Meat Science 98 (2014) 792–794

Contents lists available at ScienceDirect

Meat Science

journal homepage: www.elsevier.com/locate/meatsci

Letter to the Editor: Colorectal cancer risk and association with red meat — Is it inconsistent? Answer to the letter by Corpet, De Smet and Demeyer

Keywords:
Red meat
Colorectal cancer
Dose–response
Epidemiology
Experimental carcinogenesis

1. Introduction

In a recent overview paper we gave an account of the healthiness of red meat but some concern with the wording of the abstract was raised by Corpet et al. (2014) in a letter to the editor of Meat Science. The abstract could give the impression that the association between red meat and colorectal cancer in observational studies is largely inconsistent, which is not the case, whereas the intention was to point out that there is some inconsistency between observational and experimental data on red meat and cancer. This letter expands on this point and serves at the same time as an explanation of the statement and an answer to the letter by Corpet et al. (2014).

As detailed in the letter by Corpet and colleagues (Corpet et al., 2014), a perspectives paper on the healthiness of red meat was recently published in Meat Science (Oostindjer et al., 2014). In our opinion the perspectives paper captures the status and discussions of the workshop on this topic very well. However, the process of trying to reach an agreement on the relationship between red meat consumption and cancer risk was not an easy task and caused quite some debate among the co-authors. The following sentence, from the abstract, is criticized by Corpet and colleagues as not being scientifically correct and therefore not being representative of our consensus: "*Epidemiological and mechanistic data on associations between red and processed meat intake and CRC are inconsistent …*", as they state: "apart from some uncertainty related to age and ethnicity, epidemiological data are consistent, although the underlying mechanisms remain unclear". The sentence was introduced into the abstract — and most co-authors agreed — to cover the fact that there was obvious disagreement at the meeting; in this response to the letter by Corpet et al. (Corpet et al., 2014) we would like to answer to it.

First of all we would like to agree, that when it comes to meta-analyses, the results uniformly associate red meat intake with increased risk of colorectal cancer (CRC) (Alexander, Miller, Cushing, & Lowe, 2010; Alexander, Weed, Cushing, & Lowe, 2011; Aune et al., 2013; Chan et al., 2011; Johnson et al., 2013; Larsson & Wolk, 2006; Norat, Lukanova, Ferrari, & Riboli, 2002; Smolinska & Paluszkiewicz, 2010; Xu et al., 2013). So from this point of view there is no inconsistency and the above formulation may therefore lead to unnecessary misunderstandings. The estimated increase in risk with red meat intake is somewhat variable going from little more than 1.1 (Alexander et al., 2011; Johnson et al., 2013) to almost 1.3 per 100 g of red meat daily (Aune et al., 2013; Norat et al., 2002) in recent meta-analyses. Because of this and some issues related to age and ethnicity, it is concluded in a few of the papers that the weak effect observed could be due to confounding (Alexander et al., 2010, 2011). The debate on this issue is sometimes heated and selection of studies to include into the meta-analyses thus seems also to be a core issue. However, this scientific disagreement is not what the contentious sentence in the abstract was actually addressing because it was meant to point only to some inconsistency when it comes to comparisons between experimental and observational studies. Similar debates, exist for other nutritional relationships with CRC, e.g. for the associations observed with folate, fibre, fruit or vegetables, so obviously the disease causation is complex and mechanisms difficult to disentangle.

The potential link between red meat consumption and CRC risk from experimental data points towards several carcinogens formed as a result of haeme catalyzing the formation of toxic nitrosamines or cytotoxic lipoperoxides in the lower gut (Bingham, Hughes, & Cross, 2002; Bingham et al., 1996; Pierre, Tache, Petit, Van der Meer, & Corpet, 2003), or heterocyclic amines and PAH formed during processing (Abid, Cross, & Sinha, 2014; Felton & Knize, 2006). A large part of the experimental data also supports a cause-and-effect relationship as detailed in the consensus paper. However, nitrosamines, PAH and heterocyclic amines are genotoxins that would be expected to give linear dose–response relationships with cancer induction at any given age (Bingham et al., 2002). Lipoperoxides are cytotoxic and could result in tumor promotion which would translate into shorter time-to-tumor (Moolgavkar & Knudson, 1981). In either case, we would expect to see a linear increase in the age-standardized cancer risk with dose in observational studies, which does not seem to be the case. It is clear that other factors could also influence carcinogenesis and risk, including physical activity level, phytochemicals, calcium intake or status, food matrix effects, diet-gene interactions, etc. and this is actually a point where there is agreement across views on meat and causation of cancer (Alexander et al., 2011; Corpet, 2011). However, random factors of this kind would not be expected to affect the observation of a dose–response relationship because it would affect all exposure groups in a similar manner. So unless these protective factors are directly associated with red meat intake and need to reach a certain threshold to quench the carcinogens we should still expect a linear relationship in the range of, say 30 g/d to 100 g/d of red meat intake. However, this is not obvious from the observational studies done so far. In one meta-analysis, there is in fact a dose–response for colorectal adenomas from 20 to 90 g/d of red meat intake (Xu et al., 2013) and in other studies the evidence has been translated into risk per 100 g of red meat or similar measures; but the impression across all CRC studies, independent of study selection criteria, is that the dose–response relationship is non-linear (Alexander & Cushing, 2011; Chan et al., 2011). *This is a central inconsistency between experimental and observational studies on meat and CRC.* In reality we do not know with certainty whether the factors singled out experimentally are also causing human cancer and this

http://dx.doi.org/10.1016/j.meatsci.2014.07.032

inconsistency is also acknowledged by (Corpet et al., 2014) and the formulation (see above) suggested for the description of inconsistency by him and his colleagues would probably better represent the actual status of disagreement. It is less vague and may also prevent any unnecessary misunderstandings that epidemiological associations between red meat consumption and CRC risk are being questioned.

As it is detailed in the overview paper there is still some way to go in this field of research and hopefully cross-disciplinary collaborations will eventually bring results to bridge the knowledge gaps and bring full consensus. As a final remark it is notable that the two sides in the disagreement on the relationship between CRC and red meat consumption agree that the modulators of CRC carcinogenesis are so powerful that it would be possible to quench any influence of red meat on cancer development; so they share the same hope and vision — only the degree of certainty that red meat is a direct causative factor divides the two sides in this debate.

Conflicts of interest

LO Dragsted received support in 2011 from the company, Danske Slagterier (35354), for work on meat intake biomarkers.

NS Bryan and the University of Texas Health Science Center have financial interests in Neogenis Labs, Inc.

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6 July 2014