Pilsner Beer marinade - 4h 180 - 200(8); Pilsner Beer marinade - 6h	3.7 3 2 1.8 1.3	1.3 nd nd nd	3 4 1 2.5 7.5 5 4.5		(Melo et al. 2008)

		180 - 200(8); Douro red wine marinade - 1h		3.2	2.5		5
		180 - 200(8); Douro red wine marinade - 2h		2	2		1.5
		180 - 200(8); Douro red wine marinade - 4h		3	1		1.0
		180 - 200(8); Douro red wine marinade - 6h		2.4	nd		4.5
Ground beef patty; Kansas, USA; 100g (1.5 x 9 cm)	Electric grilled	190(10);		4.68		0.33	0.06 (Tsen et al. 2006)
		190(10); 0.02% Rosmarinic acid		1.69		0.33	0.03
			9	2			
		190(10); 0.1% Rosmarinic acid		2.76		0.45	1.94 0.48
		190(10); 0.3% Rosmarinic acid		2.88		0.44	0.72 0.2

	7			8
190(10); 0.02%	1.	0.2	0.	0.
Rosamary	3	5	43	2
powder	8			9
190(10); 0.1%	3.	0.5	0.	0.
Rosamary	0	4	41	4
powder	5			1
190(10); 0.3%	2.	0.7	0.	0.
Rosamary	5	6	46	2
powder	7			
205(15);	1	1.0	1.	3.
	0.	8	15	0
	9			7
205(15); 0.02%	3.	0.7	0.	1.
Rosmarinic acid	3	6	84	1
	2			1
205(15); 0.1%	7.	0.9	1.	2.
Rosmarinic acid	0	7	09	1
	3			
205(15); 0.3%	4.	1.1	1.	1.
Rosmarinic acid	5	8	17	4
	1			2
205(15); 0.02%	7.	0.8	0.	1.

		Rosamary powder 205(15); 0.1% Rosamary powder 205(15); 0.3% Rosamary powder	6 4 7. 4 4 4. 6 9		9 1.2 4 1.7 6	81 0. 98 1. 05	7 3 1. 6 2 0. 7		
Sirloin beef; Japan; 134 g (1cm thick)	Pan-fried	Rare; Medium; Well-done; Very well-done; Rare; Marinade 1 Medium; Marinade 1	3	n d n d 0. 0 7 1. 4 3 n d n d	nd nd nd 0. 39 nd nd		n d 0. 0 4 0. 0 4 0. 5 8 n d n d	nd 4. 3 10 .5 23 9. 4 nd nd	(Iwasaki et al. 2010) [4]

	Well-done; Marinade 1	nd	nd	nd	nd
	Very well-done; Marinade 1	0.33	nd	0.05	37.9
Grilled	Rare;	nd	nd	nd	nd
	Medium;	nd	nd	nd	nd
	Well-done;	0.24	nd	0.7	94.1
	Very well-done;	5.41	1.92	16.21	23.60.17
	Rare; Marinade 2	nd	nd	nd	nd
	Medium; Marinade 2	nd	nd	nd	nd
	Well-done; Marinade 2	nd	nd	nd	nd
	Very well-done;	4.	2.	4.	11

	Marinade 2	8 6	35	6 4	85 .5
Chur rasco	Rare (interior);	n d	nd	0. 1	10
	Medium (interior);	n d	nd	0. 4 3	42 .7
	Well-done (interior);	n d	nd	0. 5 6	55 .6
	Very well-done (interior);	0. 5 3	nd	1. 1 3	16 5. 6
	Rare (exterior);	n d	nd	0. 4 9	49 .4
	Medium (exterior);	0. 3 4	nd	1. 6 1	19 4. 9
	Well-done (exterior);	0. 5 6	nd	4. 0 7	46 3. 3
	Very well-done	1	3.	3	50

		(exterior);		5.4	67	1.8	86.1	
		Rare; Marinade 3		nd	nd	nd	nd	
		Medium; Marinade 3		nd	nd	nd	nd	
		Well-done; Marinade 3		0.21	0.28	0.14	62.8	
		Very well-done; Marinade 3		0.43	0.26	0.56	12 4.7	
Ground beef patty; Hong Kong; 30g (6.2 x 1.2 cm)	Pan-fried	200(6);	18	7.39	2.46	7.44	17.3	(Wong et al. 2012)
		200(6);0.2 mmol ascorbic acid		6.13	2.12	6.02	14.3	
		200(6);0.2 mmol Niacin		5.99	2.09	6.03	14.1	
		200(6);0.2 mmol Pyridoxamine		4.22	1.53	4.22	10	

			9				4	
Ground beef; Ohio, USA; 5g	Heat	200(20)	2 2. 6 5	1. 74	5.5 5	10 .8 8	1 2. 1 3	(Ahn and Grun. 2006)
		200(20); 0.02% BHT/BHA	9. 7	2. 09	5.0 5	10 .7 5	9. 4 3	
		200(20); 0.5% ActiVin	8. 6 2	1. 5	5.3 8	78 .3 1	5. 9 3	
		200(20); 1.0% ActiVin	6. 9	nd	5.1 6	10 9. 14	4. 4	
		200(20); 0.5% Pocynogenol	5. 2 3	2. 2	4.7 8	11 .5 5	7. 6 5	
		200(20); 1.0% Pycnogenol	5. 1 2	2. 13	4.0 8	9. 7	5. 5 8	
		200(20); 0.5% Herbalox	7. 5 9	1. 48	5.5	10 .3 7	9. 2 2	

6

		200(20); 1.0% Herbalox	5.56	0.85	5.56	10.15	5.47
Ground beef patty; Ohio, USA; 80g	Pan-fried	210(10)	6.35	1.36	2.01	2.99	9.15
		210(10); 0.02% BHT/BHA	6.51	1.16	0.96	2.18	7.99
		210(10); 0.5% ActiVin	4.69	nd	1.04	10 7.43	9.02
		210(10); 1.0% ActiVin	2.31	nd	0.72	21 0.76	6.18
		210(10); 0.5% Pocynogenol	3.38	nd	0.92	2.16	5.74
		210(10); 1.0% Pycnogenol	2.44	nd	0.79	2.02	5.85
		210(10); 0.5% Herbalox	5.99	1.04	1.02	2.3	5.66

				9				
		210(10); 1.0%		4.	nd	nd	1.	3.
		Herbalox		8			34	8
				6				
Longissimus thoracis	Grilli	250 (Final		1.	0.	0.0	0.	(Ruan
beef steak; Canada; 200g	ng	internal temp -		3	13	8	19	et al.
		71); 340 IU Vit		6				2014)
		E						
		250 (Final		1.	0.	0.0	0.	
		internal temp -		2	13	9	14	
		71); 690 IU Vit		7				
		E						
		250 (Final	3	1,	0.	0.0	0.	
		internal temp -		3	14	9	14	
		71); 1040 IU Vit		8				
		E						
		250 (Final		1,	0.	0.0	0.	
		internal temp -		2	12	7	13	
		71); 1740 IU Vit		2				
		E						

Abbreviations: TH (total HCA content measured); nd (not detected); 2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline (MeIQx), 2-amino-1-methyl-6-phenylimidazo(4,5 b)pyridine

(PhIP); 2-Amino-3,4,8-trimethylimidazo 4,5-f quinoxaline (4,8-DiMeIQx), 1-methyl-9H-pyrido[3,4-b]indole (Harman) and 9H-pyrido[3,4-b]indole (Norhaman).

[1]The type of red meat, the source of purchase and the sample dimension used for thermal treatment is listed.

[2]The parameters of the thermal treatment – temperature (^{o}C) (time – minutes); other parameters.

[3]All HCA contents are reported as ng / g of meat matrix

PAH contents were measured using HPLC unless superscripted [4] LC-MS

[5]Total sample size is calculated from the thermal processing and the final analytical sample size; the sample size is delegated as 1 if it was not specified in the publication

Table 3. Effects of thermal processing and associated parameters on the heme iron content in red meat

Red Meat [1]	Thermal Treatment	Treatment Parameters [2]	Total Sample Size [5]	Heme Iron	Reference
Beef doners; Turkey	Vendor 1			18.98	(Turhan et al. 2004)
	Vendor 2			15.18	
	Vendor 3			16.2	
	Vendor 4		12	15.82	
	Vendor 5			14.09	
	Vendor 6			15.61	
Ground beef; Utah, USA;	Boiling	71		26	(Carpenter and Clark. 1995) [3]
Round beef; Utah, USA;		71	10	47	
Beef loin; Utah, USA;		71		34	

Lamb Chop; Utah, USA;		71		17	
Beef steak; Utah, USA;160g	Boiling	Bath 60 (1h);	15	13.7	(Buchowski et al. 2006)
		Bath 77 (1h);		14.3	
		Bath 97 (1h);		16.7	
	Pressure Cooked	15 psi (1h);		13.8	
Bos taurus loin; Thailand;	Boiling	(10);	45	11	(Kongkachuichai et al. 2002)
Longissimus dorsi from sheep ;Iran; 2.5 x 2.5 cm slices	Boiling	97 (90);	3	21.96	(Pourkhalili et al. 2013) [3, 4]
				21.42	
				41.37	
				62.67	
	Frying	85 (20); Sunflower oil		32.57	
				31.36	
				65.95	

				82.01	
	Grilling (10cm above flame)	86 (10);		35.91	
				33.74	
				72.19	
				82	
Beef steak; Utah, USA;	Vendor		12	21	(Kalpalathika et al. 1991)
Burger beef; Utah, USA;	Vendor		18	20	
roast beef; Utah, USA;	Vendor		30	16.8	
Longissimus dorsi from beef;Newark, USA; 80g	Waterbath (80mL)	55	16	14.08	(Han et al. 1993)
		70		13.08	
		85		11.82	
		100		11.74	

Beef sirloin; Italy; Beef fillet; Italy; Roast beef; Italy; Beef topside; Italy; Veal fillet; Italy; Lamb chop; Italy;	Common home-cooking		3	26.4 28.6 31.4 18.9 13.3 22.5	(Lombardi-Boccia et al. 2002)
Beef entrecote;Poland; 45g	Heating in polypropylene tube	70;0 h storage 70;24 h storage 70;3 days h storage 70;0.1 mM phytic acid - 0 h storage 70;0.1 mM phytic acid - 24 h storage 70;0.1 mM phytic acid - 3 days storage 70;1 mM phytic acid - 0 h storage 70;1 mM phytic acid - 24 h storage 70;1 mM phytic acid -	4	17.1 17.6 17.7 17.2 17.9 16.7 17.6 17.7 17.1	(Stodolak et al. 2007)[3]

3 days storage	
70;5 mM phytic acid -	17.1
0 h storage	
70;5 mM phytic acid -	17.2
24 h storage	
70;5 mM phytic acid -	16.7
3 days storage	

[1]The type of red meat, the source of purchase and the sample dimension used for thermal treatment is listed.

[2]The parameters of the thermal treatment – meat internal temperature (^{o}C) (time – minutes); other parameters.

All heme iron content were determined by the Hornsey method and reported as ug heme iron / g of meat wet mass or [3] dry mass

[4]The heme iron content was measured by four different versions of the Hornsey method in the same order for each thermal treatment

[5]Total sample size is calculated from the thermal processing and the final analytical sample size

Table 4. Effects of thermal processing and associated parameters on the oxidation products in red meat

Red Meat [1]	Thermal Treatment	Treatments [2]	Total Sample Size [3]	Acid Value (mg/g lipid)	Peroxide Value (mequ/kg)	p-Anisidine value	Malondialdehyde (ug/g)	Carbonyl (nmol/mg protein)	Reference
Beef patties; California, USA;250g	Heat	Internal temperature = 77; Salt	2				0.58		(Li et al. 2010)
		Internal temperature = 77; Salt, Spice					0.14		
Restructured beef steaks; Spain;	Conventional oven	170(15); 170(15); added beef fat	1				0.1		(Serrano et al. 2007)
		170(15); 170(15); walnut					0.2		
							0.6		

Microwave Oven	700W (2.5), 300W (2.5);	0.4
	700W (2.5), 300W (2.5); added beef fat	0.1
	700W (2.5), 300W (2.5);walnut	0.5
Electric grill	210(3);	0.25
	210(3);added beef fat	0.1
	210(3);walnut	0.6
Pan-frying	170(5);	0.2
	170(5);added beef fat	0.15

		170(5);wal nut		0.6		
L. lumborum muscle from Alentejano purebred bulls; Portugal; 5 x 2.5 cm	Boiling Microwaving Grilling	80(1); 700 W (3.5)(); 225(0.5);	15	0.1 0.07 0.06		(Alfaia et al. 2010)
Longissimus thoracis from beef; France;	Jets of steam	65(0.5); 65(1); 65(2); 65(5); 65(0.5);Linseed + Rapeseed Cow Feed 65(1);Linse	8		2 2 2.5 2 2 2	(Gatelier et al. 2010)

ed + Rapeseed Cow Feed	
65(2);Linse ed + Rapeseed Cow Feed	2
65(5);Linse ed + Rapeseed Cow Feed	2
96(0.5);	2.5
96(1);	3
96(2);	3
96(5);	2.5
96(0.5); Linseed + Rapeseed Cow Feed	2.5
96(1); Linseed + Rapeseed Cow Feed	3

96(2);Linse ed + Rapeseed Cow Feed	3
96(5);Linse ed + Rapeseed Cow Feed	3
107 - 207(0.5);	2
107 - 207(1);	3
107 - 207(2);	4
107 - 207(5);	10
107 - 207(0.5);Linseed + Rapeseed Cow Feed	2
107 - 207(1);Lin	2

		seed + Rapeseed Cow Feed 107 - 207(2);Linseed + Rapeseed Cow Feed 107 - 207(5);Linseed + Rapeseed Cow Feed			4 10	
Lamb loin; Spain;	Sous-vide	60(6 h); 60(12 h); 60(24 h); 70(6 h); 70(12 h); 70(24 h); 80(6 h); 80(12 h); 80(24 h)	5	2.25 2.25 1.75 2.5 1.5 0.75 1.1 0.6 0.25	4.46 8.87 9.99 5.97 6.98 9.25 5.92 7.59 9.7	(Roldan et al. 2014)

Longissimus dorsi of beef; UK; 3 x 3 x 6 cm pieces	0.1 MPA	20(20);		0.47	(Ma et al. 2007)
	200 MPA			0.49	
	400 MPA			0.51	
	600 MPA			0.9	
	800 MPA			0.69	
	0.1 MPA	40(20);	3	0.55	
	200 MPA			0.73	
	400 MPA			1.12	
	600 MPA			0.14	
	800 MPA			0.42	
	0.1 MPA	60(20);		0.61	
	200			0.59	

MPA		
400		0.68
MPA		
600		1.25
MPA		
800		0.76
MPA		
0.1	70(20);	0.6
MPA		
200		2.36
MPA		
400		1.42
MPA		
600		0.96
MPA		
800		0.44
MPA		
0.1	20(20); Vit	0.259
MPA	E	
	20(20); Vit	0.236
	E + BHT	
	20(20);	0.03
	Na2EDTA	

200 MPA	20(20); Vit E	0.263
	20(20); Vit E + BHT	0.253
	20(20); Na2EDTA	0.043
600 MPA	20(20); Vit E	0.33
	20(20); Vit E + BHT	0.27
	20(20); Na2EDTA	0.045
0.1 MPA	40(20); Vit E	0.258
	40(20);Vit E + BHT	0.214
	40(20);Na2 EDTA	0.097
200 MPA	40(20);Vit E	0.265
	40(20);Vit E + BHT	0.216
	40(20);Na2	0.086

	EDTA	
600	40(20);Vit	0.335
MPA	E	
	40(20);Vit	0.289
	E + BHT	
	40(20);Na2	0.184
	EDTA	
0.1	60(20);Vit	0.314
MPA	E	
	60(20);Vit	0.315
	E + BHT	
	60(20);Na2	0.193
	EDTA	
200	60(20);Vit	0.345
MPA	E	
	60(20);Vit	0.316
	E + BHT	
	60(20);Na2	0.183
	EDTA	
600	60(20);Vit	0.398
MPA	E	
	60(20);Vit	0.306
	E + BHT	

		60(20);Na2 EDTA				0.145	
Beef fillet; Austria; 200 - 220	Pan-frying, braising	(5, 90);	3.17	1.43	4.8		(Saghir et al. 2005)
		(5, 90);Olive oil	3.2	2.01	8.4		
		(5, 90);Corn oil	2.1	1.47	4		
		(5, 90);partially hydrogenated plant oil	2.73	1.39	5.6		

The malondialdehyde content is determined using the 2-thiobarbituric acid reactive species (TBARS) method and carbonyl content was determined using the Oliver method. Acid, peroxide and p-anisidine values were determined using AOAC method.

[1]The type of red meat, the source of purchase and the sample dimension used for thermal treatment is listed.

[2]The parameters of the thermal treatment – temperature (^{o}C) (time – minutes); other parameters.

[3]Total sample size is calculated from the thermal processing and the final analytical sample size; the sample size is delegated as 1 if it was not specified in the publication