Red meat and colorectal cancer

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Abstract

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide. More than half of cases occur in more developed countries. The consumption of red meat (beef, pork, lamb, veal, mutton) is high in developed countries and accumulated evidence until today demonstrated a convincing association between the intake of red meat and especially processed meat and CRC risk. In this review, meta-analyses of prospective epidemiological studies addressed to this association, observed link of some subtypes of red meat with CRC risk, potential carcinogenic compounds, their mechanisms and actual recommendations of international guidelines are presented.

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide according to the World Health Organization (WHO) GLOBOCAN 2012 database.[1] More than half of cases occur in more developed, highly industrialized countries.[1,2] Increased incidence of CRC among Japanese migrants from low-risk to high-risk areas and in countries that adopt a Western lifestyle after rapid economic transformations such as Eastern Europe strongly suggested that environmental and especially dietary factors were important determinants of colorectal carcinogenesis.[3-5] As an important part of *Western diet*, the consumption of red meat (beef, pork, lamb, veal,

mutton) is high in developed countries.[5] One of the first epidemiologic evidences about the association between red meat and CRC risk is the demonstration of correlation between per capita meat intake and incidence of colon cancer in women from 23 countries in 1975.[6] Correlation was strong (r=0.9) for meat consumption in this study. Correlation does not mean causation of course, many different international lifestyle factors than red meat intake can contribute to this result,[7] so there was a great need prospective case-control or cohort studies to test the hypothesis of the link between red meat consumption and CRC risk after this correlation study.

In the last decade of twentieth century, several prospective studies have been published.[8-11] Among them, Nurses' Health Study of US reported a strong association between colon cancer and beef, pork, or lamb consumption.[8] In this large cohort study, after six years follow-up of 88,751 women, 150 colon cancer cases were documented, and the relative risk (RR) of colon cancer in women who ate beef, pork, or lamb as a main dish every day was 2.49 as compared with those reporting consumption less than once a month. The 95% confidence interval (CI) was 1.24-5.03 (P for trend=0.01). Processed meats, liver and animal fat consumptions were also positively associated with the risk of colon cancer (P values for trend: 0.04, 0.03 and 0.01 respectively) in this study. Significant trends were seen with processed meat in Iowa Women's Study[9] and Dutch Study;[10] RR for high consumption *versus* low was 1.51 and 1.72, respectively. In the Health Professionals Follow-Up Study in men, again a strong relationship was reported between red meat consumption and colon cancer risk.[11]

In the EPIC trial (The European Prospective Investigation into Cancer and Nutrition), which is published in 2005, Norat, Bingham, Ferrari and colleagues prospectively followed 478,040 men and women from 10 European countries between 1992-1998 and they observed 1329 CRCs.[12] They examined the relationship between red and processed meat, poultry, and fish and CRC risk using a proportional hazards model. They found that CRC risk was positively associated with the intake of red and processed meat. The high intake (>160 g/day) group had a risk 1.35 fold as compared with the lowest intake (<20 g/day).

On the other hand, for humans meat is a major food that contains all essential amino acids (lysine, threonine, methionine, phenylalanine, tryptophan, leucine, isoleucine and valine) and various micronutrients such as iron, zinc, selenium and vitamin B6, B12 and vitamin D.[13] It is also significant source of omega-3 polyunsaturated fatty acids (PUFAs). The critical question at this point is to become vegetarians, or to eat meat safer?[7] This review will attempt to summarize this association between red meat and CRC, potential mechanisms of this relationship, actual recommendations of international guidelines, and preventive measures.

Methods of research

A systematic literature search for publications on red and processed meat and colorectal cancer was conducted in PubMed without language restrictions until 1 November 2015 to prepare this review. The

search terms used were ("colon" OR "rectal" OR "colorectal") and "cancer" and "risk" and ("red meat" OR "processed meat") and "meta-analysis". We excluded adenomas, gene-environment interactions, reviews and letters. The reference lists of identified studies were also used as additional knowledge.

Results

After exclusion of reviews, updates of previous publications, and one study about diabetes and CRC, we identified 10 meta-analyses[2,14-24] about red meat and CRC risk (Table 1) and one meta-analysis about red meat subtypes and CRC risk.[25]

Meta-analyses for red meat and processed meat

Sandhu et al. from University of Cambridge and, London UK, published the first meta-analysis of prospective cohort studies on meat consumption and CRC risk in 2001.[14] They included 13 studies to this analysis. In this report, they concluded that daily increase of 100 g (one portion) of all meat or red meat is associated with a significant 12-17% increased risk of CRC (average RR is 1.17 with 95% CI of 1.05-1.31 for the random-effects model). A significant 49% increased risk was also found for a daily increase of 25 g of processed meat (about one slice).

The second meta-analysis was published by Norat et al., from IARC in 2002.[15] In this analysis, red meat was evaluated in 14 case-control and 9 cohort studies to estimate average RR. Processed meat was also evaluated separately in total 23 studies selected out of 22 case-controls and 7 cohorts. Average RR of CRC was found 1.35 (95% CI: 1.21-1.51) for the highest quartile of consumption of red meat. It means that CRC risk increased by 35% compared with the lowest intake group. For processed meat, average RR was 1.31 (95% CI: 1.13-1.51). Dose-response analysis showed that the intake of 120 g/d of red meat increases cancer risk by 24% and 30 g/day of processed meat increases this risk by 36% according to this meta-analysis. If average red meat intake is reduced to 70 g/week, CRC risk hypothetically decreases by 7-24%. From Karolinska Institute, Sweden, Larsson and Wolk's meta-analysis which is published in 2006, supported again the hypothesis that high consumption of red meat and of processed meat is associated with an increased risk of CRC.[16] Their quantitative assessments were based on the data from 15 prospective studies for red meat and from 14 prospective studies for processed meat consumption. The RRs of CRC for the highest versus the lowest intake categories were 1.28 (95% CI: 1.15-1.42) for red meat and 1.20 (95% CI: 1.11-1.31) for processed meat. The risk excess associated with intake of 120 g/d of red meat was +28% and with intake of 30 g/d of processed meat was +9%. In this analysis, the association with red meat appeared to be stronger for rectal cancer.

The WCRF/AICR 2007 report[17] also describes a meta-analysis based on studies included Larsson and Wolk's study[16] and their results are very close.[7]

Huxley et al., from Australia and Iran[2] reported a meta-analysis of 26 prospective cohort studies. They observed that RR was 1.21 (95% CI: 1.13-1.29) for the highest versus lowest level of consumption of red meat. RR was 1.19 (95% CI: 1.12-1.27) for processed meat. They indicated no evidence of heterogeneity across studies.

Smolinska and Paluszkiewicz, from Poland,[18] meta-analyzed the findings of 12 case-control and 10 cohort studies carried out between 1994 and 2009. This meta-analysis confirmed the carcinogenic effect of the consumption of over 50 g of red meat per day for the colon (RR: 1.21, 95% CI: 1.07-1.37) but not for the rectum (RR: 1.30. 95% CI: 0.90-1.89). They emphasized that the frequency of red meat consumption rather than total amount was associated with a higher risk. A separate information about RR of processed meat is not available in this analysis. Bastide et al., from France,[19] investigated the relation between dietary heme iron intake from red meat and colon cancer in their meta-analysis. They analyzed 5 prospective cohort studies reporting heme intake that included 566,607 individuals and 4734 cases of colon cancer. They found that the RR of colon cancer was 1.18 (95% CI: 1.06-1.32) for subjects in the highest category of heme iron intake compared with those in the lowest category. This analysis was limited only to colon cancer.

Alexander et al., from USA and Mexico,[20] updated in 2015 their previous meta-analysis[21] and reported the data from 27 prospective cohort studies. In this meta-analysis, they observed a weakly elevated RR (1.11, 95% CI: 1.03-1.19) between red meat consumption and CRC. They did not find any dose-response pattern and underlined the importance of numerous methodological considerations such as accuracy of measurement of food intake, food definitions and dietary pattern differences across populations.

Another meta-analysis of 24 prospective studies was published in 2011, by Chan et al., from UK and Netherlands.[22] They reported that the RR of CRC for the highest versus lowest intake of red and processed meat was 1.22 (95% CI: 1.11-1.34) and 1.17 (95% CI: 1.09-1.25), respectively. The RR for every 100 g/day increase for red and processed meats was 1.14 (95% CI: 1.04-1.24). When analyzed separately, RR for 100 g/day increase of red meat was 1.17 (95% CI: 1.05-1.31) and RR for 50 g/d increase of processed meat was 1.18 (95% CI: 1.10-1.28). This meta-analysis revealed that also CRC risk increases approximately linear up to 140 g/day of the intake of red and processed meat, then the curve

Table 1. Meta-analyses for the association between red meat, processed meat and colorectal cancer risk.

Author, year published	Meta-analysis center/country	Number and type of studies for red meat	RR for red meat (95% CI)*	RR for processed meat (95% CI)*
Sandhu et al., 2001	UK	13 cohort	1.17 (1.05-1.31)	1.49 (1.22-1.81)
Norat et al., 2002	IARC, France	14 case-control and 9 cohort	1.35 (1.21-1.51)	1.31 (1.13-1.51)
Larsson and Wolk, 2006	Karolinska Inst., Sweden	15 (13 cohort and 2 case-control)	1.28 (1.15-1.42)	1.20 (1.11-1.31)
Huxley et al., 2009	Australia and Iran	26 cohort	1.21 (1.13-1.29)	1.19 (1.12-1.27)
Smolinska and Paluszkiewicz, 2009	Poland	22 (12 case-control and 10 cohort)	1.21 (1.07-1.37)**	NA
Bastide et al., 2011	France	5 cohort	1.18 (1.06-1.32)**	NA
Alexander et al., 2011 and 2015	USA, Mexico	27 cohort	1.11 (1.03-1.19)	NA
Chan et al., 2011	UK and Netherlands	24 (2 case-cohort, 3 nested case-control and 19 cohort)	1.22 (1.11-1.34)	1.17 (1.09-1.25)
Johnson et al., 2013	USA	14 (8 case-control and 6 cohort)	1.13 (1.09-1.16)***	1.09 (0.93-1.25)***
Bernstein et al., 2015	USA, China, Vietnam	2 cohort	1.06 (0.97-1.16)****	1.15 (1.01-1.32)****

RR, relative risk; CI, confidence interval; NA, not available. *Highest versus lovest intake; **only for colon cancer, not for rectum; ***5 versus 0 servings/week; ****multivariable-adjusted hazard ratio.

approaches its plateau.

Johnson *et al.*, from USA,[23] performed a meta-analysis for 12 established non-screening CRC risk factors and, red and processed meat among them in 14 and 5 studies, respectively. They found significant positive correlation between CRC and red meat consumption (RR: 1.13 per 5 *versus* 0 servings, 95% CI: 1.09-1.16). The RR of processed meat for 5 *versus* 0 servings was 1.09 (95% CI: 0.93-1.25) and this was not statistically significant.

Lastly, Bernstein *et al.*,[24] from USA, China and Vietnam, published a meta-analysis of 2 large cohorts (the Nurses' Health Study and Health Professionals Follow-up Study), in 2015. They indicated that processed meat was positively associated with CRC risk [per 1 serving/day increase: hazard ratio (HR): 1.15 (95% CI: 1.01-1.32; P for trend: 0.03)]. This positive association was marked particularly with distal colon cancer. For total red meat multivariable-adjusted HR was 1.06 (95% CI: 0.97-1.16), and this was not significant (P for trend: 0.19).

As a summary, it seems that red and processed meats significantly but moderately increase CRC risk by 20-30% according to these meta-analyses.[7,26]

Red meat subtypes and colorectal cancer

As we see above, many trials addressed to the potential risk between CRC and the intake of red and processed meat. But few studies evaluated the effects of specific red meat subtypes. Some trials and one meta-analysis addressed to this subject will be summarized below (Table 2).

Brink *et al.* from Netherlands reported their observations about meat consumption and K-*ras* mutations in colon and rectal cancer based on cohort-analyses.[27] They found weak associations between beef and wild-type (wt) K-ras colon tumors (RR=1.36 with 95% CI: 0.96-1.93, P for trend=0.08), and an inverse association for pork with colon and rectal tumors with wt K-ras (RR=0.72 with 95% CI: 0.51-1.02, P for trend=0.05 for colon, RR=0.50 with 95% CI: 0.26-0.93, P for trend=0.01 for rectum). As discussed by authors, this inverse association cannot be explained and require replication and further study.

In analyses of subgroups of red meats in the EPIC trial, CRC risk was statistically significantly associated with intake of pork and lamb but not with beaf/veal.[12] Hazard ratio (HR) for highest intake of pork *versus* lowest is 1.18 (95% CI: 0.95-1.48, P trend=0.02). HR for lamb is 1.22 (95% CI: 0.96-1.55, P trend=0.03). In analyses in which intake of each meat was mutually adjusted for the other meats, only the trend for increased CRC risk with increased pork intake was remained statistically significant (P trend=0.03) in EPIC trial.

Two studies from Japan[28,29] investigated the effect of red meat subtypes in prospective cohort studies. The first Japanese study published

by Sato and his colleagues, in 2006.[28] They concluded that not only any type of red meat, but also total red meat consumption was not a risk factor for CRC. When we look at carefully to Sato's study, we see that the meat consumption is very low in the participants of this study; 70.4 g/day for highest quartile, which is the upper limit of recommended level for healthy people according to the guidelines, mentioned below.

Second study from Japanese population, was published in 2011, by Takachi *et al.*[29] They found that high consumption of red meat was significantly associated with high risk of colon cancer among women (HR=1.48, 95% CI: 1.01-2.17, P trend=0.03). A significant association was seen also between higher consumption of beef and pork and the risk of colon cancer among women (HR=1.62, 95% CI: 1.12-2.34, P trend=0.04 for beef, HR=1.42, 95% CI: 0.99-2.04, P trend=0.05 for pork).

Egeberg *et al.* from Denmark, published a new prospective cohort study about associations between red meat intake and risks for colon and rectal cancer, in 2013.[30] The aim of this study was especially to evaluate these risks including red meat subtypes. They reported 644 cases of colon cancer and 345 cases of rectal cancer among 53,988 participants during 13.4 years follow-up. They used Cox proportional hazards models to compute incidence rate ratios (IRRs). Finally, they notified that the risk for colon cancer was significantly elevated for high intake of lamb (IRR=1.07, 95% CI: 1.02-1.13, P trend=0.01) for an increment in intake of 5 g/d. The risk for rectal cancer was elevated for intake of pork (IRR=1.18, 95% CI: 1.02-1.37, P trend=0.03) for continuous intake, per 25 g/d. In this trial, substitution of fish for red meat was associated with a significantly lower risk for colon cancer, but not rectal cancer. They concluded that the risks for colon and rectal cancer differ according to the specific red meat subtype consumed.

Carr and colleagues published a meta-analysis about meat subtypes and their association with CRC, at the beginning of this year.[25] They evaluated 19 studies and they stated that beef consumption was associated with an increased risk of CRC and colon cancer, but no association was found with rectal cancer. Lamb consumption was also associated with increased risk of CRC. They announced that no association was observed for pork, and they recommended further analysis especially regarding the role of pork. But, in this meta-analysis, EPIC trial was not included into the analysis for colon and rectal cancer risks separately, and we could not find any explanation about this in authors' reply to our letter.[25,31,32]

Potential mechanisms

The exact mechanisms underlying the association between CRC risk and high intake of red and processed meat are uncertain.[12] There are several possible mechanisms and some mutagenic and/or carcinogenic

Table 2. Red meat sub-types and colorectal cancer risk.

Author, year published	Study center/country	Study type	Relative risk (95% CI) for CRC					
			Beef	P for trend	Lamb	P for trend	Pork	P for trend
Brink *et al.*, 2005	Netherlands	Cohort	1.36 (0.96-1.93)*	0.08	NA	-	0.72 (0.51-1.02)**	0.05
Norat *et al.*, 2005	EPIC (Europe)	Cohort	1.03 (0.86-1.24)	0.76	1.22 (0.96-1.55)	0.03	1.18 (0.95-1.48)	0.02
Sato *et al.*, 2006	Japan	Cohort	0.93 (0.67-1.30)	0.63	NA	-	1.13 (0.79-1.74)	0.31
Takachi *et al.*, 2011	Japan	Cohort	1.62 (1.12-2.34)***	0.04	NA	-	1.42 (0.99-2.04)***	0.05
Egeberg *et al.*, 2013	Denmark	Cohort	0.75 (0.52-1.09)*****	0.03	1.35 (1.07-1.71)****	0.01	1.63 (1.11-2.39)*****	0.03

CI, confidence interval; CRC, colorectal cancer; EPIC, the European Prospective Investigation into Cancer and Nutrition trial; NA, not available. *Only for K-ras wt colon tumors; **only for K-ras wt colon and rectal tumors; ***only for colon cancer in women; ****RR for colon cancer; *****RR for rectal cancer.

compounds in animals to explain the relationship between red meat consumption and CRC. The possible mechanistic factors include N-nitroso compounds (NOCs), heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), Heme iron in red meat, PUFAs, bile acids, non-human sialic acid and infectious agents.

N-nitroso compounds

NOCs are mutagenic and potent carcinogenic agents in animals. Dietary NOCs are synthesized exogenously during meat processing from oxides of nitrogen (nitrites or nitrates) and amines or amides; so they are present in certain processed meats such as bacon, cured meats, sausages, ham, smoked fish and smoked cheeses.[33,34] Potassium nitrite (E249), sodium nitrite (E250), sodium nitrate (E251) and potassium nitrate (E252) are all food additives approved in many countries, but their usage generally limited to 200 ppm or lower. Because they are considered irreplaceable in the prevention of *Clostridium botulinum* poisoning from consumption of cured meat by preventing spore germination.[35] Ascorbic acid and alpha-tocopherol can be used to inhibit the production of carcinogenic nitrosamines during curing of meat.[13,26] There are two major subgroups of NOCs; N-nitrosamines and N-nitrosamides. These are carcinogenic in laboratory animals and probable carcinogenic (Group 2A) to humans according to IARC. NOCs can be formed also endogenously after consumption of red and processed meat.[26] They are formed within the colon from amines and amides produced by bacterial decarboxylation of amino acids and can be N-nitrosated in the presence of a nitrosating agent.[26,36] Total N-nitroso compounds in fecal samples were found increased after high red meat intake in volunteers.[36] NOCs are alkylating agents and they can react with DNA.[26]

Heterocyclic amines and polycyclic aromatic hydrocarbons

HCAs and PAHs are potent carcinogens, which are produced during, high-temperature or on open flame cooking of meat, especially grilling, pan-frying and barbecuing for a long period.[13,37] HCAs and PAHs are produced from pyrolysis of meat.[12] High cooking temperatures cause amino acids and creatine or creatinine and sugar to react to form a variety of HCAs.[37] They are imidazoquinoline and imidazoquinoxaline derivatives and phenylimidazopyridine.[37] HCAs are also in group 2 category in the classification of the IARC. Meat cooked well-done at high temperatures is also a source of HCAs and PAHs. Martinez *et al.* evaluated meat preparation methods and showed that significant positive associations between recurrence of multiple colorectal adenomas and well/very well done meat consumption (Odds ratio=1.71, 95% CI: 1.02-2.86, P trend=0.02).[38] Benzo(α)pyrene is a well known PAH. Cross *et al.* found a positive association for red and processed meat intake and CRC, and they reported that heme iron, nitrate/nitrite, and HCAs from meat may explain these associations.[39]

Heme iron

White meat (poultry and fish) is not associated with cancer risk.[7] Inversely high intake of fish brings a significant protection. One of the main difference between red and white meat is heme molecule in muscles myoglobin, which is present in red meat in high concentrations.[5] Poultry and fish have tenfold lower amounts of heme molecule. Corpet et al demonstrated a dose-response relationship between heme iron and promotion of colon carcinogenesis.[7] Dietary heme is degraded in the small intestine by heme oxygenase 1, releasing free ferrous iron. Heme iron can promote cancer some independent pathways.[7] One of them is the catalytic role of heme iron from red meat or nitrosyl heme from processed meat in the endogenous production of NOCs. Second possible mechanism is fat peroxidation pathway. One product of this pathway is malondialdehyde, which is a carcinogen. On the other hand,

heme iron promotes the production of reactive oxygen species (ROS) which induces genetic mutations.

Dietary animal fat, polyunsaturated fatty acids and bile acids

Domesticated, farmed animals contain high amount of fat and saturated fatty acids in lean meat about 40-50%.[17] Dietary fat increases bile acid (BAs) secretion inside the gut and they increase cell loss and proliferation in the mucosa.[40] Experimental studies about promotion of carcinogenesis by high total fat intake from meat were shown inconsistent results and epidemiological studies failed to confirm a link.[26] But, some positive reports may be partly explained by high saturated fat intake. Fatty diets favor obesity which in turn increases insulin resistance, thus promote tumor growth.[41]

Another important targets in promoting carcinogenesis are omega-6 PUFAs, especially arachidonic acid,[42] and cyclooxygenase 2 (COX-2) expression.[43] Arachidonic acid (20:4ω6) is a precursor of prostaglandins (PGs) which are key mediators of inflammatory reactions. High level of COX-2 expression is found in cancer cells. PGE2 is major downstream effector of COX-2 and it inhibits apoptosis, favors invasion, motility and promotes angiogenesis. The efficacy of non-steroidal anti-inflammatory drugs, especially selective COX-2 inhibitors were shown in the reduction of colorectal polyps. Regarding red meat subtypes, most containing meat of arachidonic acid is pork muscle (2.20 mg/100 mg defatted lean) than beef and lamb muscle.[44] Omega-6/Omega-3 ratio is also highest for pork than beef and lamb (7.22 *vs* 2.11 and 1.32, respectively).

Secondary bile acids that were under-recognized causes until now, gained great importance in recent years.[45] Primary BAs (cholic acid and chenodeoxycholic acid) are derived from cholesterol, and after synthesis in the liver, they are conjugated with glycine or taurine, and then excreted and stored in the gall bladder. They are largely re-absorbed in the terminal ileum by an active transport mechanism. Only, less than 5% of BAs pool enters the colon per day. This small portion of BAs entering to colon, are metabolized by bacterial flora and they are converted into secondary BAs (deoxycholic acid and lithocholic acid). It has been shown that BAs, especially these hydrophobic secondary BAs can create chaos within colon epithelial cells.[46] They induce membrane perturbation, oxidative DNA damage, decrease in DNA repair proteins, mitotic stress, metabolic stress with mitochondrial damage and endoplasmic reticulum stress. They generate ROS and reactive nitrogen species (RNS). This excessive stress in colonic mucosa will lead to apoptosis from one hand, stimulates proliferation on the other hands. Necrotic cells induced by hydrophobic BAs may elicit an inflammatory response. We know that tumor-promoting inflammation is one of the enabling characteristics of carcinogenesis.[47] So, chronic exposure to secondary BAs to colonic mucosa which is a result of Western-style diet (high levels of red meat/high-fat/low vegetable/low micronutrient) can cause an appropriate microenvironment for colon carcinogenesis.

Non-human sialic acid and xenosialitis hypothesis

Sialic acids are monosaccharides on cell surface. The predominant sialic acids on most mammalian cells are N-glycolylneuraminic acid (Neu5Gc) and N-acetylneuraminic acid (Neu5Ac).[48] Neu5Gc is metabolically incorporated into human tissues from dietary sources (particularly red meat), and detected at even higher levels in some human cancers. Exposure to Neu5Gc-containing foods like red meat, in the presence of certain commensal bacteria can cause to generation of auto-antibodies (xeno-autoantibodies) against Neu5Gc-containing glycans in human tissues. Experimental evidence showed that inflammation due to *xenosialitis* could promote tumor progression.[48]

Infectious agents

Some epidemiological observations exist to support an infectious etiology in human cancers. For example, some neoplasms occur under immunosuppression, nutritional cancer risk factors may be linked to infections. *Fusobacterium nucleatum* and *Streptococcus bovis* was reported to be involved in colon polyps and colon cancer.[49] Both bacteria cause inflammatory reactions and production of ROS and RNS, thus acting as mutagens. Harald zur Hausen underlines a possible link between specific, thermo-resistant and potential carcinogenic bovine infectious agents and colorectal cancer incidence with high rate of beef consumption.[50] The absence of increased risk for CRC with the consumption of white meat, although the production of some carcinogens like HCAs and PAHs were recorded fried, grilled or smoked chicken and fish, also supports hypothesis of infection.

Discussion

Epidemiological studies consist of correlation studies, case-control and cohort studies. We presented here, a summary of the data from 10 meta-analyses about the relationship between red and processed meat and CRC risk. Only 5 analyses included prospective cohort trials only,[2,14,19,20,24] the others included case-control studies besides cohorts. But, statistical heterogeneity was investigated in most of them. Based accumulated data, international guidelines published up-to-date recommendations.

Last edition of European Society for Medical Oncology (ESMO) Handbook of Nutrition and Cancer in 2011,[51] notifies that consumption of red meat (beef, pork, lamb, and horse) and processed meat convincingly increases the risk of CRC. Processed meat means red meat preserved by smoking, curing, salting or by adding preservatives. There are many types of processed meats such as ham, bacon, pastrami, salami, sausages, hot dogs, *etc*. This guideline gives also some quantitative information about the risk, based on the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) study;[17] one intake of red meat per week increases the risk of CRC by about 40%, and each 50 g of processed meat increases the risk by about 20%.

American Society of Clinical Oncology (ASCO) mentions this convincing evidence between the increase of the chance of CRC and eating processed meat based on the same study,[17] under the chapter of the role of major nutrients in cancer prevention, in its website www.cancer.net.[52] According to this study, people can eat up to 18 oz (approximately 500 g) of red meat a week (or approximately 70 g/day) without raising cancer risk.

United States (US) National Cancer Institute (NCI) also reports this increased risk of CRC associated with red meat and processed meat, and potential mechanisms of this association, which is discussed above.[53]

American Cancer Society (ACS) recommends limiting intake of processed meat and red meat in its January/February 2012 issue of its Nutrition and Physical Activity Guidelines.[54] Choosing fish, poultry or beans and lean cuts, eating smaller portions are located in these guidelines.

Institut National du Cancer (INC) from France repeats this consumption of 500 g of red meat per week besides completing the rest need of protein by white meat, fish, eggs and vegetables.[55] It recommends again limiting consumption of processed meat.

Dietary modification is an important approach to cancer control. In 1981, Doll and Peto estimated that approximately 35% of cancer deaths in the United States were avoidable by modification of diet.[56] World Health Organization (WHO) indicates that excess consumption of red and preserved meat are associated with an increased risk of CRC, based on the International Agency for Research on Cancer (IARC) report.[57] Finally, processed meat was classified as carcinogenic to humans (Group 1), based on sufficient evidence by IARC, on 26 October 2015.[58]

Conclusions

As a conclusion, accumulated evidence of prospective epidemiological studies and their meta-analyses shows that red meat and processed meat convincingly increases CRC risk by 20-30%. Regarding specific red meat subtypes, the association with increased risk was found for beef consumption in two trials (one of them is weakly associated), for pork consumption in three trials and for lamb intake in one trial. An interesting observation is the existence of this risk only for pork intake and rectum cancer and lamb intake and colon cancer, respectively in one trial. Beef and pork consumption was found also to be associated with colon cancer only in women, in one trial. Whether CRC is one disease or the existence of 2 categories of CRC (colon and rectum or proximal and distal or right and left colon) and the link between etiologic factors and molecular subtypes are another hot topics of discussion, which need further investigations.[59,60]

According to guidelines today,[51-55] recommended amount of red meat for healthy people is 500 g/week or 70 g/day. They recommend also limiting intake of processed meat.

White meat (fish and poultry) is not associated with CRC risk and is recommended safely. To diminish carcinogenic effects of HCAs, diet should be high in dietary fibre sources such as wheat bran and vegetables. Formation of HCAs can be reduced by avoidance of exposure of meat surfaces to flames, usage of aluminum foil to wrap meat before oven roasting and microwave cooking.[61]

To eat meat safer, different trimming processes can be applied on the market, to decrease fat content.

Meat is an important source of nutrients and should be consumed moderately and balanced with other foods.

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