Re: Meat, Fish, and Colorectal Cancer Risk: The European Prospective Investigation into Cancer and Nutrition

In a large cohort comprising 10 populations in the European Prospective Investigation into Cancer and Nutrition, Norat et al. (1) reported that processed and red meat intake was associated with elevated rates of colorectal cancer and its subtypes. Although the authors considered several study limitations, they may have omitted one that is key: the possibility that confounding by socioeconomic position may be responsible for the diet–disease gradients.

In populations drawn from some of the countries featured in the article, markers of socioeconomic position have been shown to be associated with self-reported dietary characteristics, including meat consumption (2). Thus, persons who are socioeconomically disadvantaged are more likely to report higher intake than their affluent counterparts (2). A raised risk of colorectal cancer has also been found in persons from deprived social groups, as indexed by lower levels of educational attainment (3).

In exploring the relationship between meat consumption (indeed, most indicators of food intake) and colon cancer (indeed, most chronic disease outcomes), surprisingly few investigators adjust for socioeconomic indices, so judging the impact of this covariate on the diet-disease relationship is problematic. However, a suggestion that socioeconomic deprivation may have a role as a confounder in the meat–colon cancer relationship could be found in a study that appeared in a subgroup of study participants and reported by the authors.

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We read with interest the article by Norat et al. (1) about meat, fish, and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, which found no statistically significant association between the intake of red meat and colorectal cancer. Only when red and processed meats were combined was the observed positive association statistically significant. We would like to ask why the authors did not mention in their abstract the fact that red meat alone does not statistically significantly increase the relative risk and why they did not adjust their data for vegetable intake. Because vegetables and fruit are a good source of fiber and folate and reduce the energy density of a meal, all of which could diminish colorectal cancer risk, they are an important confounding factor. The cross-classification of red and processed meat intake with fiber intake clearly showed no increase in cancer risk if both intakes were in the highest category. The same was true for high fish intake. Many people enjoy eating red meat, fish, and poultry but do not eat processed meat.

Although the authors choose their wording very carefully, stating only that they found a “positive association,” the media took the results of this study as a proof for a causal relationship between red meat consumption and colorectal cancer. We want to point out that such an association is far from proven, as none of the prospective European studies published to date found a statistically significant association (2–5). The authors state that they could not explain the association, and there is no known mechanism. One possible explanation could be the higher content of heme iron, but in the same issue of the Journal, Chan et al. (6) published data indicating that dietary iron was not associated with colorectal adenoma in women. In addition, it was recently observed that chlorophyll from green vegetables prevents the cytotoxic and hyperproliferative effects of heme in a rat model (7).

The EPIC study offers an important opportunity to learn more about diet and cancer. Its results, however, should be communicated in a very clear way because otherwise it would only increase the already existing confusion among consumers and health care providers. Because lean (red) meat is an important contributor to mineral, vitamin, and protein nutrition and many people like to eat meat, we feel it unjustified, based on the EPIC data, to give the impression that this habit could lead to such a severe illness. Perhaps the message of this EPIC publication should read: Enjoy our meat but have your veggies with it.

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RESPONSE

Batty suggests that our findings of a positive association between high intake of red and processed meat and colorectal cancer risk might be the result of confounding by socioeconomic position. In our study population, meat intake is inversely associated with educational attainment (1), an indicator of socioeconomic position. The relative risks of colorectal cancer associated to secondary school, professional school, and university compared with primary school or less were 1.00, 1.12, and 1.02, respectively, indicating that colorectal cancer risk does not vary by educational attainment in this population. It is therefore not surprising that adjustment for educational attainment did not modify the relationship of red meat, processed meat, and fish with colorectal cancer risk.

We have previously shown that the inverse association of colorectal cancer risk with fiber intake persisted after adjustment for this indicator of socioeconomic status (2).

We appreciate the fact that initial results based on a relatively small number of cancer patients may change when precision increases with longer follow-up and when confounding is attenuated by better adjustment for covariates, as may have been the case for the study (3) cited by Batty. The number of colorectal cancer cases in the European Prospective Investigation into Cancer and Nutrition (EPIC) study is comparable to the number included in the recent combined analysis of the Nurses’ Health Study and the Health Professionals Follow Up Study (3), and our results are adjusted for main potential confounders. The cohorts in EPIC are heterogeneous in diet, lifestyle, and other potential confounders (4), but there was not a statistically significant heterogeneity in the association of red and processed meat with colorectal cancer risk when the analyses were conducted by country ($P_{\text{heterogeneity}} = .82$).

Gonder and Worm ask why we did not mention in the abstract that red meat alone does not statistically significantly increase the relative risk of colorectal cancer. The association of red meat with colorectal cancer was statistically significant when the variable was modeled as continuous ($P_{trend} = .03$) and close to statistical significance in categorical models ($P_{trend} = .08$). These
results do not provide evidence of a lack of association of high consumption of red meat and colorectal cancer risk. As discussed in our article, previous studies have provided possible explanations for the association with red meat, processed and unprocessed, but not with processed meat only. One possibility could be increased exposure to N-nitroso compounds and their precursors due to nitrites or nitrates added to meat for preservation. However, not all processed meats contain added nitrates, and we could not identify one particular type of processed meat that was more strongly associated with colorectal cancer risk than others.

Gonder and Worm ask why our analyses were not adjusted for vegetables, good sources of fiber and folate. Adjustment for vegetables did not modify our results, and this variable was not kept in the model. Our results were adjusted for fiber intake, and we showed that they were unchanged after adjustment for dietary folate in a subset of the cohort for whom dietary folate was available. As noted in the correspondence, there was some evidence that the association of red and processed meat with colorectal cancer risk might be weaker in the group of subjects with higher intake of fiber. Because, to the best of our knowledge, this possible modification by fiber of the association between meat intake and colorectal cancer risk had not been previously reported by large prospective studies, further research is needed before drawing any firm conclusions.

Finally, we see as a strong point supporting our results the fact that there was no heterogeneity of the association for red and processed meat across countries in EPIC, despite the high variability of vegetable and fiber consumption across EPIC cohorts (5). Our results support our conclusion that red and processed meat are positively associated with risk of colorectal cancer, but they do not demonstrate that high intake of red meat accompanied by high intake of vegetables is not associated with colorectal cancer risk.

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