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Review of meat and caffeine and the risk of bladder cancer

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Abstract: Bladder cancer (BCa) is a main health issue in both developed and developing countries, especially for men with an incidence that is three to five times greater than that of women. The majority of bladder cancer occurs in males and there is a 14-fold variation in the incidence internationally. About 1,596,670 new cancer cases were diagnosed in 2011. This estimate did not include carcinoma in situ (noninvasive cancer) of any site except urinary bladder. It is commonly known that nutrition has a role in preventing cancer in general. Additionally, new dispute has risen over the effect of dietary factors such as meat and coffee in bladder cancer, which has yielded contradicting results. The review relied on previous researches and studies related to our assumption that meat and caffeine intake is not proved to be directly related to BCa. The study showed that there is no credible evidence stating that BCa is the result of meat and caffeine intake. This was due to the contradiction found in the studies referred to or consulted in the study. The lack of statistical association of meat types, the different methods of cooking, samples under study, and lifestyle enrollment are all considered important variables that were neglected in previous researches. These limitations supported the lack of credibility of such studies that correlated BCa to meat and caffeine intake.

Keywords: Meat, Caffeine, Bladder Cancer

1. Introduction

The universal burden of cancer is rising mainly due to the aging population and the implementation of cancer-inducing behaviors such as smoking and occupational exposure to carcinogens, rendering it a leading cause of death in developed countries and rank second in developing countries [1]. Bladder cancer (BCa) remains a major concern with incidence of 429,793 in both sexes and 165,084 deaths in 2012 [2] worldwide ranking the 9th most common cancer and the 13th most common cause of death [3]. The highest incidence of BCa is found in Europe, North America and North Africa [4]. In Lebanon, it is the second most common diagnosed cancer in men following prostate cancer [1]. Since the well-known risk factors like gender and race do not completely explain the observed differences amongst countries, thus other likely factors like smoking, environmental and occupational carcinogens and parasites need to be recognized [5]. Family cancer history and medical history of infections and stones are also risk factors [3]. One important risk factor that involves dietary elements has been proposed to have a possible connection to BCa even though its exact role and mechanism is yet to be investigated [6].

Chemoprevention is considered a suitable model to prevention strategies. Several studies were conducted to check the association between meat, coffee consumption and BCa. In this article, we elected to review the role of the two most common factors (meat and coffee) that might be associated with increased risk of BCa and to summarize numerous studies which had conflicting results. Total meat intake had been associated with risks of the following cancers: colon and lung [7;8], stomach, rectum, pancreas, breast, testis, kidney and bladder [7] and esophagus, liver and larynx [8]. Several compounds were discussed that could have a negative impact on BCa such as cooking and processing method, nitroso-compounds (NOC), heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) [9]. Coffee is a highly consumed beverage worldwide and is a complex chemical mixture which enhances and antagonizes potentially carcinogenic exposures and may have a link to

BCa [10]. Although it has been protective against chronic diseases due its antioxidant and anti-inflammatory agents, interest has risen to investigate the relationship between coffee intake and cancer [11].

2. BCa and Meat

Meat is a source of various potentially carcinogenic compounds resulting from cooking or processing and is an essential dietary component in relation to BCa [12]. Meat can be associated with bladder carcinogenesis through several potentially carcinogenic meat-related compounds pertinent to cooking and processing, such as nitrates and nitrites, HCAs and PAHs [12]. Thus, its consumption and BCa have been studied vastly in cohort and case-control studies, but have yielded contradicting results [13].

In the large prospective NIH-AARP Diet and Health Study, 854 cases of BCa were identified from 300,933 men and women subjects [12]. In this study, a borderline statistically significant increased risk of BCa was found in those with high intake vs. low intake of red meat, especially red processed meat (HR=1-22, 95% CI=0-96-1.5; P=0.07) [12]. No association between white meat intake, processed meat, bacon, hamburger, sausages or steak and increased risk of BCa was seen without any evidence of effect modification for the meat exposure by gender, smoking or fluid intake. However, when the total nitrate or nitrite intake from processed meat was studied, each had a borderline positive association with BCa (RR= 1.29; 95% CI =1.00-1.67; P=0.11) [12]. In a recent large prospective cohort study, Lin et al studied the effect of red meat, HCAs and genetic variants on the risk of developing BCa [13]. The data showed that high intake of red meat increased consumption of HCA, and the doneness level of cooked meat increased the risk of BCa [13]. When subdividing meat into many items, they showed increased risk of BCa with high ingestion of beef steaks (OR=1.56, 95% CI=1.12-2.18), bacon (OR=1.51, 95% CI=1.23-1.85) and fried chicken without skin (OR=1.17, 95% CI=0.96-1.45). This was the only study showing that the risk of BCa also depends on the concentration of HCA ingested and the presence of unfavorable genotypes [13]. An analysis of two prospective cohorts studies (the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study) could not show a statistically significant risk between bacon consumption and BCa [14]. An Uruguayan case-control study of 225 cases, showed that ORs for higher tertile vs. lowest tertile was positively associated with total meat (OR=1.47, 95% CI=1.02-2.11), processed meat (OR=1.55, 95% CI=1.07-2.24), hot dog (OR=2.16, 95% CI=1.45-3.23), ham (OR=1.83, 95% CI=1.26-2.65) and salted meat (OR=2.37, 95% CI=1.57-3.57) [15]. The study also analyzed the cooking methods of red meat and showed that barbecued and boiled meat were positively associated, while fried meat was not [15].

When studying the association of HCAs, PAHs and NOC which are formed when cooking meat, Wu et al and Jakszyn et al showed no association between each one of them and increased risk of BCa [16;17]. NOC dibutylnitrosamine is metabolized in the liver and passes through the bladder where its metabolites that have been suspected to cause cancer in mice and rats can be absorbed and activated in the bladder mucosa [18]. Processed meats like cold cuts, sausage, bacons and the nitrates or nitrites added to processed meat are good sources of NOC. When 1660 cases of bladder cancer were studied, it was found that non-smokers had highest association of bladder cancer with the intake of salami/pastrami/corned beef weekly (OR=1.95, 95% CI=1.10-3.46) and liver monthly (OR=1.76, 95% CI=1.09-2.85) [18].

Many other studies showed contradictory findings. A recent study by Larsson et al showed no association while an earlier case-control study showed that the consumption of fried meat, pork and sausages were associated with increased risk of developing BCa (OR=1.4, 95% CI=1.0-1.8) [19]. One study from Canada showed significantly increased risk between BCa and high intake of total meat (OR=1.6, 95% CI=1.2-20), red meat and processed meat (OR=1.3, 95% CI= 1.0-1.7) [7]. In the study of the cohorts of HPFS and NHS, total and red meat as well as hot dogs or processed meat were not significantly related to the risk [14].

3. BCa and Caffeine

Coffee has been of interest to study as a risk factor for developing BCa for many decades. Coffee is a frequent and major universal dietary exposure around the world where its risk on health has been questioned [20]. It can affect the etiology of cancer in several ways ranging from carcinogenesis to cellular apoptosis [20]. Case-control studies and meta-analysis have been published since the 1970s. Moreover, Zeegers et al in their meta-analysis of multiple studies showed a slight increase in risk of BCa among coffee drinkers, but could not correlate it (20% increase to dose of coffee, overall RR of 1.25 (95% CI=1.09-1.46)) [21].

Other multiple studies (mostly pooled analysis of cohorts or case control studies) have shown contradictory evidence to support a positive or negative association between caffeine intake and risk of developing BCa. In a review of ten case-control studies conducted in multiple European Union countries, Sala et al performed a logistic regression calculation for odds ratio. The authors found that coffee drinkers did not have risk of BCa if they are non-smokers [22]. However, if the consumption of coffee was more than 10 cups per day (OR=1.8, 95% CI=1.0-3.3), there was a statistically excess risk. For the non-smokers, there was no risk associated either with the duration of consumption or the type of coffee ingested but a slight increase of risk with heavy coffee consumption (OR=2.2%, 95% CI=0-19.1). Therefore, from the pooled analysis, individuals drinking ten or more cups of coffee per day may have an increased risk [22]. Earlier, the risks of coffee intake were considered in an IARC monograph, in which the working group reviewed all the case control studies in the 1990 and reported a moderately increase in BCa risk in coffee drinkers in most of

the studies. Again, there was an increasing trend in risk with the amount of caffeine ingested (IARC) [22]. Pooled data from six European and North America reported no true association. However, there was also a significantly true increase in the risk when comparing drinkers of >5 to < 5 cups per day [23].

Recently, Zhou et al quantitatively assessed the risk of caffeine ingestion and BCa. They relied on summarizing the results of cohort studies and case controls. In their meta-analysis, the case control studies showed a significant association between caffeine (the number of cups/day) and BCa risk. However, the meta-analysis failed to confirm this, even though it showed a stronger effect of coffee consumption among non-smokers than among smokers [10]. They concluded that there is no definite evidence that caffeine ingestion is a risk factor for developing BCa because of the inconsistencies among case-control and cohort studies. A recent meta-analysis has a non-statistically significant association (RR=1.34, 95% CI=0.99-1.8) even when a dose-response analysis was taken into account [11].

4. Results

The results of the above discussed studies are inconsistent even though some were population-based with a large sample size (such as the Swedish study and the NIH-AARP study) [12; 19]. However, the authors from the two studies pointed out that using a food-frequency questionnaire as an assessment tool may lead to measurement errors, like incomplete listing of all possible foods, inaccuracy in recall of usual past diet and errors in frequency and usual serving size estimations [13;19]. Selection bias is also a concern that is difficult to manage and it may lead to misclassification and erroneous estimates [15]. There were also other risk factors other than HCAs, such as lifestyle, diet, ~~etc~~. and wide range of meat and processed meat consumption that may lead to measurement errors [24]. For example, in a study higher meat intake was evident in higher intake of energy and alcohol [19]. The same was also noted with high red meat intake and older men who were ever smokers, heavy smokers and high energy takers [7;13]. Another controversial point to take into account is the definition of processed meat because it does not have a universally accepted definition and may range from smoking, curing, salting, to adding any preservative [9].

One mechanism that meat may be involved in the carcinogenesis process is via production of HCAs and PAHs during cooking amino acids or proteinaceous foods at high temperatures or over an open flame [19], which is achieved by barbecuing, grilling or pan-frying and that humans frequently get exposed to [13]. These cooking methods contain the highest level of PAHs as a result of the pyrolysis of fatty juices that drip down onto the heat source and produce smoke [13]. HCAs are known to be mutagenic and carcinogenic in animal studies [25]. HCAs interact with DNA and form HCA-DNA adducts that can cause several kinds of genetic modifications like sister chromatid exchange and chromosomal aberrations, mutations in cancer related genes as p53, H-ras and Apc, microsatellite instability, etc. [13]. The mechanism for producing DNA adducts requires in vivo enzymatic activation initiated by N-oxidation of the compound in the liver by hepatic cytochrome P450 1A2 (CYP1A2) and then by acetyltransferase (NAT) [24]. However, there was no association between NAT2 genotype when the rapid genotype was compared to the slow one, but a strong association was evident between meat intake and BCa in rapid acetylators only [24]. A recent study showed that BCa had higher clustering of NAT1 and NAT1*14A alleles than controls (53.7% vs. 11.3%) especially among Lebanese men even those residing outside Lebanon [1]. Reason bacon had positive association in the two prospective cohort studies is that it contains nitrosamines. Although processed meats also contain these compounds but their formation is influenced by several factors such as stomach pH and the presence of vitamins [14]. Meat doneness was also compared as a surrogate measure of HCAs intake and cases had significantly higher intakes since HCAs are concentrated in well-done meats [13]. Cooked chicken without skin had more HCAs than with skin [14].

Another mechanism involves sulfotransferases (SULT) that catalyze both the bioactivation and detoxification of promutagens and procarcinogens. SULT1A1, a SULT phenol, has substrate specificity and is found in many tissues and has three polymorphisms resulting in amino acid change. On polymorphism, known as SULT1A1 Arg213His, has been shown to have a potential impact in humans [26]. His213 variant allele genotypes (Arg/His + His/His) were noted to be statistically related to decreased BCa risk and another one in never smokers with the His213 allele genotypes but not in former or current smokers [26]. SULT1A1 polymorphism was studied that showed a statistically significant decreased risk for SULT1A1*1/2 and SULT1A1*2/2 compared to SULT1A1*1/1 and no effect was seen for this allele on the cancer [24]. Additionally, nitrates and nitrites may play a role in the mechanism. They are preservation methods used to enhance color and flavor for meat products. They are also precursors to NOCs which induce tumors in many organs including the bladder [12]. When nitrate is reduced to nitrite and combined with amines found in meats, it leads to formation of NOCs and the risk was increased with high nitrate intake in case of liver (p=0.010), hot dogs/polish sausage (p=0.005) and heme (p=0.010) [18]. Heme iron, mainly from red meat, but also from fresh and processed meat, has been studied for another contribution possibly through its catalysis of endogenous NOCs production and also catalysis of lipid oxidation end products [13;18]. There are high amounts of oxymyoglobin and oxyhemoglobin on the surface of raw red meat muscle, while there are deoxymyoglobin and deoxyhemoglobin in the interior of the muscle and finally in cytochromes of mitochondria in muscles and other tissues [27]. When red meat is cooked, myoglobins, hemoglobins and cytochromes are converted into denatured protein-hemes which are the hemichromes and hemochromes. After the intake of protein-hemes, these

compounds are hydrolyzed to amino acids, peptides and heme group. The latter is absorbed and transported by the blood to the organs and tissues and induces oxidative reactions for developing tissue, biochemical and cellular damage and finally disease initiation [27]. However, this hypothesis was seen not to be related to developing risk of BCa in a recent study [17]. The same was also noted with heme, nitrates, nitrites and nitrosamines, but high levels of heme intake were non-statistically significant with stronger association among never smokers [18].

Roasted coffee contains more than thousand chemicals among which many may modify cancer risks. The main compound is caffeine that was shown to both induce and depress tumors depending on the species and phase of administration. In addition to caffeine, specific diterpenes found in coffee may have anti-carcinogenic effects by stimulating phase II enzymes known to detoxify carcinogens, inhibiting phase I enzyme that leads to carcinogenic inhibition and inducing intro cellular antioxidants defense mechanisms [28]. Many animal studies did not show any ability of caffeine to induce tumors or inhibit the carcinogenic effect of the other substances. Lopez-Abente et al suggested the role of induction of CYP1A2 (a cytochrome P450 enzyme) by high doses of caffeine, which in turn activates aromatic amines and causes DNA adducts [29] and induces N-oxidation activity depending on CYP1A2 activity [4]. This enzyme catalyses the metabolism of many toxins, drugs and metabolic alteration of many carcinogenic substances such as aromatic amines and heterocylic hydrocarbons. Its activity does not depend on polymorphism, but on inter-individual difference in activity and on some form of exposure to unidentified enzyme inducers or modifiers [30].

Several studies have studied the role of caffeine in somatic damage induced by multiple carcinogenic agents. In vitro studies indicate that caffeine may have a booster effect on the cytotoxic effect of certain compounds (for example, DNA intercalating agents) [31;32]. In addition, results have shown that caffeine consumption has a modifier effect of other exposures on the risk of cancers with ras mutations [31]. In contrast, other studies discuss its possible protective effect, by acting as an antimutagenic through formation of complex compounds [32]. All authors are, however, unanimous when it comes to establishing its influence on DNA repair and damage mechanisms.

The case-control studies must be analyzed and evaluated with caution for several reasons. First, many studies are retrospective studies. Second, some studies relied on hospital controls and third, other studies used questionnaires which can have a bias. Forth, coffee is a mixture of various compounds making it difficult to pinpoint the specific possible bladder carcinogens, but most studies have shown non-statistically significant association of high caffeine ingestion and moderate increased BCa risk [33]. Therefore, more prospective worldwide studies with accurate questionnaires are needed to investigate the effect of types of coffee. Most epidemiologic studies are in favor of no or weak association between coffee drinking and BCa. Few studies have also shown a mild increase in risk with increasing dose even though no definite trend has been established. There are many potential confounding variables which can affect the studies. One of them is tobacco smoking that can be also a risk factor for BCa. The other might be the source of water which is used to brew the coffee. Tap water might contain chlorination by-products which by themselves are carcinogenic. Last but not least, we have to consider the effect of several polymorphic enzymes (GST, NAT and SULT1A1) which are involved in the metabolism of the bladder carcinogenesis in humans and variation in the genetic susceptibility to BCa according to their polymorphism [33].

5. Conclusion

The above information shows that meat and caffeine intake is not convincingly associated with BCa due to conflicting results. This shows that the role of diet is only partially understood. More studies are necessary in order to compensate for the limited information offered by the NIH-AARP study regarding the nitrites and nitrates and to better unveil the relationship between BCa and meat intake. Limitations to circumvent for future studies include controlling for confounders such as smoking or other risk factors like lifestyle, alcohol use, occupation, obesity and exercise that could influence the association. The absence of a statistical association between any particular type of meat and BCa may be attributed to cooking differences and the type of fat used in cooking since polyunsaturated fats are more susceptible to oxidation. Case-control studies may be prone to selection bias wherein the dietary intakes of meat may differ among participants and non-participants and to recall bias. As for prospective cohort studies, they may compensate for the two biases mentioned and also apply a comprehensive information on diet, genetic profiles and subjects.

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