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Review paper

Association between red meat consumption and cancer risk

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A b s t r a c t: Cancer is leading cause of mortality worldwide. It is assumed that cancer risk is mainly affected by environmental factors including diet habits. Among other food, it is considered that red meat consumption is linked to increased risk of cancer. Formation of mutagens, heterocyclic aromatic amines, and polycyclic aromatic hydrocarbons, mainly depend on cooking methods and is the highest in pan fried and barbecued meat. Fat, N-nitroso compounds and haeme iron which are also found in meat and meat products are considered to influence the occurrence of cancer. Colorectal cancer is the most often associated with red meat consumption, but studies show that meat eating may increase the risk for other types of cancer including breast cancer, gastric cancer, prostate cancer, pancreatic cancer, lung cancer, laryngeal cancer and bladder, kidney, and endometrial tumours.

Keywords: *red meat, PAH, HAA, colorectal cancer, diet and lifestyle habits.*

Introduction

Changes in dietary habits and lifestyle have resulted in civilisation diseases including coronary heart disease, obesity, hypertension, type 2 diabetes, cancers, autoimmune disease and osteoporosis, among which, cancer is leading cause of mortality worldwide (*Carrera-Bastos et al*., 2011; *Stewart and Wild*, 2014). As reported by a WHO (World Health Organization) update from 2014, approximately 14 million new cases of cancer and 8.2 million cancer-related deaths were reported in 2012 (*Stewart and Wild*, 2014). According to the same report, it is expected in the next two decades that cancer cases per year will rise from 14 million in 2012 to 22 million (*Stewart and Wild*, 2014). The most frequent types of cancer which cause mortality are lung (1.59 million deaths), liver (745 000 deaths) and stomach (723 000 deaths) cancer followed by colorectal (694 000 deaths) breast (521 000 deaths) and oesophageal cancer (400 000 deaths). Serbia is a developing country where stress, pollution, irregular diet and bad eating habits, lack of physical activity and insufficient sleep are part of everyday life. All of this has led to increasing cancer prevalence in Serbia. WHO data shows that cancer mortality rate in Serbia was 160.1 cases per 100,000 population in 2000, and 170.8 cases per 100,000 population in 2012 (*Stewart and Wild*, 2014). In 2012, only Zimbabwe, Hungary, Armenia and Mongolia had higher cancer mortality rates than Serbia. Cancer risk is influenced 5% by genetic factors, while the remaining impact is due to environmental factors, of which 30 to 35% represents diet (*Baena Ruiz and Salinas Hernández*, 2014). Meat, especially red meat, and meat products are the types of foods most often associated with some types of cancer, which highlights the need to discuss the role of meat in cancer aetiology. In October 2015, the Working Group from the International Agency for Research on Cancer (IARC) classified consumption of processed meat as "carcinogenic to humans" (Group 1) (*International Agency for Research on Cancer*, 2015). This classification was based on their being sufficient evidence to associate meat product (i.e. processed meat) consumption with colorectal cancer as well as with stomach cancer. Taking into account substantial epidemiological data showing a positive association between consumption of red meat and colorectal cancer, the IARC classified consumption of red meat as "probably carcinogenic to humans" (Group 2A).

Carcinogens from red meat

Fat, heterocyclic aromatic amines (HAAs), polycyclic aromatic hydrocarbons (PAHs), N-nitroso compounds (NOc) and haeme iron are substances

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isolated from unprocessed or processed red meat which are considered to influence the occurrence of cancer (*Higgs*, 2000; *Williamson et al.*, 2005; *Ferguson*, 2010; *Corpet*, 2011; *Baena Ruiz and Salinas Hernández*, 2014; *Boskovic et al.,* 2015). It is also suggested that intake of red meat, as a high energy food, could have an impact on obesity, which presents a major risk factor for cancer (*World Cancer Research Fund/American Institute for Cancer Research,* 2007; *Ferguson*, 2010). Although the exact mechanism by which meat influences the increased cancer risk is not completely known, there are a few proposed hypotheses. It is supposed that intake of fat, responsible for the high energy density of meat, has an important role in carcinogenesis because it increases insulin resistance, and impacts on higher production of secondary bile acids, which act as aggressive surfactants for the mucosa (*Ferguson*, 2010; *Corpet,* 2011; *Baena Ruiz and Salinas Hernández*, 2014).

NOc are produced by the reaction of nitrite and nitrogen oxides with secondary amines and N-alkylamides (*Lijinsky*, 1999; *Ferguson*, 2010). NOc can be formed endogenously after consumption of red and processed meat or could be found in some processed meats, although some authors suggested that N-nitrosamines produced from additives in processed meat have low carcinogenic potential because of small amounts in which they are found (*Higgs*, 2000; *Demeyer et al.*, 2008; *Santarelli et al.*, 2008; *Ferguson*, 2010). It was showed that haeme iron may catalyse the formation of NOc from natural precursors in the gastrointestinal tract (*Santarelli et al.*, 2008). Haeme iron may play a critical role in understanding links between red meat and particularly colorectal cancer risk, since the higher haeme iron content is one of the major differences between red meats and white meats including poultry and fish, consumption of which is not associated with increased risk of cancer (*Egeberg*, 2013). Iron increases cell proliferation in the mucosa, through lipoperoxidation and/or cytotoxicity of faecal water (*Sesink et al.*, 1999; *Ferguson,* 2010). Furthermore, haeme iron may act as a prooxidant, and induce lipid oxidation and also cause DNA damage (*Tappel*, 2007; *Egeberg*, 2013). While some studies found iron to be carcinogenic metal, other authors consider that it is more probable that iron has a co- carcinogenic effect (*Huang*, 2003; *Ferguson*, 2010).

The method of cooking red meat also influences the risk of cancer (*Berjia et al.*, 2014). Although meat cooking, especially at high temperatures, reduces the risk of foodborne diseases, this practice causes formation of chemical compounds including carcinogens and mutagens (*Navarro et al.*, 2004; *WHO/FAO*, 2004; *Jägerstad and Skog*, 2005; *Badry*, 2010; *Aaslyng et al.*, 2013). The most common are HAAs and PAHs (*Shin et al.*, 2007; *Kimura et al.*, 2007; *Hogg*, 2007; *Larsson et al.*, 2009; *Ferguson*, 2010; *Berjia et al.*, 2014; *Boskovic et al.*, 2015). These genotoxic substances act directly on DNA, cause point mutations, deletions, insertions and initiate carcinogenesis process for a number of cancers (*Baena Ruiz and Salinas Hernández*, 2014; *Baltic and Boskovic*, 2015; *Boskovic et al.*, 2015). Their formation depends on meat type, temperature, and method of cooking (barbecuing/grilling, frying/broiling, roasting/baking) (*Jägerstad and Skog*, 2005; *Badry*, 2010; *Aaslyng et al.*, 2013; *Berjia et al.*, 2014; *Boskovic et al.*, 2015). High amounts of 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine are found in very well cooked chicken and bacon, while 2-amino-1,7-dimethylimidazo [4,5-g] quinoxaline was found in very well done pan-fried beef and steak, and in beef gravy (*Ferguson*, 2010). A recent study conducted by *Berjia et al.* (2014) showed that barbecued meat is associated with the formation of the highest concentrations of HAAs and PAHs, followed by fried meat and roasted red meat. Time of cooking has a great role in the HAAs production. Thus meat cooked for extended period mainly at higher temperatures contains a higher concentration of HAAs, which is why very well cooked meat is associated with cancer risk (*Knize et al.,* 1994; *Navarro et al.*, 2004; *Sugimura et al.*, 2004; *Felton and Knize*, 2006; *Ni et al.,* 2008; *Ferguson*, 2010).

The type of marinade also affects the formation of HAAs in meat (*Joshi et al.*, 2015). Results obtained from some studies showed that use of Asian-type marinades reduces HAA formation, while BBQ (barbecue) sauce marinade increased formation of these compounds (*Nerurkar et al.* 1999; *Viegas et al.*, 2012).

Red meat and colorectal cancer

Colorectal cancer is the third most common cancer in men and the second most common cancer in women, but it is also the cancer type most often associated with red meat consumption (*Ishibe et al.,* 2002; *Le Marchand et al.,* 2002; *Butler et al.*, 2003; *Gunter et al.,* 2005; *Wu et al.,* 2006; *Cross et al.,* 2007; *Wyness et al.,* 2011*; Kim et al.,* 2013; *Berjia et al.,* 2014).

In the meta-analysis conducted by *Norat et al.* (2002) based on case-control and cohort studies published between 1973 and 1999, it was concluded that high consumption of red and processed meat was associated with an increased risk of colorectal cancer, while total meat intake, including poultry intake, was not associated with increased cancer risk. In a meta-analysis involving almost 8,000 cases from 19 prospective studies, *Larsson and Wolk* (2006) found consistent associations between high consumption of red and processed meat and an increased colorectal cancer risk. In this meta-analysis, they also found that high intake of red and processed meat is most associated with an increase of rectal cancer, followed by distal and proximal colon cancer, respectively. The relationship between red and processed meat consumption and increase the risk of colorectal cancer was also reported by *Norat et al.* (2005). *Chan et al.* (2011) reported that consumption of red and processed meats, assessed separately, were associated with increased risk of colorectal and colon cancers, but no statistically significant association with rectal cancer was found. This finding was different than those observed when red and processed meats were combined into a single food item.

A meta-analysis of 14 prospective studies where 725,258 subjects and 7,743 cases of colorectal cancer were evaluated, during 5 to 20 years, found no association between red meat and colorectal cancer (*Cho and Smith-Warner*, 2004; *McNeill and Van Elswyk*, 2012). Also, findings from a prospective study conducted by *Oba et al.* (2006) in Japan showed no association between red meat consumption and colon cancer risk, while a high intake of processed meat was associated with increased risk. These studies indicate that fresh meat *per se* is not carcinogenic and that, as well as other types of cancer, the risk of colorectal cancer is mainly associated with the method of cooking and carcinogens produced during meat processing and preparation. Higher risks were observed for darkly browned surfaces produced by barbecuing or iron pan cooking at temperatures above 150°C, and this risk was explained due to the formation of HAAs, while there was no association found with roasted and boiled meat (*Navarro et al.*, 2004). The incidence of meat consumption also has an impact on risk of colorectal cancer. *Norat et al.* (2002) found that consumption of 120 g per day of red meat (compared with no consumption) was associated with a 24% increase in risk, while consumption of 30 g per day of processed meat (compared with no consumption) increased the risk by 36% (*Williamson et al.,* 2005). Results obtained from thirteen studies by *Sandhu et al.* (2001) showed that a daily increase of 100 g in total or red meat intake was associated with a significant 12 to 17% increase in colorectal cancer risk (*Williamson et al.,* 2005). Results from meta-analysis conducted by *Smolińska and Paluszkiewicz* (2010) showed that the frequency of red meat consumption is a crucial risk factor for colon and rectum carcinogenesis, even more important than the amount of consumed meat. In the same study, it was found that risk of rectal and colon cancer increased with consumption of red meat more than once daily and that red meat intake in amounts higher than 50 g day^{-1} could lead to colon cancer, while the dependence between red meat consumption of over 50 g daily and rectal cancer was not conclusive (*Smolińska and Paluszkiewicz*, 2010). Moreover, some studies showed that exposure to meat carcinogens increase the risk of colorectal cancer only in genetically susceptible individuals (*Le Marchand et al.*, 2002).

Apart from haeme iron, PAHs and HAAs discussed above, some findings suggest that changes in gut microbiota also influenced colorectal cancer risk. Bacterial fermentation induced by large amounts of undigested proteins and compounds formed from amino acids during bacterial metabolism caused changes in colon epithelial homeostasis which may be predisposing factors for colorectal cancer (*Kim et al.,* 2013). Further, some studies showed that meat from different origins had differing impacts on colorectal cancer. *Egeberg et al.* (2013) did not find an association between all red meat consumption and risk of colon cancer, but they observed that intake of higher amounts of beef and lamb is related to elevated colorectal cancer risk. This could be explained due to the higher amount of haeme iron in lamb and beef compared to other types of meat.

Red meat and other types of cancer

Breast cancer (*Cho et al.,* 2006; *Steck et al.*, 2007; *Larsson et al.*, 2009; *Berjia et al.*, 2014), gastric cancer (*Zhu et al.*, 2013) prostate cancer (*Cross et al.*, 2005; *Koutros et al., 2008*; *John et al.*, 2011; *Berjia et al.*, 2014), pancreatic cancer (*Anderson et al.*, 2002; *Li et al.,* 2007; *Stolzenberg-Solomon et al.*, 2007; *Berjia et al.*, 2014), lung cancer (*Dosil-Diaz et al.,* 2007), laryngeal cancer (*Oreggia et al.*, 2001; *Bosetti et al.,* 2002) as well as bladder, kidney, and endometrial tumours are also associated with meat intake (*Ferguson*, 2010; *Béjar et al.*, 2012; *Baena Ruiz and Salinas Hernández*, 2014). Scientific data about the association between meat consumption and breast cancer are inconsistent. Breast cancer is associated with some meat components including meat-derived haeme iron, NOc, HAAs and PAHs (*Cho et al.*, 2006; *Kabat and Rohan*, 2007; *Lauber and Gooderham*, 2007; *Kallianpur et al.*, 2008; *Larsson et al.,* 2009). It is important to mention that oestrogen receptor-positive breast tumours are etiologically different from receptor-negative tumours.

Red meat consumption could increase the risk, especially of hormone receptor-positive breast cancers. This was confirmed in Nurses' Health Study II which showed that a high intake of red meat by premenopausal women was associated with a significantly increased risk of ER+/PR+ breast cancer but not ER–/PR– breast cancer (*Cho et al.*, 2006; *Larsson et al.*, 2009). *Larsson et al.* (2009) conducted an epidemiologic study on 61,433 Swedish women to try to determine if there was any association of meat intake with incidence of breast cancer as defined by oestrogen receptor and progesterone receptor status. During 17.4 years, 2,952 incident cases of invasive breast cancer were determined, but statistical analyses showed that consumption of neither fresh red meat nor processed red meat had any significant association with risk of breast cancer. *Missmer et al.* (2002) also found no significant association between total meat, red or white meat consumption (all considered separately) and breast cancer risk. These results are in accordance with those of the NIH-AARP Diet and Health Study as well as other studies (*Fraser*, 1989; *Ambrosone et al.*, 1998; *Gertig, et al.,* 1999; *Missmer et al.*, 2002; *Larsson et al.*, 2009).

Along with smoking and drinking alcohol, consumption of red or processed meat is consider to be a predisposing factor for gastric cancer (*González et al.*, 2013). High levels of salt are used in the production of some processed meats, and there are data that salt and salt-rich foods probably increase the risk of gastric cancer (*D'Elia et al*., 2012; *González et al.*, 2013) which can explain the link between meat products and gastric cancer. Meta-analysis based on epidemiological studies showed that consumption of red and/or processed meat increased gastric cancer risk (*Zhu et al.*, 2013). However, the same authors noted that further investigation should be conducted in order to confirm the association, especially for red meat. Other authors did not find associated between red and processed meat consumption with increased risk of gastric cancer, but they reported increased risk for oesophageal squamous cell carcinoma (*Keszei et al.*, 2012).

In a population-based case-control study *Anderson et al.* (2002) did not find a significant association between pancreas cancer and grilled/barbecued or fried red meat intake, but when fried meat was consumed, the risk of cancer was elevated. These results are consistent with those reported by *Bosetti et al.* (2013), while *Polesel et al.* (2010) found that eating red meat is associated with pancreas cancer.

In studies carried by *Brennan et al.* (2000) and *Alavanja et al.* (2001), it was found that meat intake influenced the incidence of lung cancer. Contrary to these results, *Norat et al.*, (2005) found that consumption of pork meat has a positive effect on lung cancer. This result was not confined only to meat *per se*, but to the fact that this meat is often eaten with green leafy vegetables, and often tends to be consumed with red wine, which contains resveratrol and tannins and has a protective effect.

An association between red meat and laryngeal cancer was reported by *Oreggia et al.* (2001). They reported that red meat and total meat intake were associated with a strong increase in laryngeal cancer risk, but this effect disappeared after adjusting for total fat intake. In the same study, HAAs had an impact on laryngeal cancer risk, but no association with salted meat was reported, although some authors did find that connection and attributed it to the presence of nitrosamines (*Oreggia et al.*, 2001). This association between red or processed meat and risk of laryngeal cancer was confirmed in the study conducted by *Bosetti et al*. (2002).

Moreover, a meta-analysis of 15 prospective studies found no positive association between consumption of red or processed meat and prostate cancer risk (*Alexander et al.*, 2010).

Discussion and recommendations

Although consumption of red meat could be associated with some types of cancer, the fact that meat contains anticancer components which are also essential in human nutrition, such as selenium, zinc, omega-3 fatty acids, vitamins B_6, B_{12}, D and folic acid, indicates that meat should not be eliminated from the human diet, but meat intake should be reduced to the recommended level of up to 500g per week (cooked weight) and little, if any, processed meat (***World Cancer Research Fund/ American Institute for Cancer Research***, 2007; *Chan et al.*, 2011; *Pérez-Cueto and Verbeke*, 2012; ***World Cancer Research Fund***, 2012; *Baena Ruiz and Salinas Hernández*, 2014; *Baltic and Boskovic*, 2015). Moreover, some peptides obtained from meat and fish possess anti-cancer properties, inhibit cell proliferation and have cytotoxic effects against tumour cells (*Shahidi and Zhong*, 2008; *Ryan et al.*, 2011; *Najafian and Babji*, 2012; *Udenigwe and Aluko*, 2012; *Baltic et al*., 2014). Red meat also contains other compounds with beneficial effects on human health, including carnitine, coenzyme Q10 and creatinine (*Schmid*, 2009). Moreover, red meat, especially beef, has a better ratio of n6:n3 fatty acids and more vitamins (A, B_6, and B_{12}) and mineral substances (Fe and Zn) than does white meat

(*Oostindjer et al.*, 2014). Many authors agree that red meat is not carcinogenic *per se* and that risk of cancer is influenced by cooking practices and dietary patterns in which meat is consumed (*Biesalski*, 2005; *Ferguson*, 2010). Cooking methods such as barbecuing and frying should be avoided, as well as excessive external brownness or charring of meat during preparation, while baking, boiling, and stewing do not produce high levels of carcinogens (HAAs and PAHs) (*Anderson et al.*, 2002). Also, it was established that not only nitrate but also other chemical additives used in meat products to extend shelf life have adverse effects on human health and there is a need for more natural additives, such as natural plant extracts. Plant extracts exhibit antimicrobial and antioxidative properties, have positive effects on meat safety and quality and also prolong shelf life (*Boskovic et al.*, 2013). Phytochemicals reduce the formation of nitrosamines in the human body when consumed simultaneously with meat products (*Chung et al.,* 2013; *Oostindjer et al.*, 2014). It is suggested that addition of garlic or curcumin have cancer protective effects (*Shu et al.*, 2010; *El-Bayoumy et al.*, 2011; *Oostindjer et al.*, 2014), which is why it could be beneficial if they can be added to a marinade or in meat dishes.

Since in general, civilisation diseases are influenced by different factors, eating and lifestyle habits should be considered as the main predisposing factors for various diseases, including cancer. People's habits and diets have changed during recent decades. It has been observed in various studies that individuals who consume high amounts of red or processed meat can also commonly consume more energy rich food products, including sugar-rich drinks and condiments, eat less vegetables, drink more alcohol, take less vitamins and are less physically active (*Alexander*, 2013; *Oostindjer et al.*, 2014).

Conclusion

Although lately associated with number of diseases and conditions, because of the nutritional value of red meat, as well as the presence of minerals and vitamins, red meat still has a useful role in the human diet, and positively impacts on human health when it is consumed in moderate amounts after recommended cooking methods, and within the context of a well balanced diet.

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