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# Reduction of Red and Processed Meat Intake and Cancer Mortality and Incidence

## A Systematic Review and Meta-analysis of Cohort Studies

**Mi Ah Han, MD, PhD; Dena Zeraatkar, MSc; Gordon H. Guyatt, MD; Robin W.M. Vernooij, PhD; Regina El Dib, PhD; Ying Zhang, PhD; Abdullah Algarni, MBBS; Gareth Leung, BHSc; Dawid Storman, MD; Claudia Valli, MSc; Montserrat Rabassa, PhD; Nadia Rehman, BDS; Michael K. Parvizian, BHSc; Max Zworth, BA⪼ Jessica J. Bartoszko, HBSc; Luciane Cruz Lopes, PhD; Daegan Sit, MD; Malgorzata M. Bala, MD, PhD; Pablo Alonso-Coello, MD, PhD; and Bradley C. Johnston, PhD**

**Background:** Cancer incidence has continuously increased over the past few centuries and represents a major health burden worldwide.

**Purpose:** To evaluate the possible causal relationship between intake of red and processed meat and cancer mortality and incidence.

**Data Sources:** Embase, Cochrane Central Register of Controlled Trials, Web of Science, CINAHL, and ProQuest from inception until July 2018 and MEDLINE from inception until April 2019 without language restrictions.

**Study Selection:** Cohort studies that included more than 1000 adults and reported the association between consumption of unprocessed red and processed meat and cancer mortality and incidence.

**Data Extraction:** Teams of 2 reviewers independently extracted data and assessed risk of bias; 1 reviewer evaluated the certainty of evidence, which was confirmed or revised by the senior reviewer.

**Data Synthesis:** Of 118 articles (56 cohorts) with more than 6 million participants, 73 articles were eligible for the dose–response meta-analyses, 30 addressed cancer mortality, and 80 reported cancer incidence. Low-certainty evidence suggested that an intake reduction of 3 servings of unprocessed meat per week was associated with a very small reduction in overall cancer mortality over a lifetime. Evidence of low to very low certainty suggested that each intake reduction of 3 servings of processed meat per week was associated with very small decreases in overall cancer mortality over a lifetime; prostate cancer mortality; and incidence of esophageal, colorectal, and breast cancer.

**Limitation:** Limited causal inferences due to residual confounding in observational studies, risk of bias due to limitations in diet assessment and adjustment for confounders, recall bias in dietary assessment, and insufficient data for planned subgroup analyses.

**Conclusion:** The possible absolute effects of red and processed meat consumption on cancer mortality and incidence are very small, and the certainty of evidence is low to very low.

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Cancer is the leading cause of morbidity and mortality worldwide (1). Authorities have postulated that diet—in particular, consumption of red meat and processed meat—may be a determinant of cancer risk (2). Many primary studies have reported an association between red and processed meat consumption and cancer mortality and incidence (3–12). In response, the International Agency for Research on Cancer classified consumption of processed meat as carcinogenic to humans on the basis of evidence about colorectal cancer (group 1) and classified that of red meat as probably carcinogenic on the basis of evidence about colorectal, pancreatic, and prostate cancer (group 2A) (13). The World Cancer Research Fund and American Institute for Cancer Research advise limiting red meat consumption to no more than about 3 portions per week (<500 g weekly) and consuming very little, if any, processed meat (14).

Many systematic reviews have supported the association between red or processed meat and cancer mortality or incidence. However, most have focused on specific types of cancer and have not provided a comprehensive overview (15–18). Some have limited their analyses to comparing extreme exposure categories rather than conducting the optimal dose–response analysis that uses the entirety of data from cohort studies (19–22). Few have formally rated the certainty of evidence supporting the inference that red and processed meat consumption is causally related to cancer.

We did this systematic review addressing the possible effect of red and processed meat on cancer as part of NutriRECS (Nutritional Recommendations and accessible Evidence summaries Composed of Systematic reviews), the goal of which is to develop trustworthy guideline recommendations on nutrition (23). We did 5 parallel systematic reviews (24–27) and developed the guideline for red meat and health outcomes (28). This current review focuses on observational studies addressing cancer outcomes; we summarized re-

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sults from cohort studies by conducting dose–response meta-analyses and used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (29) to rate the certainty of evidence supporting the absolute effects of meat consumption on cancer incidence and mortality.

## METHODS

The protocol for this review was registered in PROSPERO (CRD42017074074) in August 2017.

### Data Sources and Searches

We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, CINAHL, and ProQuest from inception to July 2018 and updated our MEDLINE search to April 2019. An experienced librarian developed a search strategy (**Supplement Table 1**, available at Annals.org). We checked the reference lists of published systematic reviews to identify additional relevant studies.

### Study Selection

We included cohort studies with more than 1000 participants aged 18 years or older that reported effect estimates and corresponding 95% CIs. Studies had to report associations between red or processed meat consumption and mortality from or incidence of any of the following: cancer overall, gastrointestinal cancer (oral, esophageal, gastric, small intestinal, colorectal, hepatic, pancreatic, or gallbladder), female cancer types (ovarian, endometrial, or breast), or prostate cancer. We applied no restrictions on language or publication status.

We excluded studies if they reported only on a specific type of red meat (such as beef or lamb) or a specific type of processed meat (such as hot dogs). Studies were excluded if more than 20% of the sample was pregnant or had a major chronic illness at baseline, including cancer, and participants without these conditions were not reported separately. We also excluded studies that asked participants to recall their diet at a previous point in their life (for example, if adults recalled their diet during adolescence and childhood or middle-aged adults recalled their diet during young adulthood).

After calibration exercises, teams of 2 reviewers independently screened titles and abstracts. Articles that either reviewer judged as potentially eligible then had full-text screening. Raters resolved disagreements by discussion or, if necessary, with a third reviewer. If authors published multiple reports from the same cohort, we selected the study with the longest follow-up.

### Data Extraction and Quality Assessment

We did calibration exercises, and teams of 2 independent reviewers extracted data and addressed risk of bias, resolving discrepancies by discussion or consultation with a third reviewer. We used a predefined extraction form in Excel (Microsoft) for each study and included cohort name, country where the study was done, number of eligible participants at baseline, age and sex of participants, type of red and processed meat, amount of intake, type of cancer, years of follow-up, number of participants analyzed within exposure category, number of person-years, number of cases, and effect estimates and 95% CIs. If a study reported more than 1 adjusted effect estimate, we selected the most adjusted value.

We classified red and processed meat into the following 3 types: unprocessed red meat; processed meat; and mixed unprocessed red meat, processed meat, and unspecified red meat. Meat from mammals was classified as red meat. Processed meat was defined as meat that has been preserved by smoking, curing, salting, or adding preservatives (for example, hot dogs, charcuterie, sausage, ham, and cold-cut deli meats). Red meat was classified as unprocessed when authors explicitly described it as such and stated that processed red meat was not included. Without such a statement, we classified the exposure as an unspecified type of red meat.

To address risk of bias, we used a modified version of the Clinical Advances through Research and Information Technology risk of bias tool (30). After resolving discrepancies, we classified items rated "definitely low" and "probably low" as having low risk of bias and those rated "probably high" and "definitely high" as having high risk of bias. Through consultation with research methodologists and nutrition researchers, we developed criteria to evaluate each item (**Supplement Table 2**, available at Annals.org). We regarded all items as equally important and rated a study as having high risk of bias if 2 or more items had high risk of bias. This threshold, although somewhat arbitrary, represents a compromise between excessive stringency and problematic leniency.

### Data Synthesis and Analysis

Using dose–response meta-analysis, as proposed by Greenland and Longnecker (31) and Orsini and colleagues (32), we calculated pooled relative risks (RRs) and 95% CIs for the effect of an intake reduction of 3 servings of red or processed meat per week on cancer mortality or incidence. We chose 3 servings per week because, on the basis of the average intake of red and processed meat (approximately 2 to 4 servings of each type per week [33]), this is likely to be a maximal realistic reduction in mean for most persons. For a study to be included in dose–response meta-analyses, it needed to state the quantity of intake, number of cases, number of person-years or participants, effect estimates, and 95% CIs across exposure categories or sufficient information to calculate these details. When quantity of exposure was reported as a range, the midpoint of the upper and lower boundaries was assigned as the exposure value. When the category was open-ended, we assumed that the interval between boundaries was the same as that of the adjacent category. When authors did not report the number of person-years or participants included in a specific category but instead reported exposure by quantile, such as quartile or quintile, we assumed that numbers of person-years or participants were approximately equal in each category. We preferred to use number of person-years but

used number of participants in the absence of person-years. When studies used different units (such as servings and times) to report the exposure, we converted them into grams per day using standard conversions from the Food Standards Agency and other documents (34–41). One serving was 120 g for unprocessed red meat, 50 g for processed meat, and 100 g for mixed unprocessed red and processed meat. When studies used grams per 1000 kcal as the unit, we also converted into grams per day according to the average energy intake of the population included in the study. Studies reporting only risk estimates per unit increase in exposure (such as per 50 g/d) were also included in the dose–response meta-analysis; we calculated a regression coefficient based on the relative effect reported and meta-analyzed these regression coefficients with effects obtained from other studies (31). We examined the nonlinear association between red meat intake and cancer risk for analyses that included 5 or more studies by using restricted cubic splines with knots at 10%, 50%, and 90% and a Wald-type test, which tests the null hypothesis that the regression coefficient of the second spline is equal to 0. We presented an RR from the nonlinear model when we observed a statistically significant nonlinear association. The Appendix (available at Annals.org) gives details of the dose–response meta-analysis.

We also did meta-analyses comparing the lowest versus the highest category of intake using the Hartung–Knapp random-effects model (42) and presented DerSimonian–Laird random effects as a sensitivity analysis (43).

For both dose–response and lowest-versus-highest meta-analyses, we used meta-regression analysis to investigate whether the summary estimates are robust to risk of bias. Heterogeneity among studies was examined by inspecting forest plots for overlapping CIs, $I^2$ statistics, and $Q$ statistics. Publication bias was assessed using the Egger test in meta-analyses with more than 10 studies. All statistical analyses were done using R software, version 3.5.1 (R Foundation).

Because we have greater confidence in results from dose–response meta-analysis, we based our inferences primarily on these results and preferentially present them in the included summary-of-findings tables. For outcomes with no studies eligible for dose–response meta-analysis, we present results from lowest-versus-highest meta-analyses.

### Certainty of Evidence

We used GRADE to assess the certainty of evidence by rating each cancer outcome as high, moderate, low, or very low. One reviewer evaluated certainty of evidence, which was confirmed or revised by the senior reviewer. Evidence from observational studies begins at low certainty and may be increased to moderate or high certainty when a large effect is observed, when all plausible biases would work in a direction opposite to the observed effect, or when a dose–response gradient is present. Observational studies may be downgraded to very low certainty on the basis of risk of bias, inconsistency, indirectness, imprecision, or publication bias (44). We considered increasing certainty for dose response but ultimately decided not to do so because quantity of red meat consumption may track with other dietary and behavioral factors. This decision was influenced by the results of a parallel systematic review showing that the association between dietary patterns and cancer is similar in magnitude to that between red meat and cancer (26). We calculated the risk difference by multiplying the pooled RR reduction from the meta-analysis by the population risk for cancer incidence and mortality. Global cancer statistics (GLOBOCAN) produced by the International Agency for Research on Cancer (45) provided the cumulative risk for developing or dying of cancer before age 75 years using age-specific incidence and mortality rates based on 184 national data registries; we used these rates to estimate the population risk for cancer (lifetime risk). When the RR calculated from studies at low risk of bias differed from that from studies at high risk of bias, determined on the basis of a statistically significant test of interaction, we used the former rather than that from all eligible studies (46).

### Role of the Funding Source

This study received no external funding or other support.

## RESULTS

### Study Selection

Of the 22 882 articles identified through database searches and other sources, 9724 were duplicates. We assessed full texts of 1505 studies for eligibility, of which 118 articles reporting on 56 cohorts with 6.1 million participants were eligible. Evidence for the dose–response meta-analyses came from 73 articles (40 cohorts), of which 18 (17 cohorts) addressed consumption of unprocessed red meat, 56 (31 cohorts) processed red meat, and 60 (30 cohorts) mixed unprocessed red and processed meat (Appendix Figure 1, available at Annals.org).

### Study Characteristics

We found numerous reports addressing cancer mortality: 19 on cancer overall, 7 on gastric cancer, 8 on colorectal cancer, 3 on pancreatic cancer, 1 on ovarian cancer, 6 on breast cancer, and 11 on prostate cancer. We also found articles that reported cancer incidence: 5 on cancer overall, 2 on oral cancer, 3 on esophageal cancer, 8 on gastric cancer, 1 on small intestinal cancer, 35 on colorectal cancer, 2 on hepatic cancer, 15 on pancreatic cancer, 2 on ovarian cancer, 5 on endometrial cancer, 18 on breast cancer, and 12 on prostate cancer. Sample size in cohort studies varied from 1904 to 1 102 308 participants, followed from 3 to 34 years, and age at baseline from 36.4 to 77 years (Supplement Table 3, available at Annals.org). A total of 99 articles reported funding from public or private nonprofit organizations. Of the eligible reports addressing cancer mortality, the following proportions had high risk of bias due to lack of repeated measurement of diet and lack of adjustment for important con-

*Table 1.* Summary of Findings for Reduction of Unprocessed Red Meat Intake (3 Servings per Week) and Cancer Mortality and Incidence

| Outcome | Studies, *n* | Participants, *n* | Follow-up, *y* | Relative Risk (95% CI) | Estimated Lifetime Population Risk per 1000 Persons* | Risk Difference per 1000 Persons (95% CI) | Certainty of Evidence (GRADE) | Plain-Language Summary |
|---|---|---|---|---|---|---|---|---|
| Overall cancer mortality | 7 | 875 291 | 5–28 | 0.93 (0.91–0.94) | 105 | 7 fewer (9 fewer to 6 fewer) | Low (due to observational design) | Reduction of unprocessed red meat intake may result in a very small decrease in cancer mortality. |
| Prostate cancer mortality† | 1 | Unknown‡ | 14 | 1.56 (0.93–2.63) | 6 | 3 more (0 fewer to 10 more) | Very low (due to observational design, imprecision)§ | We are uncertain of the effects of unprocessed red meat on prostate cancer mortality. |
| Overall cancer incidence | 2 | 71 858 | 5–9 | 0.93 (0.83–1.04) | 185 | 13 fewer (31 fewer to 7 more) | Very low (due to observational design, imprecision)‖ | We are uncertain of the effects of unprocessed red meat on overall cancer incidence. |
| Esophageal cancer incidence | 1 | 472 538 | Mean, 11 | 1.00 (0.72–1.39) | 7 | 0 fewer (2 fewer to 3 more) | Very low (due to observational design, risk of bias)¶ | We are uncertain of the effects of unprocessed red meat on esophageal cancer incidence. |
| Gastric cancer incidence | 1 | 8024 | Mean, 6.7 | 0.86 (0.62–1.19) | 14 | 2 fewer (5 fewer to 3 more) | Very low (due to observational design, risk of bias)** | We are uncertain of the effects of unprocessed red meat on gastric cancer incidence. |
| Colorectal cancer incidence | 5 | 322 502 | 3–15 | 1.00 (0.92–1.09) | 20 | 0 fewer (2 fewer to 2 more) | Low (due to observational design) | Reduction of unprocessed red meat intake may have little or no effect on colorectal cancer incidence. |
| Pancreatic cancer incidence | 3 | 932 132 | 11–17 | 0.99 (0.98–1.01) | 5 | 0 fewer (0 fewer to 0 fewer) | Low (due to observational design) | Reduction of unprocessed red meat intake may have little or no effect on pancreatic cancer incidence. |
| Breast cancer incidence | 3 | 334 053 | 5–9 | 0.88 (0.72–1.06) | 46 | 6 fewer (13 fewer to 3 more) | Low (due to observational design) | Reduction of unprocessed red meat intake may have little or no effect on breast cancer incidence. |
| Prostate cancer incidence | 2 | 132 913 | 6–8 | 1.02 (0.95–1.10) | 38 | 1 more (2 fewer to 4 more) | Low (due to observational design) | Reduction of unprocessed red meat intake may have little or no effect on prostate cancer incidence. |

GRADE = Grading of Recommendations Assessment, Development and Evaluation.
* Lifetime cumulative risk from GLOBOCAN 2012 (45).
† Data are from highest-vs.-lowest meta-analysis.
‡ This study does not report the number of participants in the highest and lowest categories of intake.
§ CI around absolute effect includes both no effect and important harm.
‖ CI around absolute effect includes both important benefit and no effect.
¶ Study is at high risk of bias because diet was assessed only at baseline for 11 y of follow-up and because there was no adjustment for family history of cancer or alcohol consumption.
** Study is at high risk of bias because diet was assessed without validation and because there was no adjustment for family history of cancer.

founding variables: 9 of 19 on cancer overall, 6 of 7 on gastric cancer, 8 of 8 on colorectal cancer, 2 of 3 on pancreatic cancer, 1 of 1 on ovarian cancer, 6 of 6 on breast cancer, and 7 of 11 on prostate cancer. Of the eligible reports addressing cancer incidence, the following proportions had high risk of bias for the same reasons: 3 of 5 on cancer overall, 1 of 2 on oral cancer, 3 of 3 on esophageal cancer, 8 of 8 on gastric cancer, 0 of 1 on small intestinal cancer, 16 of 35 on colorectal cancer, 1 of 2 on hepatic cancer, 11 of 15 on pancreatic cancer, 1 of 2 on ovarian cancer, 5 of 5 on endometrial cancer, 5 of 18 on breast cancer, and 5 of 12 on prostate cancer (Supplement Table 4, available at Annals.org).

### Dose–Response Meta-analysis of a Reduction in Unprocessed Red Meat Intake of 3 Servings per Week and Cancer Mortality and Incidence

An intake reduction in unprocessed red meat of 3 servings per week was associated with a very small decrease in overall cancer mortality. This reduction was not statistically significantly associated with overall incidence of cancer or incidence of esophageal, gastric,

colorectal, pancreatic, breast, or prostate cancer. Data on prostate cancer mortality were available only for lowest-versus-highest meta-analysis, and no statistically significant association was found (Table 1). We did not find statistically significant differences between studies at lower and higher risk of bias (Supplement Table 5, available at Annals.org).

Overall cancer mortality and incidence of colorectal, pancreatic, breast, and prostate cancer had low-certainty evidence because of observational study design. The certainty of evidence was very low for prostate cancer mortality and overall cancer incidence because of observational design and imprecision and for esophageal and gastric cancer incidence because of observational design and risk of bias.

### Dose–Response Meta-analysis of a Reduction in Processed Meat Intake of 3 Servings per Week and Cancer Mortality and Incidence

An intake reduction of 3 servings of processed meat per week was associated with very small reductions in overall cancer mortality and prostate cancer mortality but not with gastric or colorectal cancer mortality. The same intake reduction was also associated with very small decreases in incidence of esophageal and colorectal cancer but not with overall cancer incidence or incidence of oral, gastric, small intestinal, hepatic, pancreatic, endometrial, or prostate cancer. Only lowest-versus-highest meta-analyses were available for pancreatic cancer mortality and ovarian cancer incidence, and no statistically significant associations were found (Table 2). We observed a statistically significant interaction with risk of bias for overall cancer mortality; therefore, we present results only for studies at low risk of bias (Supplement Table 6, available at Annals.org). We found a nonlinear association between processed meat intake and breast cancer incidence ($P$ = 0.015), and an intake reduction from 3 to 0 servings per week was associated with reduced risk for breast cancer incidence with low certainty. The RR estimates in the Figure are for processed meat consumption: Risk increased only marginally with intake greater than 3 servings per week.

The certainty of evidence was downgraded because of observational study design for overall cancer mortality; gastric and prostate cancer mortality; and incidence of small intestinal, colorectal, pancreatic, ovarian, breast, and prostate cancer. The certainty of evidence was very low for overall cancer incidence because of observational design and imprecision; it was also very low for colorectal and pancreatic cancer mortality and for incidence of oral, esophageal, gastric, hepatic, and endometrial cancer because of observational design and risk of bias (Table 2).

### Dose–Response Meta-analysis of a Reduction in Mixed Unprocessed Red and Processed Meat Intake of 3 Servings per Week and Cancer Mortality and Incidence

An intake reduction of 3 servings of mixed unprocessed red and processed meat per week was associated with a very small reduction in overall cancer mortality but not with colorectal or prostate cancer mortality. Each intake reduction of 3 servings per week in mixed unprocessed red and processed meat was associated with a very small decrease in colorectal cancer incidence but not with overall cancer incidence or incidence of oral, esophageal, gastric, small intestinal, hepatic, pancreatic, endometrial, or prostate cancer. Only lowest-versus-highest meta-analyses were available for gastric, pancreatic, ovarian, and breast cancer mortality and ovarian cancer incidence, and no statistically significant associations were found (Supplement Table 7, available at Annals.org). We found no statistically significant differences between studies at lower and higher risk of bias (Supplement Table 8, available at Annals.org). We found a nonlinear association between intake of mixed unprocessed red and processed meat and breast cancer incidence ($P$ = 0.018), and an intake reduction from 3 to 0 servings per week was associated with reduced risk for breast cancer incidence (Appendix Figure 2, available at Annals.org).

The certainty of evidence was downgraded because of observational study design for overall cancer mortality; pancreatic cancer mortality; and incidence of small intestinal, colorectal, hepatic, pancreatic, ovarian, breast, and prostate cancer. Overall cancer incidence had very-low-certainty evidence because of observational design and imprecision. Certainty of evidence was also very low for gastric, colorectal, ovarian, breast, and prostate cancer mortality; overall cancer incidence; and incidence of oral, esophageal, gastric, and endometrial cancer because of observational design and risk of bias (Supplement Table 7).

### Lowest-Versus-Highest Meta-analysis of Red Meat Intake and Cancer Mortality and Incidence

We found that lowest-versus-highest meta-analyses of red meat intake and cancer mortality and incidence were similar to the dose–response meta-analysis (Supplement Tables 9 to 11, available at Annals.org).

## DISCUSSION

This systematic review of observational studies documented low-certainty evidence that an intake reduction of 3 servings per week may result in 7 fewer deaths from cancer overall per 1000 persons for unprocessed red meat (Table 1) and 8 fewer deaths per 1000 persons for processed meat (Table 2). We also found evidence of low or very low certainty for very small reductions in prostate cancer mortality and incidence of esophageal, colorectal, and breast cancer with reduced consumption of processed meat by 3 servings per week (Table 2). We found evidence of low or very low certainty for very small reductions in overall cancer mortality, colorectal cancer incidence, and breast cancer incidence with a reduction in consumption of mixed unprocessed red and processed meat (Supplement Table 7). We did not find statistically significant associations between either exposure and mortality from or incidence of other cancer types.

Our systematic review has many strengths. We rated the certainty of evidence for red and processed meat intake and cancer risk from the entire body of evidence using GRADE guidance, thus highlighting the remaining uncertainty regarding causal relationships

*Table 2.* Summary of Findings for Reduction of Processed Meat Intake (3 Servings per Week) and Cancer Mortality and Incidence

| Outcome | Studies, *n* | Participants, *n* | Follow-up, *y* | Relative Risk (95% CI) | Estimated Lifetime Population Risk per 1000 Persons* |
|---|---|---|---|---|---|
| Overall cancer mortality† | 3 | 666 995 | 10–28 | 0.92 (0.89–0.94) | 105 |
| Gastric cancer mortality | 1 | 970 045 | 14 | 0.95 (0.86–1.04) | 10 |
| Colorectal cancer mortality | 1 | 39 867 | 30 | 0.88 (0.67–1.14) | 9 |
| Pancreatic cancer mortality§ | 1 | 8817 | 20 | 0.67 (0.28–1.59) | 4 |
| Prostate cancer mortality | 2 | 63 025 | 19–24 | 0.77 (0.66–0.90) | 6 |
| Overall cancer incidence | 2 | 71 858 | 5–9 | 0.99 (0.89–1.09) | 185 |
| Oral cancer incidence | 1 | 348 738 | Mean, 11.8 | 0.85 (0.70–1.04) | 5 |
| Esophageal cancer incidence | 1 | 348 738 | Mean, 11.8 | 0.70 (0.56–0.88) | 7 |
| Gastric cancer incidence | 4 | 565 285 | 5–18 | 0.89 (0.62–1.30) | 14 |
| Small intestinal cancer incidence | 1 | 494 000 | 8 | 0.88 (0.55–1.39) | 1 |
| Colorectal cancer incidence | 15 | 1 616 707 | 5–16 | 0.93 (0.89–0.95) | 20 |
| Hepatic cancer incidence | 1 | 477 206 | Mean, 11.4 | 1.10 (0.87–1.37) | 11 |
| Pancreatic cancer incidence | 7 | 1 321 588 | 7–18 | 0.99 (0.89–1.09) | 5 |
| Ovarian cancer incidence§ | 1 | Unknown‖‖ | Mean, 6.8 | 0.81 (0.61–1.09) | 7 |
| Endometrial cancer incidence | 2 | 172 251 | 11–21 | 0.95 (0.85–1.06) | 10 |
| Breast cancer incidence | 8 | 907 764 | 6–17 | 0.90 (0.85–0.95)*** | 46 |
| Prostate cancer incidence | 6 | 484 029 | 8–15 | 0.99 (0.97–1.01) | 38 |

GRADE = Grading of Recommendations Assessment, Development and Evaluation.
* Lifetime cumulative risk from GLOBOCAN 2012 (45).
† We found a statistically significant difference between studies at low and high risk of bias. Here, we report results from studies at low risk of bias.
‡ Study is at high risk of bias because diet was assessed only at baseline for 30 y of follow-up and because there was no adjustment for family history of cancer.
§ Data are from highest-vs.-lowest meta-analysis.
‖ Study is at high risk of bias because diet was assessed only at baseline for 20 y of follow-up and because there was no adjustment for family history of cancer.
¶ CI around absolute effect includes both important benefit and harm.
** Study is at high risk of bias because diet was assessed only at baseline for 11.8 y of follow-up and because there was no adjustment for family history of cancer.
†† 4 of 4 studies are at high risk of bias, primarily because of lack of periodic repeated measurement of diet in primary studies and lack of adjustment for family history.
‡‡ Study is at high risk of bias because diet was assessed only at baseline for 11.4 y of follow-up and because there was no adjustment for family history of cancer.
§§ $I^2$ = 66.4%; $P$ for Q test = 0.03. However, the evidence was not downgraded for inconsistency because there is overlap between CIs of most studies.
‖‖ Does not report the number of participants in the highest and lowest categories of intake.
¶¶ 2 of 2 studies are at high risk of bias, primarily because of lack of periodic repeated measurement of diet in primary studies and lack of adjustment for family history.
*** Nonlinear relationship. Effect estimate presented represents reduction of intake from 3 to 0 servings/wk.

between meat consumption and cancer. We focused on dose–response analyses, which provide the most compelling evidence to assess these associations, and supported our findings with lowest-versus-highest analyses that provided similar results. Our review included an extensive search for all cohort studies with more than 1000 participants. We focused on studies that clearly separated unprocessed red meat from processed meat, but we also analyzed studies that did not make the distinction; these mixed analyses showed intermediate exposure effects compared with our estimates specific to unprocessed red and processed meat. Pairs of independent reviewers assessed eligibility, risk of bias, and data collection, with third-party adjudication of any discrepancies. When studies at low and high risk of bias produced discrepant results, we focused on those at low risk of bias. Presentation of results included not only relative but also absolute effects, which enabled us to document the very small reductions in cancer mortality and incidence over a lifetime associated with realistic decreases in meat consumption of 3 servings per week. These estimates

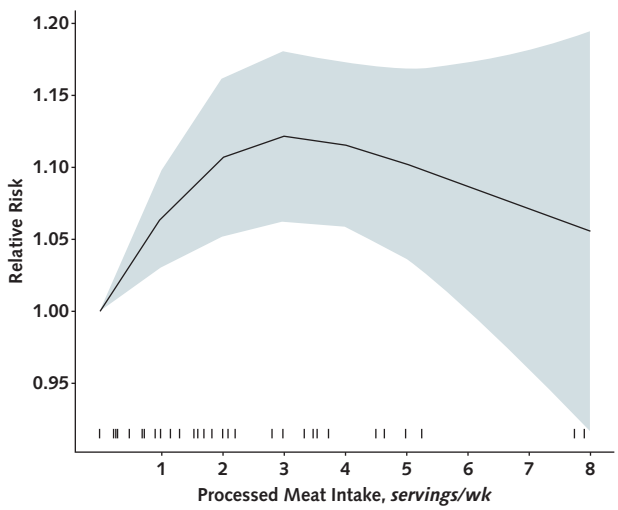
*Table 2*–Continued

| Risk Difference per 1000 Persons (95% CI) | Certainty of Evidence (GRADE) | Plain-Language Summary |
|---|---|---|
| 8 fewer (12 fewer to 6 fewer) | Low (due to observational design) | Reduction of processed meat intake may result in a very small decrease in cancer mortality. |
| 1 fewer (1 fewer to 0 fewer) | Low (due to observational design) | Reduction of processed meat intake may have little or no effect on gastric cancer mortality. |
| 1 fewer (3 fewer to 1 more) | Very low (due to observational design, risk of bias)‡ | We are uncertain of the effects of processed meat on colorectal cancer mortality. |
| 1 fewer (3 fewer to 2 more) | Very low (due to observational design, risk of bias)‖ | We are uncertain of the effects of processed meat on pancreatic cancer mortality. |
| 1 fewer (2 fewer to 1 fewer) | Low (due to observational design) | Reduction of processed meat intake may result in a very small decrease in prostate cancer mortality. |
| 2 fewer (20 fewer to 17 more) | Very low (due to observational design, imprecision)¶ | We are uncertain of the effects of processed meat on overall cancer incidence. |
| 1 fewer (2 fewer to 0 fewer) | Very low (due to observational design, risk of bias)** | We are uncertain of the effects of processed meat on oral cancer incidence. |
| 2 fewer (3 fewer to 1 fewer) | Very low (due to observational design, risk of bias)** | We are uncertain of the effects of processed meat on esophageal cancer incidence. |
| 2 fewer (5 fewer to 4 more) | Very low (due to observational design, risk of bias)†† | We are uncertain of the effects of processed meat on gastric cancer incidence. |
| 0 fewer (0 fewer to 0 fewer) | Low (due to observational design) | Reduction of processed meat intake may have little or no effect on small intestinal cancer incidence. |
| 1 fewer (2 fewer to 1 fewer) | Low (due to observational design) | Reduction of processed meat intake may result in a very small decrease in colorectal cancer incidence. |
| 1 more (1 fewer to 4 more) | Very low (due to observational design, risk of bias)‡‡ | We are uncertain of the effects of processed meat on hepatic cancer incidence. |
| 0 fewer (1 fewer to 0 fewer) | Low (due to observational design)§§ | Reduction of processed meat intake may have little or no effect on pancreatic cancer incidence. |
| 1 fewer (3 fewer to 1 more) | Low (due to observational design) | Reduction of processed meat intake may have little or no effect on ovarian cancer incidence. |
| 1 fewer (2 fewer to 1 more) | Very low (due to observational design, risk of bias)¶¶ | We are uncertain of the effects of processed meat on endometrial cancer incidence. |
| 5 fewer (7 fewer to 2 fewer) | Low (due to observational design) | Reduction of processed meat intake may result in a very small decrease in breast cancer incidence. |
| 0 fewer (1 fewer to 0 fewer) | Low (due to observational design) | Reduction of processed meat intake may have little or no effect on prostate cancer incidence. |

inform the general public, as well as researchers, policymakers, and guideline developers, about the effects they might expect if indeed a causal relationship exists between red and processed meat consumption and cancer.

The main limitation of this review was its basis in observational studies prone to confounding; even with appropriate adjusted analyses, causal inferences from such studies are necessarily limited. Additional limitations included high risk of bias in some studies due to limited assessment of dietary intake and lack of adjustment for known confounders. Limitations in dietary assessment included measurement error due to recall-based methods and failure to report the alternative diets of patients with low consumption of red meat. Lack of adequate adjustment for potential confounders was one of the main sources of potential bias among eligible studies (47). We dealt with this issue by considering the possibility that studies at low and high risk of bias yielded systematically different estimates of effect; when this was the case, we focused on those at low risk of bias. Studies most often did not report sufficient data to inform our a priori planned subgroup analyses (that is, analyses of red vs. white processed meat and method of red meat preparation). Many studies did not

***Figure.*** Nonlinear association between processed meat intake and breast cancer incidence.




The solid black line represents the point estimate, the shaded region represents the 95% CIs, and the tick marks represent the positions of the study-specific estimates.

report complete information for the purpose of dose–response meta-analysis.

Our results were consistent with those of previous systematic reviews of the RRs of cancer incidence and mortality associated with processed meat intake, which we identified in MEDLINE searches to April 2019. A recent systematic review summarized results from a meta-analysis on meat consumption and risk for 15 types of cancer, including 24 meta-analyses for total red meat and 39 for processed meat published between 2005 and 2015 (48). The authors concluded that a convincing association existed between larger intake of red meat and cancer, especially for colorectal, lung, esophageal, and gastric cancer. Similarly, they concluded that increased consumption of processed meat was associated with colorectal, esophageal, gastric, and bladder cancer. Several recent systematic reviews have also reported an association between red meat and specific cancer risks (49–53). Some of the meta-analyses relied on extreme exposure categories (48–50) and pooled case–control studies together with cohort studies (48), and many did not consider absolute effects or certainty of evidence on an outcome-by-outcome basis (15, 16, 49–54). Evidence of an association between unprocessed meat consumption and risk for cancer, however, proved difficult to compare between our review and previous systematic reviews, even for relative effects. Most primary studies did not distinguish between unprocessed and processed red meat, and most previous systematic reviews focused on total red meat, which included both unprocessed and processed meat (18–21, 55, 56). Our review provides up-to-date evidence separately for unprocessed red meat and processed meat, including the absolute effect and certainty of evidence for each outcome.

Regarding the implications of the results of our own and prior reviews, decision makers might expect that if red meat itself has a sufficient concentration of carcinogenic compounds to be causally related to cancer, the relative increases in incidence and mortality would be similar across cancer types regardless of whether meat was unprocessed or processed. Therefore, as noted in prior reviews (57, 58), results suggest that carcinogens may be added during meat processing procedures, such as curing, smoking, salting, or adding chemical preservatives (13, 57, 59). This suggests the desirability of future research addressing preservatives and processing procedures of red meat. For example, such research could focus on the direct relationship between preservatives and health outcomes (60, 61). On the other hand, differential levels of confounding may instead explain the gradient in cancer incidence and mortality between unprocessed and processed meat: For instance, lower socioeconomic status might be more strongly associated with consumption of processed than unprocessed red meat (62, 63).

Given the widespread consumption of red and processed meat and the large burden of cancer worldwide, this systematic summary provides relevant and useful information about important health concerns. Our systematic review and meta-analysis of cohort studies supports the association between red and processed meat intake and increased risk for cancer. The magnitude of red meat's effect on cancer over a lifetime of exposure was, however, very small, and the overall certainty of evidence was low or very low. Persons making recommendations about consumption of red and processed meat should be mindful of the remaining uncertainty regarding causation and, if indeed causal mechanisms are at play, the very small absolute effects.

From Chosun University, Gwangju, Republic of Korea (M.A.H.); McMaster University, Hamilton, Ontario, Canada (D.Z., G.H.G., G.L., N.R., M.K.P., M.Z., J.J.B.); Dalhousie University, Halifax, Nova Scotia, Canada, and Netherlands Comprehensive Cancer Organisation, Utrecht, the Netherlands (R.W.V.); Science and Technology Institute, Universidade Estadual Paulista, São José dos Campos, São Paulo, Brazil, and Dalhousie University, Halifax, Nova Scotia, Canada (R.E.); Beijing University of Chinese Medicine, Beijing, China (Y.Z.); Aseer Central Hospital, Abha, Saudi Arabia (A.A.); Jagiellonian University Medical College, Kraków, Poland (D.S.); Iberoamerican Cochrane Centre Barcelona, Biomedical Research Institute Sant Pau, and CIBER de Epidemiología y Salud Pública, Barcelona, Spain (C.V., M.R.); University of Sorocaba, Sorocaba, Sao Paulo, Brazil (L.C.L.); University of British Columbia, Vancouver, British Columbia, Canada (D.S.); Jagiellonian University Medical College, Krakow, Poland (M.M.B.); McMaster University, Hamilton, Ontario, Canada, and Iberoamerican Cochrane Centre Barcelona, Biomedical Research Institute Sant Pau, and CIBER de Epidemiología y Salud Pública, Barcelona, Spain (P.A.); and Dalhousie University, Halifax, Nova Scotia, and McMaster University, Hamilton, Ontario, Canada (B.C.J.).

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**Reproducible Research Statement:** *Study protocol:* Registered in PROSPERO (CRD42017074074). *Statistical code:* See Methods and **Appendix** (available at Annals.org). Code is available on request. *Data set:* See the tables and **Appendix**. Data are available on request from Dr. Han (e-mail, mahan@chosun.ac.kr).

**Corresponding Author:** Gordon H. Guyatt, MD, Department of Health Research Methods, Evidence and Impact, McMaster University, 1280 Main Street West, Hamilton, Ontario L8N 3Z5, Canada; e-mail, guyatt@mcmaster.ca.

Current author addresses and author contributions are available at Annals.org.

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**Current Author Addresses:** Dr. Han: Department of Preventive Medicine, College of Medicine, Chosun University, 309 Pilmun-daero, Dong-gu, Gwangju 61452, Korea.
Ms. Zeraatkar, Drs. Guyatt and Rehman, Mr. Leung, Mr. Parvizian, Mr. Zworth, and Ms. Bartoszko: McMaster University Health Sciences Center, 1280 Main Street West, Hamilton, Ontario L8S 4L8, Canada.
Dr. Vernooij: Department of Research, Netherlands Comprehensive Cancer Organisationn, Godebaldkwartier 419, Utrecht 3511DT, the Netherlands.
Dr. El Dib: Institute of Science and Technology, Universidade Estadual Paulista, Avenida Engenheiro Francisco José Longo, 777, Jardim São Dimas, São José dos Campos, Sao Paolo 12245-000, Brazil.
Dr. Zhang: Center for Evidence-based Chinese Medicine, Beijing University, 11 Beisanhuan Dong Lu, Chaoyang District, Beijing 100029, China.
Dr. Algarni: Department of Internal Medicine, Aseer Central Hospital, 4076 Al Muruj, Unit 3, Al Rabwah, Abha 62523, Saudi Arabia.
Drs. Storman and Bala: Department of Hygiene and Dietetics, Jagiellonian University Medical College, 7 Kopernika Street, Kraków 31-034, Poland.
Ms. Valli and Drs. Rabassa and Alonso-Coello: Iberoamerican Cochrane Centre, Instituto de Investigación Biomédica de Sant Pau (IIB Sant Pau-CIBERESP), Carrer de Sant Antoni Maria Claret, 167, Barcelona 08025, Spain.
Dr. Lopes: University of Sorocaba (UNISO), Rodovia Raposo Tavares, Km 92,5, Sorocaba, Sao Paulo 180230-000, Brazil.
Dr. Sit: University of British Columbia, 107-1165 West 13th Avenue, Vancouver, British Columbia V6H 1N4, Canada.
Dr. Johnston: Department of Community Health and Epidemiology, Centre for Clinical Research, Dalhousie University, 5790 University Avenue, Room 404, Halifax, Nova Scotia B3J 0E4, Canada.

**Author Contributions:** Conception and design: M.A. Han, D. Zeraatkar, G.H. Guyatt, M.M. Bala, P. Alonso-Coello, B.C. Johnston.
Analysis and interpretation of the data: M.A. Han, D. Zeraatkar, R. El Dib, M. Rabassa, N. Rehman, D. Sit, M.M. Bala, P. Alonso-Coello, B.C. Johnston.
Drafting of the article: M.A. Han, R. El Dib, D. Sit, B.C. Johnston.
Critical revision of the article for important intellectual content: M.A. Han, D. Zeraatkar, G.H. Guyatt, R.W.M. Vernooij, D. Sit, M.M. Bala, P. Alonso-Coello, B.C. Johnston.
Final approval of the article: M.A. Han, D. Zeraatkar, G.H. Guyatt, R.W.M. Vernooij, R. El Dib, Y. Zhang, A. Algarni, G. Leung, D. Storman, C. Valli, M. Rabassa, N. Rehman, M.K. Parvizian, M. Zworth, J.J. Bartoszko, L.C. Lopes, D. Sit, M.M. Bala, P. Alonso-Coello, B.C. Johnston.
Statistical expertise: M.A. Han, D. Zeraatkar.
Administrative, technical, or logistic support: M.A. Han, D. Zeraatkar.
Collection and assembly of data: M.A. Han, D. Zeraatkar, R.W.M. Vernooij, Y. Zhang, A. Algarni, G. Leung, D. Storman, C. Valli, M. Rabassa, M.K. Parvizian, M. Zworth, J.J. Bartoszko, L.C. Lopes, D. Sit, B.C. Johnston.

## Appendix: Technical Appendix

This appendix presents additional details on dose–response meta-analysis. We use our analysis addressing the association between unprocessed red meat intake and fatal stroke as an example.

Our systematic review identified 3 cohort studies reporting the association between unprocessed red meat and fatal stroke. The first 2 studies presented results across categories of exposure. The third reported results from a regression in which intake of unprocessed red meat was treated as a continuous variable. The relative effect presented in the third study corresponds to an increase in intake of 120 g/d.

Data are presented in Supplement Table 12, along with definitions of variables.

The following code loads the data and the necessary packages for the analysis.

```
library(dosresmeta)
library(metafor)
library(rms)
attach(filename)
```

The following code generates the natural logarithm of effect estimates and the associated SEs, which are stored in variables called log_point and se_point, respectively.

```
filename$log_point<-log(Adj_point)
filename$se_point<-(log(filename$CI_upper)-log(filename$CI_lower))/(2*1.96)
```

The following code approximates covariances of relative effects from the first 2 studies using the method proposed by Greenland and Longnecker (31) and estimates a corrected trend using generalized least-squares regression.

```
twostageresults <- dosresmeta(formula = log_point ~ Quantity, id = Ref, type = RType,
cases = Events, n = PY, data = filename,
se = se_point, proc = "2stage", method="reml")
summary(twostageresults)
```

The estimated trend (that is, the regression coefficient) for the first 2 studies can be extracted from the above dose–response meta-analysis. Note that regression coefficients extracted from the dose–response meta-analysis correspond to 1 unit of intake (in this case, 1 g/d) but can be converted to correspond with any quantity of intake and can subsequently be meta-analyzed with the third study that treats the exposure as a continuous variable.

Here, we calculate effects for 1 serving per day and assume that each serving is equal to 120 g.

The following code meta-analyzes the relative effect from the third study with the relative effects from the first 2 studies that were derived on the basis of the method of Greenland and Longnecker (31).

```
serving <- 120
point1 <- 1.17
```

```
upperci1<- 1.33
lowerci1<- 1.03
bi1<-log(point1)/serving
si1<-((log(upperci1)-log(lowerci1))/(2*1.96*serving))^2
contbi<-c(bi1)
contsi<-c(si1)
Si<-unlist(twostageresults$Si)
newbi<-c(twostageresults$bi, contbi)
newsi<- c(Si, contsi)
meta<- rma.uni(yi=newbi*serving, vi=(sqrt(newsi)*serving)^2)
summary(meta)
```

The results from this analysis can be converted from 1 serving per day to a reduction of 3 servings per day by calculating the inverse of the effect, dividing by 7, multiplying by 3, and then subsequently exponentiating. This process can also be replicated for the upper and lower bounds of the CIs. This yields relative effect estimates corresponding to a reduction of 3 servings per week.

```
exp(-meta$beta/7*3)
exp(-meta$ci.lb/7*3)
exp(-meta$ci.ub/7*3)
```

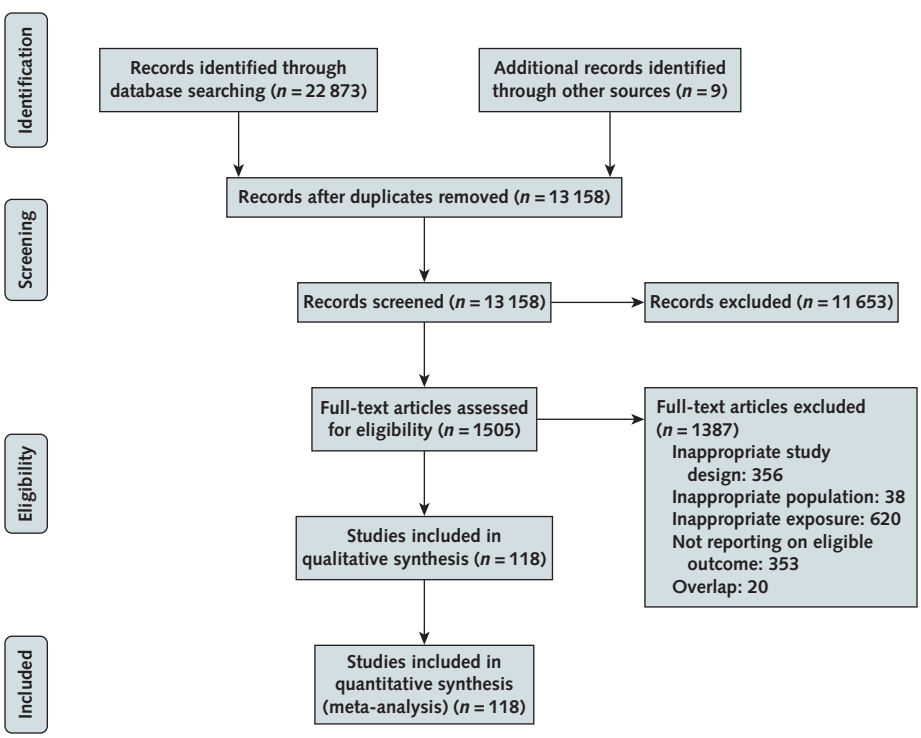
The following code tests for nonlinearity using restricted cubic splines with knots at 10%, 50%, and 90%.

```
knots <- quantile(filename$Quantity, c(0.10, 0.50, 0.90))
nonlinear <-dosresmeta(formula = log_point ~ rcs(Quantity, knots), id = Ref,
type = RType, cases = Events, n = PY,
data = filename, se = se_point)
summary(nonlinear)
waldtest(b=coef(nonlinear), Sigma=vcov(nonlinear), Terms = 2)
```

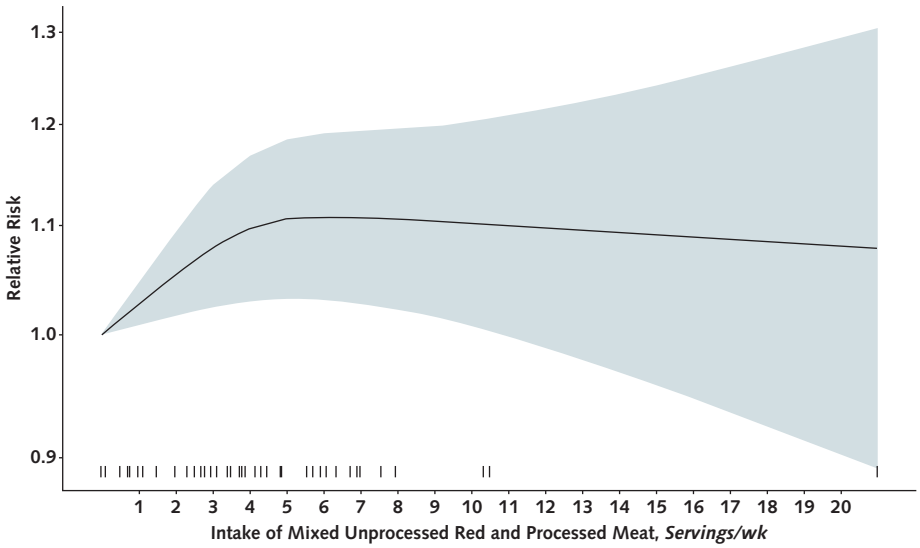
### Web-Only Reference

64. **Crippa A, Orsini N.** Multivariate dose-response meta-analysis: the dosresmeta R package. J Stat Softw. 2016;72. doi:10.18637/jss.v072.c01

***Appendix Figure 1.*** Evidence search and selection.



***Appendix Figure 2.*** Nonlinear association between intake of mixed unprocessed red and processed meat and breast cancer incidence.




The solid black line represents the point estimate, the shaded region represents the 95% CIs, and the tick marks represent the positions of the study-specific estimates.

## Correction: Nutritional Recommendations (NutriRECS) on Consumption of Red and Processed Meat

On the author disclosure forms accompanying recent related articles on red and processed meat consumption and health outcomes (1-6), Bradley Johnston did not indicate a grant from Texas A&M AgriLife Research to fund investigator-driven research related to saturated and polyunsaturated fats. This funding is for work in the field of nutrition and the start of funding period was within the 36-month reporting period required in Section 3 of the disclosure form of the International Committee of Medical Journal Editors (ICMJE). Dr. Johnston has updated his disclosure form to include this research funding and also to note funding received from the International Life Science Institute (North America) that ended before the 36-month ICMJE reporting period. The corrected disclosure forms now accompany the articles (1-6).

**References**


1. **Zeraatkar D, Han MA, Guyatt GH, et al.** Red and processed meat consumption and risk for all-cause mortality and cardiometabolic outcomes. A systematic review and meta-analysis of cohort studies. Ann Intern Med. 2019;171:703-10. [PMID: 31569213] doi:10.7326/M19-0655

2. **Han MA, Zeraatkar D, Guyatt GH, et al.** Reduction of red and processed meat intake and cancer mortality and incidence. A systematic review and meta-analysis of cohort studies. Ann Intern Med. 2019;171:711-20. [PMID: 31569214] doi: 10.7326/M19-0699

3. **Zeraatkar D, Johnston BC, Bartoszko J, et al.** Effect of lower versus higher red meat intake on cardiometabolic and cancer outcomes. A systematic review of randomized trials. Ann Intern Med. 2019;171:721-31. [PMID: 31569236] doi:10.7326/M19-0622

4. **Vernooij RWM, Zeraatkar D, Han MA, et al.** Patterns of red and processed meat consumption and risk for cardiometabolic and cancer outcomes. A systematic review and meta-analysis of cohort studies. Ann Intern Med. 2019;171:732-41. [PMID: 31569217] doi:10.7326/M19-1583

5. **Valli C, Rabassa M, Johnston BC, et al; NutriRECS Working Group**. Health-related values and preferences regarding meat consumption. A mixed-methods systematic review. Ann Intern Med. 2019;171:742-55. [PMID: 31569219] doi: 10.7326/M19-1326

6. **Johnston BC, Zeraatkar D, Han MA, et al.** Unprocessed red meat and processed meat consumption: dietary guideline recommendations from the nutritional recommendations (NutriRECS) consortium. Ann Intern Med. 2019;171:756-64. [PMID: 31569235] doi:10.7326/M19-1621