Ingestion of dietary nitrate and nitrite and cancer risk

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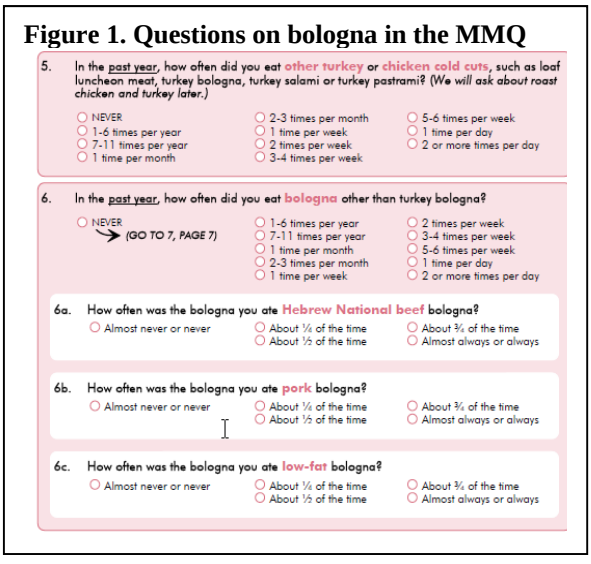
In 2007, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report concluded that the "evidence on red meat and processed meat is stronger than it was in the mid-1990s", and there is "convincing" evidence that red and processed meats increase the risk of colorectal cancer. However, the report also stated "epidemiological evidence on other methods of preserving and preparing meats and other animal foods is sparse; the overall evidence remains suggestive, at best."[1]

Nitrite and nitrate are added to most processed meats to prevent bacterial growth and to produce the characteristic red-pink color of cured meats. In 2006, a working group at the International Agency for Research on Cancer (IARC) reviewed nitrate and nitrite exposures and concluded that nitrate and nitrite ingested under conditions that cause endogenous nitrosation are probable human carcinogens.[1-3]

Using USDA food consumption data, we find that red meat composes the largest proportion of meat consumed in the U.S., and nearly a quarter of the meat consumed is processed. One of the proposed mechanisms relating red and processed meat to carcinogenesis is the formation of *N*-nitroso compounds (NOCs); these compounds can induce tumors in all species, at a variety of anatomic sites, and in a wide range of target cells.[4]

The complexity of estimating exposure to nitrate, nitrite, and NOCs makes population-based studies challenging. Many classifications of processed meat include disparate methods such as mincing, smoking, and preserving with salting and other preservation methods. The resulting food groups have many compounds with varying carcinogenic properties. In some cases, processed meat may refer only to processed red meat, rather than all meats that have been processed/ preserved. In spite of the fact that a high proportion of meat consumed in the U.S. and Europe is processed or preserved, most food frequency questionnaires (FFQs) have limited questions about intake of these meats. The typical approach of combining all of these meats in one line-item is not conducive to studying potential mechanisms.

Figure 1. Questions on bologna in the MMQ


5. In the past year, how often did you eat other turkey or chicken cold cuts, such as loaf luncheon meat, turkey bologna, turkey salami or turkey pastrami? *(We will ask about roast chicken and turkey later.)*

○ NEVER ○ 1-6 times per year ○ 7-11 times per year ○ 1 time per month ○ 2-3 times per month ○ 1 time per week ○ 2 times per week ○ 3-4 times per week ○ 5-6 times per week ○ 1 time per day ○ 2 or more times per day

6. In the past year, how often did you eat bologna other than turkey bologna?

○ NEVER → *(GO TO 7, PAGE 7)* ○ 1-6 times per year ○ 7-11 times per year ○ 1 time per month ○ 2-3 times per month ○ 1 time per week ○ 2 times per week ○ 3-4 times per week ○ 5-6 times per week ○ 1 time per day ○ 2 or more times per day

6a. How often was the bologna you ate Hebrew National beef bologna?

○ Almost never or never ○ About ¼ of the time ○ About ½ of the time ○ About ¾ of the time ○ Almost always or always

6b. How often was the bologna you ate pork bologna?

○ Almost never or never ○ About ¼ of the time ○ About ½ of the time ○ About ¾ of the time ○ Almost always or always

6c. How often was the bologna you ate low-fat bologna?

○ Almost never or never ○ About ¼ of the time ○ About ½ of the time ○ About ¾ of the time ○ Almost always or always

At the National Cancer Institute, we developed the Meat Mutagen Questionnaire (MMQ) with a comprehensive set of questions on processed meat. Using the Continuing Survey of Food Intakes by Individuals (CSFII 1994-96), we identified 104 smoked and processed meat food codes consumed in the U.S. during 1994-96.[5] We then reviewed the meat items for frequency of consumption and grouped them on the basis of the type of meat and the food additive composition. This resulted in the following meat categories: bacon, sausage, bologna, hot dogs, smoked fish, deli ham, turkey ham, other turkey or chicken cold cuts, salami, pepperoni, beef luncheon meats, other cold cuts, corned beef, baked ham, liverwurst, smoked turkey, and meat spread/potted meat. We used these categories to develop the MMQ for epidemiologic studies; Figure 1 shows an example for bologna.

In order to develop a database for nitrate, nitrite, and NOCs for red and processed queried in the MMQ, we identified 10 meat types that constituted 90 percent of the total number of mentions of processed meats in the CSFII 1994-1996. The 10 meat types were linked to the USDA Food and Nutrient Database. For each meat type, a composite was prepared using brand name meats that were available from grocery stores in one area in the U.S.[6] We found large variability in the nitrate and nitrite content of different processed meats, although NOC levels were below the limit of detection. In addition to measuring the nitrate and nitrite values in processed meats, we also determined nitrate and nitrite values for all foods included in the 124 line-item FFQ used in the National Institutes of Health (NIH)-AARP Diet and Health Study using values from articles published between 1967 and 2008. If more than one value was available, we calculated means of the published measurement or we used one value even if multiple values were available if it best represented the timeframe for the NIH-AARP Study. We used standardized recipes for foods from the CSFII for mixed foods including vegetable soup, beef stew, chicken pot pie, salads and sandwiches, meatloaf, chicken parmesan, etc. We added this data to a Windows-based application, CHARRED (www.charred.cancer.gov), to provide researchers the ability to estimate nitrite and nitrate intake from meats.

Processed Meat, Dietary Nitrate and Nitrite in the NIH-AARP Study

NCI investigators have evaluated the role of red and processed meat, as well as nitrate and nitrite for mortality and numerous cancers in a large prospective cohort. The NIH-AARP Study is a cohort of 566,402 men and women aged 50-71 years at enrollment, residing in one of 6 U.S. states or 2 metropolitan areas who completed an extensive baseline questionnaire in 1995–1996.

Mortality: Meat intake varies substantially around the world, but the impact of consuming high levels of meat in relation to chronic disease mortality is ambiguous. We investigated the association between types of meat and cause-specific mortality in the NIH-AARP Study. During 10 years of follow-up, we identified 47,976 male deaths and 23,276 female deaths.[7] Men and women in the highest versus the lowest quintile of red and processed meat intake had elevated risks for cancer and cardiovascular disease mortality.[7]

All cancers: During 8 years of follow-up, we ascertained 53,396 cancers (36,907 male cases and 16,489 female cases). Individuals in the highest, versus lowest, quintile of processed meat intake had an elevated risk for colorectal and lung cancer.[8] We also conducted detailed analyses for each cancer separately adjusting for more cancer-specific confounders. Out findings are summarized below:

Esophageal and gastric cancer: After 10 years of follow-up, there were 215 esophageal squamous cell carcinomas, 630 esophageal adenocarcinomas, 454 gastric cardia adenocarcinomas, and 501 non-cardia gastric adenocarcinomas.[9] Nitrite intake from processed meat increased the risk for esophageal adenocarcinoma (P-trend = 0.029). Processed meat, nitrite, and nitrate from processed meats were not associated with gastric cardia or noncardia cancer. Additionally, there was no association between usual adult total dietary intake of dietary nitrate and nitrite and risk of esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastric cardia adenocarcinoma, or distal gastric adenocarcinomas.

Colorectal cancer: During 7 years of follow-up, we ascertained 2,719 colorectal cancer cases. When comparing the fifth to the first quintile, processed meat and nitrate from processed meats were both positively associated with colorectal cancer (hazard ratio, HR=1.16, 95% confidence interval, CI: 1.01-1.32; P-trend=0.017; HR=1.13, 95% CI: 0.97-1.32; P-trend= 0.009). Nitrate from processed meats was also positively associated with rectal cancer (HR=1.26, 95% CI: 0.97-1.63; P-trend=0.006).[10]

Pancreatic cancer: After 10 years of follow-up, we identified 1,728 incident pancreatic cancer cases making this the largest cohort study to date to evaluate this hypothesis.[11] There was no association

between total nitrate or nitrite intake across all foods and pancreatic cancer in men or women. However, men in the highest quintile of summed nitrate/nitrite intake from processed meat had a somewhat elevated risk for this malignancy (HR=1.18; 95% CI: 0.95-1.47; P-trend= 0.11).

Thyroid cancer: After 7 years of follow-up, there were 370 incident thyroid cancer cases (170 men, 200 women).[12] Among men, nitrate intake was positively associated with thyroid cancer risk (highest vs. lowest quintile HR=2.28, 95% CI: 1.29–4.04; P-trend<0.001); however, we observed no trend with intake among women. We found positive associations between nitrate intake and both papillary (highest vs. lowest quintile HR=2.10, 95% CI: 1.09-4.05; P-trend<0.05) and follicular thyroid cancer (HR=3.42; 95% CI: 1.03–11.4; p-trend<0.01) among men. Nitrite intake was associated with an increased risk of follicular thyroid cancer (highest quintile HR= 2.74; 95%CI: 0.86-8.77; p-trend=0.04) among men.

Bladder cancer: During 7 years of follow-up, 854 transitional cell bladder-cancer cases were identified. Individuals in the top compared to the bottom quintile of total dietary nitrite had an increased risk of bladder cancer (HR=1.28; 95% CI: 1.02-1.61; P-trend=0.06), as did those in the highest quintile of nitrate plus nitrite intake from processed meat (HR=1.29; 95% CI: 1.00-1.67; P-trend =0.11). [13]

Glioma: During follow-up, 585 participants were diagnosed with glioma. We found significant positive trends between nitrite intake from plant sources and risk of glioma (HR for quintile 5 versus quintile 1, 1.59; 95% confidence interval, 1.20-2.10; P for trend = 0.028). Examination of interactions between dietary intakes (e.g., nitrite and vitamin C) and a limited analysis of diet at ages 12 to 13 years provided no support for the NOC hypothesis.[14]

Ovarian cancer: 709 incident epithelial ovarian cancer cases were identified after 11 years of follow-up. Women in the highest intake quintile of dietary nitrate had a 31% increased risk (95% CI: 1.01-1.68; P-trend=0.06) of epithelial ovarian cancer, compared with those in the lowest intake quintile.[15] There was no association for total dietary nitrite overall; however, those in the highest intake category of animal sources of nitrite had a 34% increased risk of this malignancy (95% CI: 1.05-1.69; P-trend=0.02).

Renal cell carcinoma: Over 9 years of follow-up, we identified 1,814 cases of RCC (498 clear cell and 115 papillary adenocarcinomas). We found no association between intake of nitrate and/or nitrite from processed meats and risk of renal cell carcinoma.[16] However, further analyses by histologic type showed that those in the highest quintile of nitrite intake from animal sources had an elevated risk of the clear cell subtype (HR=1.68, 95% CI, 1.25–2.27). We found no association for nitrite intake from plant sources or nitrate intake overall.

We have developed methods for estimating nitrate and nitrite in epidemiologic studies. Using these tools we have evaluated the associations between red and processed meat, as well as nitrate and nitrite for multiple cancers in a very large prospective cohort. Further work is needed to improve exposure estimates and develop biomarkers that can easily be incorporated into population-based studies. The role of oral and gut bacteria in the metabolism of nitrate and nitrite has not been addressed in this abstract but is essential to consider. [17]

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