

Carcinogenicity of consumption of red and processed meat

In October, 2015, 22 scientists from ten countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the carcinogenicity of the consumption of red meat and processed meat. These assessments will be published in volume 114 of the IARC Monographs.¹

Red meat refers to unprocessed mammalian muscle meat—for example, beef, veal, pork, lamb, mutton, horse, or goat meat—including minced or frozen meat; it is usually consumed cooked. Processed meat refers to meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Most processed meats contain pork or beef, but might also contain other red meats, poultry, offal (eg, liver), or meat byproducts such as blood.

Red meat contains high biological-value proteins and important micronutrients such as B vitamins, iron (both free iron and haem iron), and zinc. The fat content of red meat varies depending on animal species, age, sex, breed, and feed, and the cut of the meat. Meat processing, such as curing and smoking, can result in formation of carcinogenic chemicals, including *N*-nitroso-compounds (NOC) and polycyclic aromatic hydrocarbons (PAH). Cooking improves the digestibility and palatability of meat, but can also produce known or suspected carcinogens, including heterocyclic aromatic amines (HAA) and PAH. High-temperature cooking by pan-frying, grilling, or barbecuing generally produces the highest amounts of these chemicals.^{2,3}

Depending on the country, the proportion of the population that consumes red meat varies worldwide from less than 5% to up to 100%, and from less than 2% to 65% for processed meat. The mean intake of red meat by those who consume it is about 50–100 g per person per day, with high consumption equalling

more than 200 g per person per day.⁴ Less information is available on the consumption of processed meat.

The Working Group assessed more than 800 epidemiological studies that investigated the association of cancer with consumption of red meat or processed meat in many countries, from several continents, with diverse ethnicities and diets. For the evaluation, the greatest weight was given to prospective cohort studies done in the general population. High quality population-based case-control studies provided additional evidence. For both designs, the studies judged to be most informative were those that considered red meat and processed meat separately, had quantitative dietary data obtained from validated questionnaires, a large sample size, and controlled for the major potential confounders for the cancer sites concerned.

The largest body of epidemiological data concerned colorectal cancer. Data on the association of red meat consumption with colorectal cancer were available from 14 cohort studies. Positive associations were seen with high versus low consumption of red meat in half of those studies, including a cohort from ten European countries spanning a wide range of meat consumption and other large cohorts in Sweden and Australia.⁵⁻⁷ Of the 15 informative case-control studies considered, seven reported positive associations of colorectal cancer with high versus low consumption of red meat. Positive associations of colorectal cancer with consumption of processed meat were reported in 12 of the 18 cohort studies that provided relevant data, including studies in Europe, Japan, and the USA.^{5,8-11} Supporting evidence came from six of nine informative case-control studies. A meta-analysis of colorectal cancer in ten cohort studies reported a statistically significant dose–response relationship, with a 17% increased risk (95% CI 1.05–1.31) per 100 g per

day of red meat and an 18% increase (95% CI 1.10–1.28) per 50 g per day of processed meat.¹²

Data were also available for more than 15 other types of cancer. Positive associations were seen in cohort studies and population-based case-control studies between consumption of red meat and cancers of the pancreas and the prostate (mainly advanced prostate cancer), and between consumption of processed meat and cancer of the stomach.

On the basis of the large amount of data and the consistent associations of colorectal cancer with consumption of processed meat across studies in different populations, which make chance, bias, and confounding unlikely as explanations, the majority of the Working Group concluded that there is sufficient evidence in human beings for the carcinogenicity of the consumption of processed meat. Chance, bias, and confounding could not be ruled out with the same degree of confidence for the data on red meat consumption, since no clear association was seen in several of the high quality studies and residual confounding from other diet and lifestyle risk is difficult to exclude. The Working Group concluded that there is limited evidence in human beings for the carcinogenicity of the consumption of red meat.

There is inadequate evidence in experimental animals for the carcinogenicity of consumption of red meat and of processed meat. In rats treated with colon cancer initiators and promoted with low calcium diets containing either red meat or processed meat, an increase in the occurrence of colonic preneoplastic lesions was reported in three and four studies, respectively.¹³⁻¹⁵

The mechanistic evidence for carcinogenicity was assessed as strong for red meat and moderate for processed meat. Mechanistic evidence is mainly available for the



Published Online
October 26, 2015
[http://dx.doi.org/10.1016/S1470-2045\(15\)00444-1](http://dx.doi.org/10.1016/S1470-2045(15)00444-1)

For more on the IARC Monographs see <http://monographs.iarc.fr/>

Upcoming meetings

Feb 2–9, 2016, Volume 115:
Some industrial chemicals;
May 24–31, 2016, Volume 116:
Coffee and some other hot beverages

IARC Monograph Working Group Members

B W Stewart (Australia)—meeting chair; S De Smet (Belgium); D Corpet, M Meurillon (France); G Caderni (Italy); S Rohrmann; P Verger (Switzerland); S Sasazuki, K Wakabayashi (Japan); M P Weijenberg (Netherlands); A Wolk (Sweden); M Cantwell; T Norat; P Vineis (UK); F A Beland, E Cho, D M Klurfeld, L Le Marchand, R Sinha, M Stern, R Turesky, K Wu (USA)

Declaration of interests

TN was involved in a research project funded by the World Cancer Research Fund, a registered charity. All other working group members declare no competing interests.

Invited Specialists

None

Representatives

A Christodoulidou, for the European Food Safety Authority (EFSA), Italy; I Margaritis, for the French Agency for Food, Environment and Occupational Health and Safety (ANSES), France; Y Totsuka, for the National Cancer Center Research Institute, Japan

Declaration of interests

All representatives declare no competing interests.

Observers

D D Alexander, for the EpidStat Institute, USA; B L Booren, for the North American Meat Institute, USA; J Carretier, for the Léon Bérard Centre, France;

JJ Hlywka, for the Kraft Heinz Company, USA; D A Kovich, for the National Pork Producers Council, USA; H J Lazaneo, for the National Meat Institute (INAC), Uruguay; M McCullough, for the American Cancer Society, USA; S McNeill, for Beef Checkoff, USA

Declaration of interests
DDA has received consulting fees from Beef Checkoff for research on red meat and cancer. BLB receives a salary from the North American Meat Institute (NAMI) and the North American Meat Institute Foundation (NAMIF). BLB publicly represents in media, government, and scientific meetings, among others, the NAMI and NAMIF position and analysis of scientific evidence. DAK is employed by the National Pork Producers Council, USA. SMcN is an employee of the National Cattlemen's Beef Association and is a contractor to the Beef Checkoff. All other observers declare no competing interests.

IARC/WHO Secretariat

L Benbrahim-Tallaa; V Bouvard; F El Ghissassi; C Espina; E Feletto; J Gomes; Y Grosse; N Guha; K Z Guyton; I Huybrechts; D Loomis; H Mattock; A Muelle; I Romieu; C Santamaria-Ulloa; M Stepien; K Straif

Declaration of interests

All secretariat declare no competing interests.

For the **Preamble to the IARC Monographs** see <http://monographs.iarc.fr/ENG/Preamble/index.php>

For **IARC declarations of interests** see <http://monographs.iarc.fr/ENG/Meetings/vol.114-participants/>

digestive tract. A meta-analysis published in 2013 reported a modest but statistically significant association between consumption of red or processed meat and adenomas (preneoplastic lesions) of the colorectum that was consistent across studies.¹⁶ For genotoxicity and oxidative stress, evidence was moderate for the consumption of red or processed meat. In human beings, observational data showed slight but statistically significant associations with APC gene mutation or promoter methylation that were identified in 75 (43%) and 41 (23%) of 185 archival colorectal cancer samples, respectively.¹⁷ Consuming well done cooked red meat increases the bacterial mutagenicity of human urine. In three intervention studies in human beings, changes in oxidative stress markers (in urine, faeces, or blood) were associated with consumption of red meat or processed meat.¹⁸ Red and processed meat intake increased lipid oxidation products in rodent faeces.¹³

Substantial supporting mechanistic evidence was available for multiple meat components (NOC, haem iron, and HAA). Consumption of red meat and processed meat by man induces NOC formation in the digestive tract. High red meat consumption (300 or 420 g/day) increased levels of DNA adducts putatively derived from NOC in exfoliated colonocytes or rectal biopsies in two intervention studies.^{19,20} Few human data, especially from intervention studies, were available for processed meat. Haem iron mediates formation of NOC, and of lipid oxidation products in the digestive tract of human beings and rodents. Haem iron effects can be experimentally suppressed by calcium, supporting its contribution to carcinogenic mechanisms. Meat heated at a high temperature contains HAA. HAA are genotoxic, and the extent of conversion of HAA to genotoxic metabolites is greater in man than in rodents. Meat smoked or

cooked over a heated surface or open flame contains PAH. These chemicals cause DNA damage, but little direct evidence exists that this occurs following meat consumption.

Overall, the Working Group classified consumption of processed meat as "carcinogenic to humans" (Group 1) on the basis of sufficient evidence for colorectal cancer. Additionally, a positive association with the consumption of processed meat was found for stomach cancer.

The Working Group classified consumption of red meat as "probably carcinogenic to humans" (Group 2A). In making this evaluation, the Working Group took into consideration all the relevant data, including the substantial epidemiological data showing a positive association between consumption of red meat and colorectal cancer and the strong mechanistic evidence. Consumption of red meat was also positively associated with pancreatic and with prostate cancer.

We declare no competing interests.

Véronique Bouvard, Dana Loomis, Kathryn Z Guyton, Yann Grosse, Fatiha El Ghissassi, Lamia Benbrahim-Tallaa, Neela Guha, Heidi Mattock, Kurt Straif, on behalf of the International Agency for Research on Cancer Monograph Working Group

International Agency for Research on Cancer, Lyon, France

- International Agency for Research on Cancer. Volume 114: Consumption of red meat and processed meat. IARC Working Group. Lyon; 6–13 September, 2015. *IARC Monogr Eval Carcinog Risks Hum* (in press).
- Alaejos MS, Afonso AM. Factors that affect the content of heterocyclic aromatic amines in foods. *Comp Rev Food Sci Food Safe* 2011; **10**: 52–108.
- Alomirah H, Al-Zenki S, Al-Hooti S, et al. Concentrations and dietary exposure to polycyclic aromatic hydrocarbons (PAHs) from grilled and smoked foods. *Food Control* 2011; **22**: 2028–35.
- Food and Agriculture Organization of the United Nations Statistics Division. Food balance. 2015. http://faostat3.fao.org/browse/FB/*E (accessed July 9, 2015).
- Norat T, Bingham S, Ferrari P, et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst* 2005; **97**: 906–16.
- Larsson SC, Rafter J, Holmberg L, Bergkvist L, Wolk A. Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. *Int J Cancer* 2005; **113**: 829–34.
- English DR, MacInnis RJ, Hodge AM, Hopper JL, Haydon AM, Giles GG. Red meat, chicken, and fish consumption and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 1509–14.
- Oba S, Shimizu N, Nagata C, et al. The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. *Cancer Lett* 2006; **244**: 260–67.
- Bernstein AM, Song M, Zhang X, et al. Processed and unprocessed red meat and risk of colorectal cancer: analysis by tumor location and modification by time. *PLoS One* 2015; **10**: e0135959.
- Cross AJ, Ferrucci LM, Risch A, et al. A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. *Cancer Res* 2010; **70**: 2406–14.
- Chao A, Thun MJ, Connell CJ, et al. Meat consumption and risk of colorectal cancer. *JAMA* 2005; **293**: 871–82.
- Chan DS, Lau R, Aune D, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *PLoS One* 2011; **6**: e20456.
- Pierre F, Freeman A, Tache S, van der Meer R, Corpet DE. Beef meat and blood sausage promote the formation of azoxymethane-induced mucin-depleted foci and aberrant crypt foci in rat colons. *J Nutr* 2004; **134**: 2711–16.
- Pierre F, Santarelli R, Tache S, Gueraud F, Corpet DE. Beef meat promotion of dimethylhydrazine-induced colorectal carcinogenesis biomarkers is suppressed by dietary calcium. *Br J Nutr* 2008; **99**: 1000–06.
- Santarelli RL, Vendeuvre JL, Naud N, et al. Meat processing and colon carcinogenesis: cooked, nitrite-treated, and oxidized high-heme cured meat promotes mucin-depleted foci in rats. *Cancer Prev Res (Phila)* 2011; **3**: 852–64.
- Aune D, Chan DS, Vieira AR, et al. Red and processed meat intake and risk of colorectal adenomas: a systematic review and meta-analysis of epidemiological studies. *Cancer Causes Control* 2013; **24**: 611–27.
- Gay LJ, Mitrou PN, Keen J, et al. Dietary, lifestyle and clinicopathological factors associated with APC mutations and promoter methylation in colorectal cancers from the EPIC-Norfolk study. *J Pathol* 2012; **228**: 405–15.
- Pierre FH, Martin OC, Santarelli RL, et al. Calcium and alpha-tocopherol suppress cured-meat promotion of chemically induced colon carcinogenesis in rats and reduce associated biomarkers in human volunteers. *Am J Clin Nutr* 2013; **98**: 1255–62.
- Le Leu RK, Winter JM, Christophersen CT, et al. Butyrylated starch intake can prevent red meat-induced O6-methyl-2-deoxyguanosine adducts in human rectal tissue: a randomised clinical trial. *Br J Nutr* 2015; **114**: 220–30.
- Lewin MH, Bailey N, Bandaletova T, et al. Red meat enhances the colonic formation of the DNA adduct O6-carboxymethyl guanine: implications for colorectal cancer risk. *Cancer Res* 2006; **66**: 1859–65.