Prudence Rose Carr
Dr. sc. hum.

Meat consumption and associations with risk and outcomes of colorectal neoplasms

Fach/Einrichtung: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Priv. -Doz. Dr sc.hum. Michael Hoffmeister

The evidence that red and processed meat is a risk factor for colorectal cancer (CRC) has accumulated and in 2007 (updated in 2011), the World Cancer Research Fund/American Institute for Cancer Research judged red and processed meat to be a convincing risk factor for CRC. Most recently, in 2015, the International Agency for Research on Cancer classified the consumption of processed meat as "carcinogenic to humans", and red meat as "probably carcinogenic to humans". However, the exact mechanisms to explain these associations remain unclear. Furthermore, in contrast to the convincing evidence linking red and processed meat and CRC risk, evidence for its role in CRC survival is limited. Hence, more evidence is needed to evaluate specific requirements for CRC survivors. The aim of this dissertation was therefore to further investigate the associations of meat consumption with risk and outcomes of colorectal neoplasms.

A systematic review and meta-analysis was conducted to evaluate the associations between red meat subtypes and risk of colorectal, colon or rectal cancer, or colorectal adenoma risk. Comparing highest versus lowest intake, beef consumption was associated with an increased risk of CRC (Relative risk [RR]: 1.11, 95% confidence interval [CI]: 1.01-1.22) and colon cancer (RR: 1.24, 95% CI: 1.07-1.44), but no association was found with rectal cancer (RR: 0.95, 95% CI 0.78-1.16). Higher consumption of lamb was associated with increased risk of CRC (RR: 1.24, 95% CI: 1.08-1.44). No association was observed for pork (RR: 1.07, 95% CI: 0.90 -1.27), or for poultry consumption and risk of colorectal adenomas or cancer. Results from this meta-analysis suggest that red meat subtypes differ in their association with CRC and its subsites, however further analysis of data from prospective cohort studies is warranted, especially regarding the role of pork.

In a large cross-sectional study of 15,950 participants (KolosSal study), associations between meat intake and the most advanced findings from colonoscopy were investigated. No association between red or processed meat consumption and prevalence of any adenomas or advanced adenomas (highest vs lowest, red meat, prevalence ratio [PR]: 1.07, 95% CI: 0.83-

1.37, processed meat, PR: 1.11, 95% CI: 0.91-1.36) was observed. In site-specific analyses, processed meat was associated with prevalence of advanced adenomas in the rectum (highest vs lowest; PR: 1.87, 95% CI: 1.19-2.95) only. Additional large studies are still warranted to clarify potential difference in association by location. No association was observed between poultry consumption and the prevalence of colorectal polyps in this study.

Higher intake of red and processed meat was associated with an increased risk of colorectal, colon and rectal cancer in a large population based case-control study from Germany (DACHS study). No major differences were observed among the molecular tumour features analysed, for associations with CRC risk defined by microsatellite instability (MSI), CpG island methylator phenotype (CIMP), BRAF, p53 or oestrogen receptor-β expression status. Red and processed meat intake was associated less strongly with risk of KRAS-mutated CRC (Odds ratio [OR] >1 time/day vs ≤ 1 time/week: 1.49, 95% CI: 1.09-2.03) than with risk of KRAS-wildtype CRC (OR 1.82, 95% CI: 1.42-2.34; $p_{heterogeneity}$ 0.04). BRAF-mutated tumours were not associated with red and processed meat intake in presence of microsatellite stability and CIMP-low/negative. Further large studies are needed to confirm these results and to help further elucidate potential underlying mechanisms.

Finally, among stage I-III CRC patients (DACHS study), baseline red and processed meat intake was not associated with overall (>1 time/day vs <1 time/day, hazard ratio [HR]: 0.85, 95% CI: 0.67-1.09), CRC-specific (HR: 0.83, 95% CI: 0.61-1.14), cardiovascular disease-specific (HR: 0.92, 95% CI: 0.51-1.68), non-CRC-specific (HR: 0.88, 95% CI: 0.59-1.30) and recurrence free (HR: 1.03, 95% CI: 0.80-1.33) survival. An association with worse overall survival was found among patients with KRAS-mutated CRC (HR: 1.99, 95% CI: 1.10-3.56), but not with MSI or CIMP positivity. A much lower proportion of survivors reported daily consumption of red and processed meat at five-year follow-up than at baseline (concordance rate 39%, kappa-value: 0.10, 95% CI: 0.07-0.13), possibly indicating that patients who survive change their diet after diagnosis. Future studies should aim to examine dietary intake at a number of time points both before and after CRC diagnosis to evaluate dietary changes and their impact on survival and other health outcomes.

The results from this dissertation provide new insight into the role of red and processed meat in relation to colorectal carcinogenesis and CRC survival. Further studies however, are still needed to validate the present findings, to elucidate the underlying mechanisms and to continue the investigation into dietary strategies for CRC prevention and prognosis.