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REVIEW

Effect of Lower Versus Higher Red Meat Intake on Cardiometabolic and Cancer Outcomes

A Systematic Review of Randomized Trials

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Background: Few randomized trials have evaluated the effect of reducing red meat intake on clinically important outcomes.

Purpose: To summarize the effect of lower versus higher red meat intake on the incidence of cardiometabolic and cancer outcomes in adults.

Data Sources: EMBASE, CENTRAL, CINAHL, Web of Science, and ProQuest from inception to July 2018 and MEDLINE from inception to April 2019, without language restrictions.

Study Selection: Randomized trials (published in any language) comparing diets lower in red meat with diets higher in red meat that differed by a gradient of at least 1 serving per week for 6 months or more.

Data Extraction: Teams of 2 reviewers independently extracted data and assessed the risk of bias and the certainty of the evidence.

Data Synthesis: Of 12 eligible trials, a single trial enrolling 48 835 women provided the most credible, though still low-certainty, evidence that diets lower in red meat may have little or no effect on all-cause mortality (hazard ratio [HR], 0.99 [95% CI, 0.95 to 1.03], cardiovascular mortality (HR, 0.98 [CI, 0.91 to 1.06]), and cardiovascular disease (HR, 0.99 [CI, 0.94 to 1.05]). That trial also provided low- to very-low-certainty evidence that diets lower in red meat may have little or no effect on total cancer mortality (HR, 0.95 [CI, 0.89 to 1.01]) and the incidence of cancer, including colorectal cancer (HR, 1.04 [CI, 0.90 to 1.20]) and breast cancer (HR, 0.97 [0.90 to 1.04]).

Limitations: There were few trials, most addressing only surrogate outcomes, with heterogeneous comparators and small gradients in red meat consumption between lower versus higher intake groups.

Conclusion: Low- to very-low-certainty evidence suggests that diets restricted in red meat may have little or no effect on major cardiometabolic outcomes and cancer mortality and incidence.

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Observational studies have reported that intake of red meat is associated with cardiometabolic disease and cancer (1–8). Dietary guidelines from the United States, United Kingdom, and the World Cancer Fund/American Institute for Cancer Research recommend limiting intake of red and processed meat (8–10). Such recommendations are primarily based on observational studies that are at high risk for confounding.

Randomized trials generally provide higher-certainty evidence supporting causal relationships (11, 12). The few systematic reviews of trials addressing red meat consumption have evaluated only surrogate outcomes, such as blood pressure and lipid levels (13–15).

In this systematic review of randomized trials, we investigate the effect of lower versus higher red meat intake on the incidence of major cardiometabolic and cancer outcomes. The review was performed by the Nutritional Recommendations (NutriRECS) working group as part of a new initiative to develop trustworthy guideline recommendations in nutrition (16). In addition to this review, we performed 4 parallel systematic reviews that focused on observational studies addressing the effect of red and processed meat consumption on cardiometabolic and cancer outcomes (17–19), and a review of health-related values and preferences related to meat consumption (20). These reviews were used to underpin guideline recommendations for consumption of red and processed meats (21).

METHODS

We registered the systematic review protocol in PROSPERO (CRD42017074074) on 10 August 2017 (22).

Data Source and Searches

We searched MEDLINE, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the Web of Science from inception until July 2018, and MEDLINE from inception through to April 2019, with no restrictions on language or date of publication (Section I of the **Supplement**, available at Annals.org). We also searched ProQuest Dissertations and Theses Global (1989 to 2018); trial registries, in-

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cluding ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform Search Portal, to April 2019; and bibliographies of eligible studies and relevant systematic reviews.

Study Selection

We included English-language and non–English-language reports of randomized trials of adults allocated to consume diets that included varying quantities of unprocessed red meat (measured as servings or times/week, or as g/d) or processed meat (meat preserved by smoking, curing, salting, or adding preservatives) for 6 months or more (23). Eligible trials compared diets lower in red or processed meat with diets higher in red or processed meat that differed by a gradient of at least 1 serving per week (Table 1). If a trial reported more than 2 study groups (24, 25), we used the groups with the largest gradient in red meat intake or combined groups if red meat intake was equal. Studies in which more than 20% of the participants were pregnant or had cancer or a chronic health condition, other than cardiometabolic diseases, were excluded.

Outcomes of interest, which were determined a priori and in consultation with the guideline panel, were all-cause mortality, cardiovascular mortality, adverse cardiometabolic events and major morbidity, cancer mortality and incidence, quality of life, and surrogate outcomes (weight, body mass index, blood lipid levels, blood pressure, and hemoglobin level) (22). Pairs of reviewers screened titles and abstracts for initial eligibility and reviewed the full text of potentially eligible studies, independently and in duplicate. Reviewers resolved disagreements by discussion and third-party adjudication if needed.

Data Extraction and Quality Assessment

Using standardized, piloted forms, pairs of reviewers conducted calibration exercises and independently extracted information on study design, participant characteristics, interventions, comparators, and outcomes of interest and resolved disagreement by discussion or, if necessary, third-party adjudication. When details related to methods or results were unavailable or unclear, we contacted study authors for additional information.

Reviewers, independently and in duplicate, assessed the risk of bias of eligible trials by using a modified version of the Cochrane Collaboration's risk of bias instrument for randomized trials (26–28). The modified version categorizes risk of bias as "definitely low," "probably low," "probably high," or "definitely high" for each of the following domains: sequence generation, allocation sequence concealment, blinding, missing participant outcome data, selective outcome reporting, and other bias (for example, prematurely terminated studies). We resolved any disagreements by discussion or, if necessary, third-party adjudication. We collapsed ratings of "probably low" and "definitely low" into "low risk of bias" and ratings of "probably high" and "definitely high" into "high risk of bias." Among the 8 risk of bias domains, we considered a study to be at high risk of bias if, at the outcome level, 2 or more domains were at high risk of bias (Section I of the Supplement).

Data Synthesis and Analysis

We reported risk ratios (RRs), hazard ratios (HRs), and mean differences (MDs) with their 95% CIs for the lowest versus highest category of red meat intake, at the last reported time point. We used the Hartung–Knapp–Sidik–Jonkman approach to pool data (29, 30). To calculate absolute risk differences, we multiplied the effect estimate for each outcome with the population risk estimates from the Emerging Risk Factors Collaboration study for cardiometabolic outcomes (31) or from GLOBOCAN for cancer outcomes (32, 33) and, when this was not available, the control group estimate from the largest study (Section I of the Supplement).

We investigated heterogeneity by using the Cochran Q test and the I^2 statistic (34). We used R Project, version 3.3.0 (R Foundation for Statistical Computing), for all analyses.

To rate the certainty of the evidence for each outcome, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach (11, 35–39). Reviewers, independently and in duplicate, assessed the certainty of evidence for each outcome, and resolved disagreements by discussion.

Role of the Funding Source

This systematic review was conducted without financial support.

RESULTS

Study Selection

Electronic searches yielded 13 190 unique articles (Appendix Figure, available at Annals.org). Of these, 24 articles (24, 25, 40–62) reporting on 12 unique randomized trials met eligibility criteria. In 2 instances, authors provided clarification about study characteristics or outcomes: Turner-McGrievy and colleagues (24) clarified the aggregated change in weight for vegan/vegetarian and semi-vegetarian/omnivorous groups, and Griffin and associates (44) clarified reported effect estimates.

Study Characteristics

Trials ranged in size from 32 to 48 835 participants (Table 1). The mean age of participants ranged from 22.4 to 70.9 years. The largest study, the Women's Health Initiative (WHI), enrolled postmenopausal women (45). Five trials, including the WHI, enrolled overweight and obese participants (24, 25, 41, 45, 59, 60); 5 focused on participants with medical conditions, such as diabetes or hypercholesterolemia (42, 43, 57, 58, 61); and 1 enrolled older (>64 years) healthy individuals (41). Only 1 trial explicitly reported participants' consumption of both unprocessed red meat and processed meat (62).

All trials used parallel designs, except for a small crossover trial in patients with hypercholesterolemia (57). Intervention and control diets varied widely. The primary protein intake in the low red meat group was from plant sources in 4 trials (40, 60, 58, 61); from animal protein sources in 5 trials (25, 43, 44, 57, 59); and from a mix of plant and animal protein in 3 trials (24, 41, 42). The largest trial, the WHI trial, compared a low-fat

Table 1. Study Characteristics

Study, Year (Reference)	Study Name; Registration Number	Funding Source	Participants, *n*	Women, %	Sample (Country)	Study Group Definition	Gradient in Meat Reduction Between Groups	Duration of Intervention, *mo*	Duration of Follow-up, *mo*
Benassi-Evans et al, 2009 (40)	NR; NR	Meat and Livestock Australia medical research grant	High-carbohydrate diet: 17 High-protein diet: 16	0.0	Overweight or obese (Australia)	High-carbohydrate, low-red-meat weight loss diet: red meat <1 time/wk High-protein, high-red-meat weight loss diet: red meat 4 times/wk	Actual between-group difference in meat gradient NR	12	12
Davis et al, 2017 (41)	MedLey; NR	National Health and Medical Research Council; Cobram Estate (extra-virgin olive oil); Peanut Company of Australia (peanuts); Grains & Legumes Nutrition (legumes); Simplot Australia Pty. Ltd (legumes and tuna); Goodman Fielder Ltd (canola oil); Almond Board of Australia (almonds)	Mediterranean diet: 85 Habitual diet: 81	56.4	Healthy elderly (Australia)	Mediterranean diet with abundant extra-virgin olive oil, vegetables, fresh fruit, whole-grain cereals, nuts, legumes, fish, <1 serving of red meat/wk Control diet: Participants were asked to maintain their habitual diet	At 4 mo, the between-group difference in gradient of red and white meat was approximately 4.2 servings/wk (excluded ham, salami, bacon)	6	6
de Lorgeril et al, 1999 (42)	Lyon Diet Heart Study; NR	INSERM (Reseau Clinique); Ministry of Research; CNAMTS; CETIOM; ONIDOL; Astra-Calve BSN; Fondation pour la Recherche Médicale	Mediterranean diet: 1467* Prudent diet: 1383*	9.2	Survivors of a first myocardial infarction (France)	Mediterranean diet with more bread, more root vegetables and green vegetables, more fish, less meat (beef, lamb, and pork to be replaced with poultry), no day without fruit, and butter and cream to be replaced with a canola oil–based margarine supplied to patients Prudent Western-type diet: Participants received no dietary advice from the investigators and were advised by their attending physicians to follow a prudent diet	At 4 y, the between-group difference in gradient of red and processed meats was approximately 1.9 servings/wk	27–36	48
de Mello et al, 2008 (43)	NR; NR	Ministry of Science and Technology; National Council for Scientific and Technological Development; Hospital de Clínicas	Chicken-based diet plus active placebo: 16 Enalapril plus usual diet: 16	57.1	Type 2 diabetes (Brazil)	Chicken-based diet plus placebo: All meat in the usual diet was replaced with dark chicken meat (skinless leg quarter), without changing the total amount of protein intake Enalapril (10 mg/d) plus usual diet: usual diet according to recommendations of the American Diabetes Association (about 50% of protein from red meat)	Actual between-group difference in meat gradient NR	12	12

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Table 1–Continued

Study, Year (Reference)	Study Name; Registration Number	Funding Source	Participants, *n*	Women, %	Sample (Country)	Study Group Definition	Gradient in Meat Reduction Between Groups	Duration of Intervention, *mo*	Duration of Follow-up, *mo*
Griffin et al, 2013 (44)	NR; ACTRN1260900030720	Meat and Livestock Australia	High-carbohydrate diet: 35 High-protein diet: 36	100.0	Young overweight or obese women (Australia)	High-carbohydrate diet: 100 g (raw) of any type of meat during the day; set amounts of red (beef or lamb) and white (poultry or pork) meat (80 g raw weight) prescribed for evening meal—red meat, 1 serving or 1 time/wk; white meat, 4 times/week; fish, 2 times/wk High-protein diet: 100 g (raw) of any type of meat during the day; set amounts of red (beef or lamb) and white (poultry or pork) meat (200 g raw weight) prescribed for evening meal—red meat, 4 servings or 4 times/wk; white meat, 1 time/wk; fish, 2 times/wk	Actual between-group difference in meat gradient NR	12	12
Women's Health Initiative trial (45-56)	Women's Health Initiative Dietary Modification Trial; NCT00000611	National Institutes of Health, U.S. Department of Health and Human Services	Low-fat diet: 19 541 Habitual diet: 29 294	100.0	>70% overweight or obese; >30%–40% hypertensive women (United States)	Low-fat diet group had extensive behavioral support (≥4 sessions/y for duration of study) to reduce total dietary fat to 20% and to increase intake of vegetables and fruit to ≥5 servings and grains to ≥6 servings daily Habitual diet received a copy of the Dietary Guidelines for Americans as well as other diet and health-related educational materials	At 3 years, the between-group difference in gradient of red meat was approximately 1.4 servings/wk (approximately 20.2% [95% CI, 14.8%–25.5%])	72–144	72–204.6
Hunninghake et al, 2000 (57)	NR; NR	National Cattlemen's Beef Association	Lean white meat diet: 107 Lean red meat diet: 95	42.7	Hypercholesterolemia (United States)	Patients were instructed to consume up to 170 g per day of lean meat, including red meat, poultry, fish, or shellfish Lean white meat group: Participants were instructed to consume ≥80% of their meat consumption as lean white meat, defined as poultry or fish Lean red meat group: Participants were instructed to consume ≥80% of their total meat in the form of lean beef, veal, or pork	Actual between-group difference in meat gradient NR	9	9

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Table 1–Continued

Study, Year (Reference)	Study Name; Registration Number	Funding Source	Participants, *n*	Women, %	Sample (Country)	Study Group Definition	Gradient in Meat Reduction Between Groups	Duration of Intervention, *mo*	Duration of Follow-up, *mo*
Lanza et al, 2007 (58)	Polyp Prevention Trial; NR	NR	Low-fat and high-fiber diet: 1037 Usual diet: 1042	35.0	Large-bowel adenomatous polyp (United States)	Diet low in fat (20% of calories from fat) and high in fiber (18 g of dietary fiber per 1000 kcal) and fruits and vegetables (3.5 servings/1000 kcal) Usual diet group given a standard brochure on healthy eating	At 4 y, the between-group difference in gradient of red and processed meats was approximately 1.7 servings/wk	48	96.8
Murphy et al, 2012 (59)	NR; ACTRN1260800019030	Australian Pork Ltd., Pork Cooperative Research Centre	Pork diet: 84 Habitual diet: 80	NR	Overweight or obese (Australia)	Pork diet group: Participants were instructed to consume 7 servings (men) or 5 servings (women) of pork per week. Control group: Participants were asked to maintain their habitual diet	At 6 mo, the between-group difference in gradient of red meat was approximately 3.6 servings/wk	6	6
Poddar et al, 2013 (60)	NR; NR	Mushroom Council; Australian Mushroom Growers' Association	Mushroom diet: 36 Meat diet: 37	87.7	Overweight or obese (United States)	Mushroom diet: Mushrooms (8 oz) were substituted for meat at 3 servings/wk Meat diet: Participants were asked to eat 3 servings/week of ≥90% lean ground beef	Actual between-group difference in meat gradient NR	12	6–12
Turner-McGrievy et al, 2015 (24)	New Dietary Interventions to Enhance the Treatments for weight-loss (New DIETs); NR	NR	Vegan diet: 12 Vegetarian diet: 13 Pesco-vegetarian diet: 13 Semi-vegetarian diet: 13 Omnivorous diet: 12	73.0	Overweight or obese (United States)	Vegan diet: Did not contain any animal products; emphasized plant-based foods Vegetarian diet: Did not contain meat, fish, or poultry but did contain eggs and dairy, in addition to plant-based foods Pesco-vegetarian diet: Did not contain meat or poultry but did contain fish and shellfish, eggs, and dairy, in addition to plant-based foods Semi-vegetarian diet: Contained all foods, including meat, poultry, fish and shellfish, eggs, and dairy, in addition to plant-based foods; red meat limited to once per week, poultry ≤5 times/wk Omnivorous diet: Contained all foods	Actual between-group difference in meat gradient NR	6	6

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Table 1–Continued

Study, Year (Reference)	Study Name; Registration Number	Funding Source	Participants, *n*	Women, %	Sample (Country)	Study Group Definition	Gradient in Meat Reduction Between Groups	Duration of Intervention, *mo*	Duration of Follow-up, *mo*
Yaskolka-Meir et al, 2019 (25)	DIRECT-PLUS; NR	German Research Foundation; Deutsche Forschungsgemeinschaft, Obesity Mechanism; Israel Ministry of Health; Israel Ministry of Science and Technology; California Walnut Commission	Mediterranean diet: 98 Control diet: 98	22.0	Abdominal adiposity (Israel)	Mediterranean diet: Participants were guided to follow a calorie-restricted diet low in simple carbohydrates; rich in vegetables; and low in red meat, with poultry and fish replacing beef and lamb. Main sources of added fat were 30–45 g of olive oil and a handful of nuts (5–7 nuts, <20 g) per day, including 28 g walnuts/d (84% fat, mostly ω-3 α- linolenic acid) Control group: Participants were not guided to restrict calories, but received basic health-promoting guidelines for a healthy diet	Actual between-group difference in meat gradient NR	6	6

NR = not reported.
* Person-years.

dietary intervention aimed at reducing total dietary fat to 20% with a usual diet group given diet and health-related materials (45–56). The duration of interventions ranged from 6 months (24, 25, 41, 59) to 12 years (51).

Risk of Bias

Trials were most often rated as high risk of bias for lack of blinding (not possible for participants) and missing outcome data overall (**Supplement Table 1**, available at Annals.org). However, some trials were rated as low risk of bias for specific outcomes (all-cause mortality, cardiovascular disease, type 2 diabetes, adenocarcinoma) because there were either more outcome events than missing data for dichotomous outcomes or there were less than 10% missing data for continuous outcomes. Selective reporting bias was detected in 4 trials (40, 42, 44, 57). Other biases included a non-paired analysis of data from a crossover trial (57) and early termination for benefit in the Lyon Diet Heart Study (42).

Outcomes

None of the trials reported on a combination of fatal and nonfatal myocardial infarction, fatal infarction, nonfatal coronary heart disease, prostate cancer, and satisfaction with diet. Only 2 trials, the Lyon Diet Heart Study and the WHI trial (42, 54), addressed all-cause mortality and other patient-important, major morbid cardiovascular outcomes. The Lyon Diet Heart Study reported an implausibly large treatment effect, potentially due to stopping the trial early for benefit, and had a sample size (605 participants) more than 80 times smaller than the WHI trial (48 835 participants); for this reason the 2 trials were not pooled (63). Results presented below and in **Table 2** regarding all-cause mortality and cardiovascular outcomes are based on the WHI trial results. Results of the Lyon Diet Heart Study are presented in Section II of the **Supplement** (available at Annals.org).

All-Cause Mortality and Cardiometabolic Outcomes

Low-certainty evidence from the WHI trial showed that a diet lower in red meat may have little or no effect on all-cause mortality (HR, 0.99 [95% CI, 0.95 to 1.03]) (54). The certainty of evidence was rated down for serious indirectness. The trial investigated reducing dietary fat intake, which led to reduction of red meat intake (rather than directly investigating reduction of red meat intake). Compared with the usual diet control group, the low-fat dietary intervention group reduced their consumption of red meat by about 20% (approximately 1.4 servings per week).

Evidence showing little or no effect on cardiovascular mortality (HR, 0.98 [CI, 0.91 to 1.06]), fatal and nonfatal cardiovascular disease (HR, 0.99 [CI, 0.94 to 1.05]), nonfatal myocardial infarction (RR, 1.05 [CI, 0.96 to 1.16]), fatal and nonfatal stroke (RR, 0.98 [CI, 0.89 to 1.07]), fatal stroke (HR, 0.97 [CI, 0.69 to 1.36]), nonfatal stroke (HR, 1.03 [CI, 0.90 to 1.17]), and risk for type 2 diabetes (HR, 0.96 [95% CI, 0.90 to 1.03]) was consid-

Table 2. Summary of Findings for Lower Intake of Red Meat* and Mortality Outcomes

Outcome	Trials, *n*	Participants, *n*	Follow-up, *y*	Hazard Ratio (95% CI)	Population Risk Over 10.8 y for Cardiometabolic Outcomes and Over a Lifetime for Cancer Outcomes, *n/n (%)*	Risk Difference per 1000 Persons (95% CI)	GRADE Certainty of Evidence	Plain-Language Summary
All-cause mortality	1	48 835	Up to 17.05 y	0.99 (0.95–1.03)	113/1000 (11.3)†	2 fewer cases (12 fewer to 7 more cases)	Low‡	Reduction of red meat may have little or no effect on all cancer mortality.
Cardiovascular mortality	1	48 835	Up to 13.8 y	0.98 (0.91–1.06)	41/1000 (4.1)†	3 fewer (11 fewer to 8 more cases)	Very low‡§	We are uncertain of the effects of red meat on cardiovascular mortality.
Fatal myocardial infarction	NR	NR	NR	NR	NR	NR	NR	NR
Fatal stroke	1	48 835	Up to 8.0 y	0.97 (0.69–1.36)	19/1000 (1.9)†	2 fewer cases (16 fewer to 35 more cases)	Very low‡‖¶	We are uncertain of the effects of red meat on fatal stroke.
Breast cancer mortality	1	48 835	Up to 16.1 y	0.91 (0.72–1.15)	14/1000 (1.4)**	5 fewer cases (11 fewer to 10 more cases)	Very low‡††	We are uncertain of the effects of red meat on breast cancer mortality.
Total cancer mortality	1	48 835	Up to 12.3 y	0.95 (0.89–1.01)	105/1000 (10.5)**	12 fewer cases (26 fewer to 2 more cases)	Very low‡¶‡‡	We are uncertain of the effects of red meat on breast cancer mortality.

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; NR = not reported.
* Studies did not differentiate between red and processed meat. Most red meat is consumed as unprocessed, and our estimates of effect are therefore likely to apply predominantly to red meat.
† Data from reference 31.
‡ Downgraded twice for indirectness (trial investigated reducing dietary fat, which led to reduction of red meat, and not red meat directly) and there was a very small between-group gradient in red meat consumption (difference of approximately 1.4 servings/wk).
§ Downgraded for risk of bias related to missing participant outcome data; although the total number of events in the Women's Health Initiative trial was not reported, it is highly likely that the number of events was substantially lower than the number of missing participant outcomes.
‖ Downgraded for high risk of bias related to missing participant outcome data because there were far more missing participant outcomes (4484) than total events (141).
¶ Downgraded for imprecision because the CI around the absolute effect includes both appreciable benefit and no appreciable benefit.
** Data from reference 33.
†† Downgraded for risk of bias related to missing participant outcome data because there were far more outcome data missing (18 145) than total number of cancer events (296).
‡‡ Downgraded for risk of bias related to missing participant outcome data because there were far more outcome data missing (11 125) than total number of cancer events (2049).

ered of low or very low certainty owing to indirectness, risk of bias, or imprecision (Table 2 and Supplement Table 2, available at Annals.org).

Cancer

Because of risk of bias, imprecision, and serious indirectness, the WHI trial (53) provided very-low-certainty evidence that a diet lower in red meat may have little or no effect on cancer mortality (HR, 0.95 [CI, 0.89 to 1.01]) (Table 2). Similarly, the WHI trial provided very-low-certainty evidence that a diet lower in red meat may have little or no effect on colorectal, pancreatic, esophageal, and stomach cancer in women (51, 53, 55). This evidence was rated down to very low certainty owing to risk of bias, imprecision, or serious indirectness (Supplement Table 3, available at Annals.org). The WHI trial (46, 53, 55) also found that a diet lower in red meat may have little or no effect on the risk for invasive breast cancer (HR, 0.97 [95% CI, 0.90 to 1.04]); breast cancer mortality (HR, 0.91 [95% CI, 0.72 to 1.15]); or risk for gynecologic, ovarian, endometrial cancer, and ductal carcinoma in situ (Table 2 and Supplement Table 3). Such evidence was considered low or very low certainty owing to risk of bias, imprecision or serious indirectness (Supplement Table 3).

One trial of 2079 participants (58) provided very-low-certainty evidence (imprecision and serious indirectness) that a diet lower in red meat may have little or no effect on the risk for adenoma recurrence (HR, 1.04 [CI, 0.98 to 1.09]) (Supplement Table 3).

Quality of Life

The WHI trial (39 416 participants) provided very-low-certainty evidence, owing to risk of bias and serious indirectness, that a diet lower in red meat may have little or no effect on quality of life as measured by the RAND 36-Item Health Survey: general health (MD, 1.7 units [CI, 1.5 to 2.0 units]), physical functioning (MD, 2.0 units [CI, 1.7 to 2.3 units]), vitality (MD, 1.9 units [CI, 1.6 to 2.2 units]), and global quality of life (MD, 0.09 unit [CI, 0.07 to 0.12 units]) (45) (Supplement Table 4, available at Annals.org). The judgment of little or no effect is based on the minimal important difference estimates for the domain scores on the RAND-36 instrument, which range from 3.5 to 7, whereas the important difference for the global score is 1.7 (64).

Surrogate Outcomes

Aside from a trivial effect on high-density lipoprotein (HDL) cholesterol based on 6 trials (2320 participants) (0.77 mg/dL [CI, 0.07 to 1.54 mg/dL]; 0.02 mmol/L [CI, 0.002 to 0.04 mmol/L]; I^2 = 0%), low- to very low-certainty evidence suggests diets lower in red meat may have little or no effect on surrogate outcomes, such as cholesterol, weight, blood pressure, and hemoglobin (Supplement Table 4).

DISCUSSION

On the basis of evidence from 24 articles reporting on 12 randomized trials, our review shows that diets lower in red meat may have little or no effect on all-cause mortality, nonfatal cardiovascular disease, and diabetes (low-certainty evidence) and, although we are very uncertain, may have little or no effect on cancer mortality and incidence. Although no effect estimates for the major cardiometabolic or cancer outcomes met conventional criteria for statistical significance, 13 of 21 outcomes demonstrated a trivial to very small absolute risk reduction (range, 1 to 12 fewer events per 1000 persons over 8 to 17 years) in those who consume approximately 1 to 3 fewer servings of red meat per week. We found some improvements in quality of life and HDL cholesterol level, but the effects were very small: For HDL cholesterol level, the MD was 0.77 mg/dL (0.02 mmol/L), and for quality of life, the effects on the RAND-36 Health Survey ranged from 1.7 to 2.0 on 3 domains in which the minimally important differences ranges from 3.5 to 7.0.

Strengths of our review include adherence to a priori methods based on a registered protocol (22); a comprehensive search strategy without language restrictions; and inclusion of evidence on 8 cardiometabolic outcomes, 13 cancer outcomes, and 10 surrogate outcomes. We used explicit eligibility criteria, duplicate screening, abstraction of data, and risk-of-bias assessments with third-party adjudication of discrepancies and GRADE guidance to rate the certainty of evidence for each outcome.

Our review had limitations. First, many of the data were derived from a single large study in postmenopausal women: the WHI trial. Although 12 trials proved eligible, only 2 reported on the most patient-important outcomes—cardiovascular mortality and major morbidity, diabetes, and cancer mortality and incidence—and we considered only the WHI trial to have trustworthy results. Eleven studies proved at high risk of bias overall, primarily because of lack of blinding and substantial missing participant outcome data.

In addition, participants consuming alternative diets may have made different choices regarding smoking, exercise, or other lifestyle factors. In clinical trials of dietary interventions, particularly primary prevention trials, studies must follow participants for decades to capture important outcomes, such as cancer incidence (65). Of trials that met our eligibility criteria, only the WHI and the less trustworthy Lyon Diet Heart Study followed participants for 2 or more years. The choice to substitute red meat with poultry, fish, plant sources of protein, or whole or refined carbohydrates may result in different effects for some outcomes (66, 67). Thus, failure to demonstrate effects of decreased meat consumption may be related to trials' varying sources of protein replacement (for example, fish) in the diets lower in red meat (68). We had planned to address these issues through subgroup analyses (22, 69), but the paucity of trials made this impossible. The trials achieved only small differences between red meat in-

take in the intervention and control groups, equivalent to about 1 to 3 servings per week. In particular, the WHI study (61), on which we relied for our most important estimates, achieved a difference of 1.4 servings per week between the low-fat and the usual diet group (70). The failure to find differences in outcomes may be a result of the small gradient in red meat intake between the experimental and control groups. Had studies achieved larger gradients in consumption, researchers might have observed statistically significant and possibly an important effect on health outcomes.

Finally, only 1 study specified the proportion of red meat that was consumed as processed (42, 62). Observational studies have suggested that processed meat may have a larger adverse effect than unprocessed red meat (3, 6, 17, 19). Most red meat is, however, consumed as unprocessed (71), and our estimates therefore are likely to apply predominantly to red meat.

Our review of randomized trials relies largely on the WHI trial for estimates of effect on important major morbid cardiometabolic and cancer outcomes. Our results for surrogate outcomes are consistent with those of previous systematic reviews of trials, suggesting that red meat has little or no effect on blood pressure and blood lipids (13–15) (**Supplement**). Regarding important outcomes, systematic reviews of observational studies assessing diets that vary in red meat have, in contrast, reported positive associations between red meat intake and all-cause (6, 7, 19), cardiovascular (4, 6), and cancer (6, 17) mortality.

The discrepancy between results from randomized trials and observational studies may be explained by unadjusted confounders in the observational studies or by smaller gradients in red meat intake in trials and, thus, lower power, or the shorter follow-up in trials. Furthermore, compared with randomized trials, observational studies do not face the same limitations caused by poor adherence, missing end points, and financing, allowing investigators to better capture and evaluate important outcomes (such as cancer) that often take decades to develop (65).

Our results from the evaluation of randomized trials do not support the recommendations in the United Kingdom, United States, or World Cancer Research Fund guidelines on red meat intake (8–10). One could argue, however, that neither do they seriously challenge those recommendations: We found only low- to very-low-certainty evidence that diets lower in red meat compared with those higher in red meat have minimal or no influence on all-cause mortality, cancer mortality, cardiovascular mortality, myocardial infarction, stroke, diabetes, and incidence of gastrointestinal and gynecologic cancer. Our results highlight the uncertainty regarding causal relationships between red meat consumption and major cardiometabolic and cancer outcomes.

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Appendix Figure. Evidence search and selection.