Red Meat Consumption and Mortality

Results From 2 Prospective Cohort Studies

An Pan, PhD; Qi Sun, MD, ScD; Adam M. Bernstein, MD, ScD; Matthias B. Schulze, DrPH; JoAnn E. Manson, MD, DrPH; Meir J. Stampfer, MD, DrPH; Walter C. Willett, MD, DrPH; Frank B. Hu, MD, PhD

Background: Red meat consumption has been associated with an increased risk of chronic diseases. However, its relationship with mortality remains uncertain.

Methods: We prospectively observed 37 698 men from the Health Professionals Follow-up Study (1986-2008) and 83 644 women from the Nurses' Health Study (1980-2008) who were free of cardiovascular disease (CVD) and cancer at baseline. Diet was assessed by validated food frequency questionnaires and updated every 4 years.

Results: We documented 23 926 deaths (including 5910 CVD and 9464 cancer deaths) during 2.96 million person-years of follow-up. After multivariate adjustment for major lifestyle and dietary risk factors, the pooled hazard ratio (HR) (95% CI) of total mortality for a 1-serving-per-day increase was 1.13 (1.07-1.20) for unprocessed red meat and 1.20 (1.15-1.24) for processed red meat. The corresponding HRs (95% CIs) were 1.18 (1.13-1.23) and 1.21 (1.13-1.31) for CVD mortality and 1.10 (1.06-1.14) and 1.16 (1.09-1.23) for cancer mortality. We estimated that substitutions of 1 serving per day of other foods (including fish, poultry, nuts, legumes, low-fat dairy, and whole grains) for 1 serving per day of red meat were associated with a 7% to 19% lower mortality risk. We also estimated that 9.3% of deaths in men and 7.6% in women in these cohorts could be prevented at the end of follow-up if all the individuals consumed fewer than 0.5 servings per day (approximately 42 g/d) of red meat.

Conclusions: Red meat consumption is associated with an increased risk of total, CVD, and cancer mortality. Substitution of other healthy protein sources for red meat is associated with a lower mortality risk.

Arch Intern Med. 2012;172(7):555-563. Published online March 12, 2012. doi:10.1001/archinternmed.2011.2287

MEAT IS A MAJOR SOURCE of protein and fat in most diets. Substantial evidence from epidemiological studies shows that consumption of meat, particularly red meat, is associated with increased risks of diabetes,[1] cardiovascular disease (CVD),[2] and certain cancers.[3] Several studies also suggest an elevated risk of mortality associated with red meat intake. However, most of these studies have been performed in populations with a particularly high proportion of vegetarians (such as Seventh-Day Adventists in the United States[4] and several studies in Europe[5]). A recent large cohort study[6] with 10 years of follow-up found that a higher intake of total red meat and total processed meat was associated with an increased risk of mortality. However, this study did not differentiate unprocessed from processed red meat, and diet and other covariates were assessed at baseline only. Furthermore, to our knowledge, no study has examined whether substitution of other dietary components for red meat is associated with a reduced mortality risk.

See Invited Commentary at end of article

Therefore, we investigated the association between red meat intake and cause-specific and total mortality in 2 large cohorts with repeated measures of diet and up to 28 years of follow-up: the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS). We also estimated the associations of substituting other healthy protein sources for red meat with total and cause-specific mortality.

Author Affiliations: Departments of Nutrition (Drs Pan, Sun, Bernstein, Stampfer, Willett, and Hu) and Epidemiology (Drs Manson, Stampfer, Willett, and Hu), Harvard School of Public Health, and Channing Laboratory (Drs Sun, Stampfer, Willett, and Hu) and Division of Preventive Medicine (Dr Manson), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; Wellness Institute of the Cleveland Clinic, Lyndhurst, Ohio (Dr Bernstein); and Department of Molecular Epidemiology, German Institute of Human Nutrition, Nuthetal, Germany (Dr Schulze).

METHODS

STUDY POPULATION

We analyzed data from 2 prospective cohort studies: the HPFS (initiated in 1986, n = 51 529 men aged 40-75 years) and the NHS (started in 1976, n = 121 700 women aged 30-55 years). Detailed descriptions of the cohorts are provided elsewhere.[7,8] Questionnaires were administered biennially to collect and update medical, lifestyle, and other health-related information, and the follow-up rates exceeded 90% in each 2-year cycle for both cohorts.

In the present analysis, we used 1986 for the HPFS and 1980 for the NHS as baseline, when we assessed diet using a validated food frequency questionnaire (FFQ); 49 934 men and 92 468 women returned the baseline FFQ. We excluded 5617 men and 5613 women who had a history of CVD or cancer at baseline and 6619 men and 3211 women who left more than 9 blank responses on the baseline FFQ, had missing information about meat intake, or reported implausible energy intake levels (<500 or >3500 kcal/d). After the exclusions, data from 37 698 men and 83 644 women were available for the analysis. The excluded participants and those who remained in the study were similar with respect to red meat intake and obesity status at baseline. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health.

ASSESSMENT OF MEAT CONSUMPTION

In 1980, a 61-item FFQ was administered to the NHS participants to collect information about their usual intake of foods and beverages in the previous year. In 1984, 1986, 1990, 1994, 1998, 2002, and 2006, similar but expanded FFQs with 131 to 166 items were sent to these participants to update their diet. Using the expanded FFQ used in the NHS, dietary data were collected in 1986, 1990, 1994, 1998, 2002, and 2006 from the HPFS participants. In each FFQ, we asked the participants how often, on average, they consumed each food of a standard portion size. There were 9 possible responses, ranging from "never or less than once per month" to "6 or more times per day." Questionnaire items about unprocessed red meat consumption included "beef, pork, or lamb as main dish" (pork was queried separately beginning in 1990), "hamburger," and "beef, pork, or lamb as a sandwich or mixed dish." The standard serving size was 85 g (3 oz) for unprocessed red meat. Processed red meat included "bacon" (2 slices, 13 g), "hot dogs" (one, 45 g), and "sausage, salami, bologna, and other processed red meats" (1 piece, 28 g). The reproducibility and validity of these FFQs have been described in detail elsewhere.[9,10] The corrected correlation coefficients between the FFQ and multiple dietary records were 0.59 for unprocessed red meat and 0.52 for processed red meat in the HPFS,[9] and similar correlations were found in the NHS.[10]

ASCERTAINMENT OF DEATH

The ascertainment of death has been documented in previous studies.[11] Briefly, deaths were identified by reports from next of kin, via postal authorities, or by searching the National Death Index, and at least 95% of deaths were identified.[11] The cause of death was determined after review by physicians and were primarily based on medical records and death certificates. We used the *International Classification of Diseases, Eighth Revision*, which was widely used at the start of the cohorts, to distinguish deaths due to cancer (codes 140-207) and CVDs (codes 390-459 and 795).

ASSESSMENT OF COVARIATES

In the biennial follow-up questionnaires, we inquired and updated information on medical, lifestyle, and other health-related factors, such as body weight; cigarette smoking status; physical activity level; medication or supplement use; family history of diabetes mellitus, myocardial infarction, and cancer; and history of diabetes mellitus, hypertension, and hypercholesterolemia. In NHS participants, we also ascertained menopausal status and postmenopausal hormone use.

STATISTICAL ANALYSIS

We used time-dependent Cox proportional hazards regression models to assess the association of red meat consumption with cause-specific and total mortality risks during follow-up. We conducted analyses separately for each cohort. In multivariate analysis, we simultaneously controlled for intakes of total energy, whole grains, fruits, and vegetables (all in quintiles) and for other potential nondietary confounding variables with updated information at each 2- or 4-year questionnaire cycle. These variables included age; body mass index (calculated as weight in kilograms divided by height in meters squared) (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0); race (white or nonwhite); smoking status (never, past, or current [1-14, 15-24, or ≥25 cigarettes per day]); alcohol intake (0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d in women; 0, 0.1-4.9, 5.0-29.9, or ≥30.0 g/d in men); physical activity level (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 hours of metabolic equivalent tasks per week); multivitamin use (yes or no); aspirin use (yes or no); family history of diabetes mellitus, myocardial infarction, or cancer; and baseline history of diabetes mellitus, hypertension, or hypercholesterolemia. In women, we also adjusted for postmenopausal status and menopausal hormone use.

To better represent long-term diet and to minimize within-person variation, we created cumulative averages of food intake from baseline to death from the repeated FFQs.[12] We replaced missing values in each follow-up FFQ with the cumulative averages before the missing values. We stopped updating the dietary variables when the participants reported a diagnosis of diabetes mellitus, stroke, coronary heart disease, angina, or cancer because these conditions might lead to changes in diet.

We conducted several sensitivity analyses to test the robustness of the results: (1) we further adjusted for intakes of other major dietary variables (fish, poultry, nuts, legumes, and dairy products, all in quintiles) or several nutrients or dietary components (glycemic load, cereal fiber, magnesium, and polyunsaturated and trans fatty acids, all in quintiles) instead of foods; (2) we corrected for measurement error[13] in the assessment of red meat intake by using a regression calibration approach using data from validation studies conducted in the HPFS[9] in 1986 and in the NHS[10] in 1980 and 1986; (3) we repeated the analysis by using simply updated dietary methods (using the most recent dietary variables to predict mortality risk in the next 4 years)[12] or continue to update a participant's diet even after he or she reported a diagnosis of major chronic disease or using only baseline dietary variables; and (4) we used the energy density of red meat intake (serving/1000 kcal $\times$ d^{-1}) as the exposure instead of the crude intake. In addition, we used restricted cubic spline regressions with 4 knots to examine a dose-response relation between red meat intake and risk of total mortality.

We estimated the associations of substituting 1 serving of an alternative food for red meat with mortality by including both as continuous variables in the same multivariate model, which also contained nondietary covariates and total energy intake. The difference in their β coefficients and in their own variances and covariance were used to estimate the hazard ratios (HRs) and 95% CIs for the substitution associations.[14] We calculated population-attributable risk (95% CI) to estimate the proportion of deaths in the 2 cohorts that would be prevented at the end of follow-up if all the participants were in the low-intake group.[15] For these analyses, we compared participants in the low–red meat intake category (<0.5 servings daily, or 42 g/d) with the remaining participants in the cohorts.

The HRs from the final multivariate-adjusted models in each cohort were pooled to obtain a summary risk estimate with the use of an inverse variance–weighted meta-analysis by the random-effects model, which allowed for between-study heterogeneity. Data were analyzed using a commercially available software program (SAS, version 9.2; SAS Institute, Inc), and statistical significance was set at a 2-tailed $\alpha = .05$.

Table 1. Baseline Age-Standardized Characteristics of Participants in the 2 Cohorts According to Quintiles of Total Red Meat Consumption

	Total Red Meat Intake Quintile, Servings per Day				
Characteristic	Q1	Q2	Q3	Q4	Q5
Health Professionals Follow-up Study					
Participants, No.	7431	7813	7308	7606	7540
Age, mean, y	53.8	52.6	52.5	52.5	52.2
Total red meat intake, mean, servings per day	0.22	0.62	1.01	1.47	2.36
Physical activity, mean, MET-h/wk	27.5	22.7	20.2	18.8	17.2
Body mass index, mean[a]	24.7	25.3	25.5	25.7	26.0
White race, %	93.1	95.1	95.2	95.8	95.8
Current smoker, %	5.0	7.3	9.8	11.3	14.5
Diabetes mellitus, %	2.0	2.0	2.2	2.4	3.5
Hypertension, %	19.5	19.7	19.3	19.6	20.2
High cholesterol, %	14.8	11.1	9.7	9.0	7.9
Family history of diabetes mellitus, %	19.5	18.6	19.1	20.0	19.3
Family history of myocardial infarction, %	35.1	31.8	30.9	31.4	30.0
Family history of cancer, %	33.7	34.5	35.0	33.9	33.6
Current multivitamin use, %	49.1	42.5	40.3	39.5	36.6
Current aspirin use, %	24.6	26.4	25.9	27.8	27.4
Dietary intake, mean					
Total energy, kcal/d	1659	1752	1886	2091	2396
Alcohol, g/d	8.4	10.7	11.2	12.4	13.4
Fruit, servings per day	2.83	2.35	2.21	2.13	2.04
Vegetables, servings per day	3.29	2.89	2.91	2.97	3.07
Whole grains, servings per day	1.93	1.58	1.50	1.51	1.48
Nuts, servings per day	0.45	0.45	0.44	0.47	0.49
Legumes, servings per day	0.45	0.38	0.39	0.43	0.47
Dairy products, servings per day	1.65	1.80	1.89	2.02	2.14
Fish, servings per day	0.55	0.43	0.38	0.36	0.32
Poultry, servings per day	0.64	0.58	0.55	0.55	0.53
Nurses' Health Study					
Participants, No.	16 499	17 247	16 461	16 603	16 834
Age, mean, y	47.3	46.0	45.8	45.3	46.0
Total red meat intake, mean, servings per day	0.53	1.04	1.52	2.01	3.10
Physical activity, mean, MET-h/wk	16.9	13.9	13.8	13.3	12.4
Body mass index, mean[a]	23.9	24.3	24.4	24.5	24.7
White race, %	96.9	97.9	97.8	98.0	97.2
Current smoker, %	25.5	29.1	28.2	29.7	31.6
Diabetes mellitus, %	1.6	1.8	2.1	2.2	2.9
Hypertension, %	15.2	15.7	15.5	15.4	16.4
High cholesterol, %	6.0	5.3	5.2	4.5	4.7
Family history of diabetes, %	26.7	27.9	28.1	29.0	29.9
Family history of myocardial infarction, %	19.4	19.0	19.0	18.6	19.0
Family history of cancer, %	17.1	16.7	16.1	16.6	16.3
Postmenopausal, %	31.3	31.3	30.8	31.1	31.1
Current menopausal hormone use, %[b]	20.6	20.4	21.0	21.3	20.7
Current multivitamin use, %	37.9	33.6	33.1	32.8	32.3
Current aspirin use, %	43.2	46.9	46.3	48.3	49.1
Dietary intake, mean					
Total energy, kcal/d	1202	1371	1523	1705	2030
Alcohol, g/d	5.8	6.3	6.6	6.5	6.6
Fruit, servings per day	2.21	2.05	2.04	2.03	2.02
Vegetables, servings per day	1.89	1.83	1.92	1.98	2.08
Whole grains, servings per day	1.53	1.37	1.35	1.36	1.28
Nuts, servings per day	0.16	0.13	0.13	0.14	0.15
Legumes, servings per day	0.44	0.44	0.45	0.49	0.52
Dairy products, servings per day	1.81	1.80	1.82	1.87	1.83
Fish, servings per day	0.50	0.40	0.39	0.35	0.33
Poultry, servings per day	0.64	0.59	0.59	0.58	0.58

Abbreviation: MET-h, hours of metabolic equivalent tasks.
[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.
[b] Current menopausal hormone use in postmenopausal women.

RESULTS

In the HPFS, with up to 22 years of follow-up (758 524 person-years), we documented 8926 deaths, of which 2716 were CVD deaths and 3073 were cancer deaths. In the NHS, with up to 28 years of follow-up (2 199 892 person-years), we documented 15 000 deaths, of which 3194 were CVD deaths and 6391 were cancer deaths. For both cohorts combined, we documented 23 926 deaths (including 5910 CVD deaths and 9464 cancer deaths) during 2.96 million person-years of follow-up. Men and women with higher intake of red meat were less likely to be physically active and were more likely to be current smokers, to drink alcohol, and to have a higher body mass index (**Table 1**).

Table 2. All-Cause Mortality According to Red Meat Intake in the Health Professionals Follow-up Study and the Nurses' Health Study

Variable	Frequency of Consumption Quintiles[a] Q1	Q2	Q3	Q4	Q5	*P* Value for Trend	HR (95% CI) for a 1-Serving-per-Day Increase
Health Professionals Follow-up Study							
Total red meat, servings per day[b]	0.25 (0.13-0.37)	0.61 (0.53-0.70)	0.95 (0.87-1.04)	1.36 (1.24-1.49)	2.07 (1.83-2.47)	NA	NA
Cases/person-years, No.	1713/151 212	1610/152 120	1679/151 558	1794/152 318	2130/151 315	NA	NA
Age-adjusted model	1 [Reference]	1.06 (0.99-1.14)	1.14 (1.06-1.21)	1.21 (1.14-1.30)	1.45 (1.36-1.54)	<.001	1.19 (1.16-1.23)
Multivariate model[c]	1 [Reference]	1.12 (1.05-1.20)	1.21 (1.13-1.30)	1.25 (1.16-1.34)	1.37 (1.27-1.47)	<.001	1.14 (1.10-1.17)
Unprocessed red meat, servings per day[b]	0.17 (0.07-0.24)	0.43 (0.37-0.47)	0.66 (0.58-0.73)	0.95 (0.87-1.04)	1.46 (1.29-1.67)	NA	NA
Cases/person-years, No.	1855/150 676	1722/149 097	1535/154 352	1819/150 925	1995/153 474	NA	NA
Age-adjusted model	1 [Reference]	1.06 (0.99-1.13)	1.00 (0.94-1.07)	1.15 (1.08-1.23)	1.34 (1.25-1.42)	<.001	1.22 (1.18-1.27)
Multivariate model[c]	1 [Reference]	1.11 (1.04-1.18)	1.14 (1.06-1.22)	1.20 (1.12-1.28)	1.29 (1.20-1.38)	<.001	1.17 (1.12-1.21)
Processed red meat, servings per day[b]	0.02 (0-0.07)	0.13 (0.10-0.14)	0.21 (0.20-0.26)	0.39 (0.34-0.46)	0.74 (0.64-1.00)	NA	NA
Cases/person-years, No.	1917/171 619	1395/131 069	1661/152 481	1717/152 128	2236/151 227	NA	NA
Age-adjusted model	1 [Reference]	0.99 (0.93-1.06)	1.13 (1.05-1.20)	1.14 (1.07-1.22)	1.38 (1.30-1.47)	<.001	1.34 (1.28-1.40)
Multivariate model[c]	1 [Reference]	1.06 (0.99-1.14)	1.15 (1.07-1.23)	1.18 (1.10-1.27)	1.27 (1.19-1.36)	<.001	1.18 (1.12-1.24)
Nurses' Health Study							
Total red meat, servings per day[b]	0.51 (0.37-0.61)	0.85 (0.76-0.96)	1.14 (1.03-1.32)	1.49 (1.33-1.71)	2.17 (1.85-2.66)	NA	NA
Cases/person-years, No.	2946/438 326	2759/442 134	2658/439 712	2872/440 329	3765/439 391	NA	NA
Age-adjusted model	1 [Reference]	1.07 (1.01-1.12)	1.09 (1.04-1.15)	1.24 (1.18-1.30)	1.61 (1.53-1.69)	<.001	1.30 (1.28-1.33)
Multivariate model[c]	1 [Reference]	1.08 (1.02-1.14)	1.11 (1.05-1.17)	1.18 (1.12-1.24)	1.24 (1.17-1.30)	<.001	1.11 (1.08-1.13)
Unprocessed red meat, servings per day[b]	0.37 (0.28-0.46)	0.61 (0.56-0.68)	0.86 (0.77-1.00)	1.13 (1.01-1.28)	1.64 (1.43-2.05)	NA	NA
Cases/person-years, No.	3079/441 041	2885/441 207	2545/439 306	2709/431 097	3782/447 240	NA	NA
Age-adjusted model	1 [Reference]	1.05 (1.00-1.11)	0.98 (0.93-1.03)	1.09 (1.03-1.14)	1.48 (1.41-1.55)	<.001	1.31 (1.28-1.35)
Multivariate model[c]	1 [Reference]	1.07 (1.01-1.12)	1.07 (1.01-1.12)	1.10 (1.05-1.16)	1.19 (1.13-1.25)	<.001	1.10 (1.06-1.13)
Processed red meat, servings, per day[b]	0.05 (0-0.11)	0.14 (0.13-0.16)	0.23 (0.21-0.28)	0.36 (0.33-0.42)	0.64 (0.56-0.87)	NA	NA
Cases/person-years, No.	3076/442 594	2799/420 403	2778/455 365	2814/441 369	3533/440 161	NA	NA
Age-adjusted model	1 [Reference]	1.06 (1.01-1.12)	1.10 (1.04-1.16)	1.18 (1.12-1.24)	1.49 (1.42-1.56)	<.001	1.61 (1.54-1.69)
Multivariate model[c]	1 [Reference]	1.04 (0.99-1.10)	1.08 (1.03-1.14)	1.14 (1.08-1.20)	1.20 (1.14-1.27)	<.001	1.21 (1.15-1.27)
Pooled Results[d]							
Total red meat	1 [Reference]	1.10 (1.05-1.14)	1.15 (1.06-1.26)	1.21 (1.14-1.28)	1.30 (1.18-1.43)	<.001	1.12 (1.09-1.15)
Unprocessed red meat	1 [Reference]	1.08 (1.05-1.12)	1.10 (1.03-1.17)	1.15 (1.05-1.25)	1.23 (1.14-1.34)	<.001	1.13 (1.07-1.20)
Processed red meat	1 [Reference]	1.05 (1.00-1.09)	1.11 (1.04-1.18)	1.15 (1.11-1.20)	1.23 (1.16-1.30)	<.001	1.20 (1.15-1.24)

Abbreviations: HR, hazard ratio; NA, not applicable.
[a] Data are given as HR (95% CI) except where indicated otherwise.
[b] Data are given as median (interquartile range).
[c] The multivariate model was adjusted for age (continuous); body mass index (calculated as weight in kilograms divided by height in meters squared) category (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0); alcohol consumption (0, 0.1-4.9, 5.0-29.9, or ≥30.0 g/d in men; 0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d in women); physical activity level (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 hours of metabolic equivalent tasks per week); smoking status (never, past, or current [1-14, 15-24, or ≥25 cigarettes per day]); race (white or nonwhite); menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, or postmenopausal current users); family history of diabetes mellitus, myocardial infarction, or cancer; history of diabetes mellitus, hypertension, or hypercholesterolemia; and intakes of total energy, whole grains, fruits, and vegetables, all in quintiles.
[d] Results from the multivariate model were combined using the random-effects model.

In addition, a higher red meat intake was associated with a higher intake of total energy but lower intakes of whole grains, fruits, and vegetables. Unprocessed and processed red meat consumption was moderately correlated (r=0.40 in the HPFS and 0.37 in the NHS). However, red meat consumption was less correlated with intakes of poultry and fish (Spearman correlation coefficients, r=−0.04 and −0.18 in the HPFS and r=0.05 and −0.12 in the NHS, respectively). During follow-up, red meat intake declined in men and women (eFigure; http://www.archinternmed.com). For example, the mean daily intake of unprocessed red meat dropped from 0.75 to 0.63 servings from 1986 to 2006 in men and from 1.10 to 0.55 servings from 1980 to 2006 in women.

Unprocessed and processed red meat intakes were associated with an increased risk of total, CVD, and cancer mortality in men and women in the age-adjusted and fully adjusted models (**Tables 2**, **3**, and **4**). When treating red meat intake as a continuous variable, the elevated risk of total mortality in the pooled analysis for a 1-serving-per-day increase was 12% (HR, 1.12; 95% CI, 1.09-1.15) for total red meat, 13% (HR, 1.13; 95% CI, 1.07-1.20) for unprocessed red meat, and 20% (HR, 1.20; 95% CI, 1.15-1.24) for processed red meat. The HRs (95% CIs) for CVD mortality were 1.16 (1.12-1.20) for total red meat, 1.18 (1.13-1.23) for unprocessed red meat, and 1.21 (1.13-1.31) for processed red meat. The HRs (95% CIs) for cancer mortality were 1.10 (1.07-1.13) for total red meat, 1.10 (1.06-1.14) for unprocessed red meat, and 1.16 (1.09-1.23) for processed red meat. We found no statistically significant differences among specific unprocessed red meat items or among specific processed red meat items for the associations with total mortality (eTable 1). However, bacon and hot dogs tended to be associated with a higher risk than other items. Spline regression analysis showed that the association between red meat intake and risk of total

Table 3. Cardiovascular Mortality According to Red Meat Intake in the Health Professionals Follow-up Study and the Nurses' Health Study

Variable	Frequency of Consumption Quintiles[a] Q1	Q2	Q3	Q4	Q5	*P* Value for Trend	HR (95% CI) for a 1-Serving-per-Day Increase
Health Professionals Follow-up Study							
Total red meat							
Cases/person-years, No.	537/152 293	490/153 126	506/152 623	518/153 454	665/152 647	NA	NA
Age-adjusted model	1 [Reference]	1.05 (0.93-1.19)	1.11 (0.98-1.26)	1.15 (1.02-1.30)	1.48 (1.32-1.66)	<.001	1.21 (1.16-1.27)
Multivariate model[b]	1 [Reference]	1.09 (0.96-1.24)	1.16 (1.03-1.32)	1.17 (1.03-1.33)	1.35 (1.19-1.53)	<.001	1.14 (1.08-1.20)
Unprocessed red meat							
Cases/person-years, No.	578/151 850	528/150 172	446/155 316	532/152 087	632/154 719	NA	NA
Age-adjusted model	1 [Reference]	1.08 (0.95-1.20)	0.97 (0.86-1.10)	1.11 (0.98-1.25)	1.41 (1.26-1.58)	<.001	1.26 (1.18-1.34)
Multivariate model[b]	1 [Reference]	1.10 (0.97-1.24)	1.08 (0.95-1.22)	1.14 (1.01-1.29)	1.32 (1.16-1.49)	<.001	1.19 (1.10-1.27)
Processed red meat							
Cases/person-years, No.	594/172 817	423/131 953	510/153 537	512/153 206	677/152 631	NA	NA
Age-adjusted model	1 [Reference]	0.99 (0.88-1.12)	1.14 (1.01-1.29)	1.13 (1.00-1.27)	1.37 (1.23-1.53)	<.001	1.34 (1.24-1.46)
Multivariate model[b]	1 [Reference]	1.05 (0.93-1.19)	1.15 (1.01-1.30)	1.15 (1.02-1.31)	1.25 (1.11-1.41)	.003	1.17 (1.07-1.29)
Nurses' Health Study							
Total red meat							
Cases/person-years, No.	601/440 429	570/444 046	517/441 619	598/442 319	908/441 994	NA	NA
Age-adjusted model	1 [Reference]	1.11 (0.99-1.25)	1.09 (0.97-1.22)	1.33 (1.19-1.49)	1.98 (1.79-2.20)	<.001	1.44 (1.38-1.50)
Multivariate model[b]	1 [Reference]	1.14 (1.01-1.27)	1.11 (0.99-1.26)	1.28 (1.13-1.43)	1.45 (1.30-1.63)	<.001	1.17 (1.11-1.22)
Unprocessed red meat							
Cases/person-years, No.	617/443 224	646/443 182	481/441 163	549/432 988	901/449 850	NA	NA
Age-adjusted model	1 [Reference]	1.21 (1.08-1.35)	0.96 (0.85-1.09)	1.15 (1.03-1.29)	1.82 (1.65-2.02)	<.001	1.46 (1.39-1.54)
Multivariate model[b]	1 [Reference]	1.22 (1.09-1.37)	1.09 (0.96-1.23)	1.19 (1.06-1.34)	1.39 (1.24-1.55)	<.001	1.17 (1.10-1.24)
Processed red meat							
Cases/person-years, No.	671/444 737	551/422 411	586/457 265	572/443 383	814/442 609	NA	NA
Age-adjusted model	1 [Reference]	0.98 (0.88-1.10)	1.10 (0.99-1.23)	1.16 (1.03-1.29)	1.65 (1.49-1.83)	<.001	1.79 (1.64-1.95)
Multivariate model[b]	1 [Reference]	0.97 (0.87-1.09)	1.10 (0.99-1.23)	1.12 (0.99-1.25)	1.29 (1.15-1.43)	<.001	1.26 (1.15-1.39)
Pooled Results[c]							
Total red meat	1 [Reference]	1.12 (1.03-1.22)	1.13 (1.04-1.24)	1.23 (1.13-1.34)	1.40 (1.29-1.53)	<.001	1.16 (1.12-1.20)
Unprocessed red meat	1 [Reference]	1.16 (1.05-1.28)	1.09 (1.00-1.18)	1.17 (1.07-1.27)	1.36 (1.25-1.47)	<.001	1.18 (1.13-1.23)
Processed red meat	1 [Reference]	1.01 (0.92-1.10)	1.12 (1.03-1.22)	1.13 (1.04-1.23)	1.27 (1.18-1.38)	<.001	1.21 (1.13-1.31)

Abbreviations: HR, hazard ratio; NA, not applicable.
[a] Data are given as HR (95% CI) except where indicated otherwise.
[b] The multivariate model was adjusted for age (continuous); body mass index (calculated as weight in kilograms divided by height in meters squared) category (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0); alcohol consumption (0, 0.1-4.9, 5.0-29.9, or ≥30.0 g/d in men; 0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d in women); physical activity level (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 hours of metabolic equivalent tasks per week); smoking status (never, past, or current [1-14, 15-24, or ≥25 cigarettes per day]); race (white or nonwhite); menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, or postmenopausal current users); family history of diabetes mellitus, myocardial infarction, or cancer; history of diabetes mellitus, hypertension, or hypercholesterolemia; and intakes of total energy, whole grains, fruits, and vegetables, all in quintiles.
[c] Results from multivariate model were combined using the random-effects model.

mortality was linear ($P < .001$ for linearity; **Figure 1**). Furthermore, no significant interaction was detected between red meat intake and body mass index or physical activity level ($P > .10$ for both tests).

Additional adjustment for other foods (fish, poultry, nuts, beans, and dairy products) or nutrients (glycemic load, cereal fiber, magnesium, and polyunsaturated and trans fatty acids) did not appreciably alter the results. Additional adjustment for saturated fat and cholesterol moderately attenuated the association between red meat intake and risk of CVD death, and the pooled HR (95% CI) dropped from 1.16 (1.12-1.20) to 1.12 (1.07-1.18). Similarly, additional adjustment for heme iron moderately attenuated the association, and the pooled HR (95% CI) dropped from 1.16 (1.12-1.20) to 1.11 (1.05-1.17). Additional adjustment for husband's educational level as a surrogate of socioeconomic status in women did not change the results.

The results were not materially changed when we continued to update dietary information even after the diagnosis of chronic diseases (eTable 2) or simply updated the dietary variables (eTable 3). Also, using the energy density of red meat intake as the exposure showed similar findings (eTable 4). In the sensitivity analysis that accounted for measurement error in diet, the associations became even stronger. For example, the HR was 1.25 (95% CI, 1.16-1.35) for a 1-serving-per-day increase in total red meat intake with mortality in the HPFS, and it was 1.83 (95% CI, 1.54-2.20) in the NHS. However, the associations were attenuated in analyses using only baseline dietary data (eTable 5).

In the substitution analyses, replacing 1 serving of total red meat with 1 serving of fish, poultry, nuts, legumes, low-fat dairy products, or whole grains daily was associated with a lower risk of total mortality: 7% (HR, 0.93; 95% CI, 0.90-0.97) for fish, 14% (HR, 0.86; 95% CI, 0.82-0.91) for poultry, 19% (HR, 0.81; 95% CI, 0.77-0.86) for nuts, 10% (HR, 0.90; 95% CI, 0.86-0.94) for legumes, 10% (HR, 0.90; 95% CI, 0.86-0.94) for low-fat dairy products, and 14% (HR, 0.86; 95% CI, 0.82-0.88) for whole grains (**Figure 2**). The corresponding substitution estimates were 5%, 13%, 18%, 8%, 9%, and 13% for replacement of unprocessed red meat and 10%, 17%, 22%, 13%, 13%, and 16% for replacement of processed red meat.

Table 4. Cancer Mortality According to Red Meat Intake in the Health Professionals Follow-up Study and the Nurses' Health Study

Variable	Frequency of Consumption Quintiles[a] Q1	Q2	Q3	Q4	Q5	*P* Value for Trend	HR (95% CI) for a 1-Serving-per-Day Increase
Health Professionals Follow-up Study							
Total red meat							
Cases/person-years, No.	598/152 206	558/153 082	561/152 574	646/153 343	710/152 584	NA	NA
Age-adjusted model	1 [Reference]	1.03 (0.91-1.15)	1.05 (0.93-1.18)	1.20 (1.07-1.34)	1.33 (1.20-1.49)	<.001	1.17 (1.12-1.22)
Multivariate model[b]	1 [Reference]	1.05 (0.94-1.18)	1.07 (0.95-1.20)	1.18 (1.05-1.33)	1.24 (1.09-1.40)	<.001	1.12 (1.06-1.17)
Unprocessed red meat							
Cases/person-years, No.	650/151 745	588/150 121	540/155 255	613/152 008	682/154 661	NA	NA
Age-adjusted model	1 [Reference]	1.00 (0.89-1.12)	0.97 (0.86-1.08)	1.06 (0.95-1.18)	1.25 (1.12-1.39)	<.001	1.18 (1.11-1.26)
Multivariate model[b]	1 [Reference]	1.01 (0.90-1.13)	1.03 (0.91-1.15)	1.05 (0.94-1.18)	1.18 (1.05-1.33)	<.001	1.13 (1.05-1.21)
Processed red meat							
Cases/person-years, No.	669/172 756	487/131 895	580/153 463	589/153 122	748/152 551	NA	NA
Age-adjusted model	1 [Reference]	0.97 (0.86-1.09)	1.09 (0.98-1.22)	1.09 (0.97-1.21)	1.28 (1.15-1.42)	<.001	1.31 (1.21-1.41)
Multivariate model[b]	1 [Reference]	1.00 (0.89-1.12)	1.07 (0.96-1.20)	1.07 (0.95-1.20)	1.15 (1.02-1.29)	<.001	1.17 (1.07-1.27)
Nurses' Health Study							
Total red meat							
Cases/person-years, No.	1264/439 774	1191/443 495	1185/440 970	1263/441 727	1488/441 393	NA	NA
Age-adjusted model	1 [Reference]	1.04 (0.96-1.13)	1.08 (1.00-1.17)	1.19 (1.10-1.29)	1.39 (1.29-1.50)	<.001	1.21 (1.17-1.25)
Multivariate model[b]	1 [Reference]	1.05 (0.97-1.14)	1.10 (1.01-1.19)	1.15 (1.06-1.25)	1.17 (1.08-1.28)	<.001	1.09 (1.05-1.13)
Unprocessed red meat							
Cases/person-years, No.	1308/442 572	1222/442 671	1120/440 530	1215/432 361	1526/449 225	NA	NA
Age-adjusted model	1 [Reference]	1.02 (0.94-1.10)	0.97 (0.90-1.06)	1.09 (1.01-1.18)	1.33 (1.24-1.44)	<.001	1.22 (1.17-1.27)
Multivariate model[b]	1 [Reference]	1.04 (0.96-1.12)	1.03 (0.95-1.12)	1.11 (1.02-1.20)	1.17 (1.08-1.27)	<.001	1.09 (1.04-1.14)
Processed red meat							
Cases/person-years, No.	1294/444 119	1230/421 760	1236/456 687	1204/442 791	1427/442 002	NA	NA
Age-adjusted model	1 [Reference]	1.08 (1.00-1.17)	1.11 (1.03-1.20)	1.14 (1.05-1.23)	1.35 (1.25-1.46)	<.001	1.41 (1.31-1.52)
Multivariate model[b]	1 [Reference]	1.05 (0.97-1.14)	1.08 (1.00-1.17)	1.08 (1.00-1.17)	1.14 (1.05-1.23)	.001	1.14 (1.05-1.24)
Pooled Results[c]							
Total red meat	1 [Reference]	1.05 (0.98-1.12)	1.09 (1.02-1.16)	1.16 (1.08-1.24)	1.19 (1.11-1.28)	<.001	1.10 (1.07-1.13)
Unprocessed red meat	1 [Reference]	1.03 (0.97-1.10)	1.03 (0.96-1.10)	1.09 (1.02-1.16)	1.17 (1.10-1.26)	<.001	1.10 (1.06-1.14)
Processed red meat	1 [Reference]	1.03 (0.97-1.10)	1.08 (1.01-1.15)	1.08 (1.01-1.15)	1.14 (1.07-1.22)	<.001	1.16 (1.09-1.23)

Abbreviations: HR, hazard ratio; NA, not applicable.
[a] Data are given as HR (95% CI) except where indicated otherwise.
[b] The multivariate model was adjusted for age (continuous), body mass index (calculated as weight in kilograms divided by height in meters squared) category (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0); alcohol consumption (0, 0.1-4.9, 5.0-29.9, and ≥30.0 g/d in men; 0, 0.1-4.9, 5.0-14.9, ≥15.0 g/d in women); physical activity level (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 hours of metabolic equivalent tasks per week); smoking status (never, past, or current 1-14 cigarettes per day, current 15-24 cigarettes/d, or current ≥25 cigarettes/d); race (white or nonwhite); menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, or postmenopausal current users); family history of diabetes mellitus, myocardial infarction, or cancer; history of diabetes mellitus, hypertension, or hypercholesterolemia; and intakes of total energy, whole grains, fruits, and vegetables in all quintiles.
[c] Results from the multivariate model were combined using the random-effects model.

We estimated that 9.3% (95% CI, 5.9%-12.7%) in men and 7.6% (95% CI, 3.5%-11.7%) in women of total deaths during follow-up could be prevented if all the participants consumed fewer than 0.5 servings per day of total red meat in these cohorts; the estimates were 8.6% (95% CI, 2.3%-14.7%) in men and 12.2% (95% CI, 3.3%-21.0%) in women for CVD deaths. However, only 22.8% of men and 9.6% of women were in the low-risk category of total red meat intake.

COMMENT

In these 2 large prospective cohorts of US men and women, we found that a higher intake of red meat was associated with a significantly elevated risk of total, CVD, and cancer mortality, and this association was observed for unprocessed and processed red meat, with a relatively greater risk for processed red meat. Substitution of fish, poultry, nuts, legumes, low-fat dairy products, and whole grains for red meat was associated with a significantly lower risk of mortality.

Red meat is a major food source of protein and fat, and its potential associations with risks of diabetes mellitus,[1] CVD,[2] cancer,[3] and mortality[4-6] have attracted much attention. Several studies[4,5] have suggested that vegetarians have greater longevity compared with nonvegetarians, but this might not be ascribed to the absence of red meat only. Sinha et al[6] showed in the National Institutes of Health–AARP (formerly known as the American Association of Retired Persons) study that higher intakes of red and processed meats were associated with an elevated risk of mortality. However, that study did not distinguish unprocessed and processed red meats and did not update dietary information during follow-up.

The strengths of the present study include a large sample size, high rates of long-term follow-up, and detailed and repeated assessments of diet and lifestyle. All the participants were health professionals, minimizing potential confounding by educational attainment or differential access to health care. In addition, the FFQs used in these studies were validated against multiple diet records.[9,10] However, the measurement errors inherent in dietary assessments were inevitable, including misclassification of ham or cold cuts as unprocessed red meat and inaccurate assessment of red meat content in mixed dishes. Because of the prospective study design, any measurement errors of meat intake are independent of study outcome ascertainment and, therefore, are likely to attenuate the associations toward the null.[16] In the sensitivity analysis accounting for measurement errors, the risk estimates became stronger. Moreover, we calculated cumulative averages for dietary variables to better represent a person's long-term diet pattern and to minimize the random measurement error caused by within-person variation. As expected, the analyses using baseline diet only yielded weaker associations. We also stopped updating the dietary information after a diagnosis of major chronic disease assuming that participants could have changed their diet after receiving the diagnosis. Finally, because the participants were predominantly non-Hispanic white health professionals, the generalizability of the observed associations may be limited to similar populations.

Several mechanisms may explain the adverse effect of red meat intake on mortality risk. Regarding CVD mortality, we previously reported that red meat intake was associated with an increased risk of coronary heart disease,[2,14] and saturated fat and cholesterol from red meat may partially explain this association.[12] The association between red meat and CVD mortality was moderately attenuated after further adjustment for saturated fat and cholesterol, suggesting a mediating role for these nutrients. However, we could not assess whether lean meat has the same health risks as meat with higher fat content. Furthermore, dietary iron, particularly heme iron primarily from red meat, has been positively associated with myocardial infarction and fatal coronary heart dis-

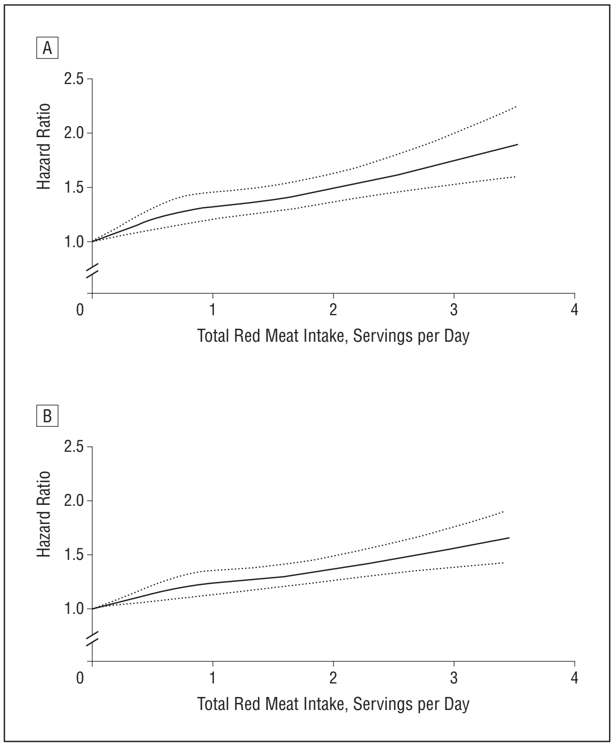

Figure 1. Dose-response relationship between red meat intake and risk of all-cause mortality in the Health Professionals Follow-up Study (A) and the Nurses' Health Study (B). The results were adjusted for age (continuous); body mass index (calculated as weight in kilograms divided by height in meters squared) category (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35); alcohol consumption (0, 0.1-4.9, 5.0-29.9, ≥30.0 g/d in men; 0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d in women); physical activity level (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 hours of metabolic equivalent tasks per week); smoking status (never, past, or current [1-14, 15-24, or ≥25 cigarettes per day]); race (white or nonwhite); menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, or postmenopausal current users); family history of diabetes mellitus, myocardial infarction, or cancer; history of diabetes mellitus, hypertension, or hypercholesterolemia; and intakes of total energy, whole grains, fruits, and vegetables, all in quintiles. Broken lines represent 95% CI.

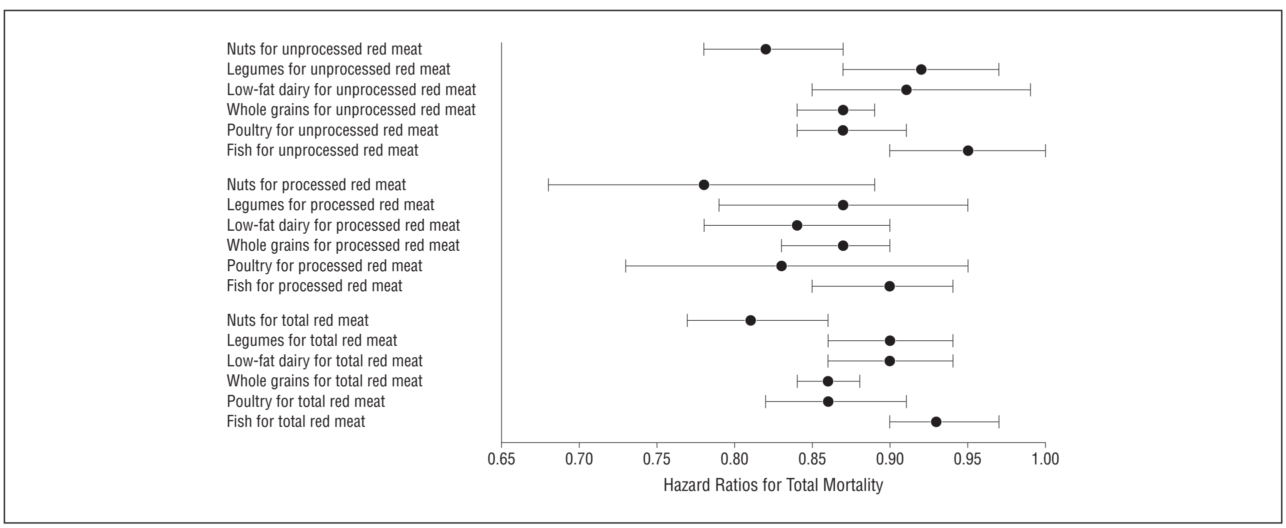

Figure 2. Hazard ratios and 95% CIs (error bars) for total mortality associated with replacement of other food groups for red meat intake. Adjusted for age (continuous); body mass index (calculated as weight in kilograms divided by height in meters squared) category (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0); alcohol consumption (0, 0.1-4.9, 5.0-29.9, ≥30.0 g/d in men; 0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d in women); physical activity level (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 hours of metabolic equivalent tasks per week); smoking status (never, past, or current [1-14, 15-24, or ≥25 cigarettes per day]); race (white or nonwhite); menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, or postmenopausal current users); family history of diabetes mellitus, myocardial infarction, or cancer; history of diabetes mellitus, hypertension, or hypercholesterolemia; total energy intake; and the corresponding 2 dietary variables in the models.

ease.[17-20] The associations between red meat and CVD mortality were moderately attenuated after additional adjustment for heme iron. This finding suggests that heme iron intake may partially explain this association, although some studies using biomarkers of iron status found no association of ferritin and transferrin saturation levels with risk of total mortality.[21] Unprocessed and processed meats contain similar amounts of saturated fat and heme iron; however, other constituents in processed meat, particularly sodium and nitrites, might explain the additional harm of processed meats. The high sodium content may increase CVD risk through its effect on blood pressure.[22,23] Nitrites and nitrates are frequently used in the preservation of processed meats, and blood nitrite concentrations have been related to endothelial dysfunction[24] and impaired insulin response in adults.[25]

Regarding cancer mortality, red meat intake has been associated with increased risks of colorectal cancer and several other cancers.[26] Several compounds in red meat or created by high-temperature cooking, including *N*-nitroso compounds (nitrosamines or nitrosamides) converted from nitrites,[27] polycyclic aromatic hydrocarbons, and heterocyclic amines,[28-30] are potential carcinogens. Heme iron and iron overload might also be associated with increased cancer risk through promotion of *N*-nitroso compound formation,[31] increased colonic cytotoxicity and epithelial proliferation,[32] increased oxidative stress, and iron-induced hypoxia signaling.[33]

In conclusion, we found that greater consumption of unprocessed and processed red meats is associated with higher mortality risk. Compared with red meat, other dietary components, such as fish, poultry, nuts, legumes, low-fat dairy products, and whole grains, were associated with lower risk. These results indicate that replacement of red meat with alternative healthy dietary components may lower the mortality risk.

Accepted for Publication: December 20, 2011.
Published Online: March 12, 2012. doi:10.1001/archinternmed.2011.2287
Correspondence: Frank B. Hu, MD, PhD, Departments of Nutrition and Epidemiology, Harvard School of Public Health, 655 Huntington Ave, Boston, MA 02115 (frank.hu@channing.harvard.edu).
Author Contributions: Drs Pan and Hu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Pan, Willett, and Hu. *Acquisition of data*: Manson, Stampfer, Willett, and Hu. *Analysis and interpretation of data*: Pan, Sun, Bernstein, Schulze, Manson, Stampfer, Willett, and Hu. *Drafting of the manuscript*: Pan. *Critical revision of the manuscript for important intellectual content*: Sun, Bernstein, Schulze, Manson, Stampfer, Willett, and Hu. *Statistical analysis*: Pan, Sun, and Hu. *Obtained funding*: Manson, Stampfer, Willett, and Hu. *Administrative, technical, and material support:* Manson, Stampfer, Willett, and Hu. *Study supervision*: Manson, Stampfer, Willett, and Hu.
Financial Disclosure: None reported.
Funding/Support: This study was supported by grants DK58845, CA55075, CA87969, HL34594, and 1U54CA155626-01 from the National Institutes of Health and by career development award K99HL098459 from the National Heart, Lung, and Blood Institute (Dr Sun).
Role of the Sponsors: The funding sources were not involved in the data collection, data analysis, manuscript writing, and publication.
Online-Only Material: The eTables and eFigure are available at http://www.archinternmed.com.
Additional Contributions: We are indebted to the participants in the HPFS and the NHS for their continuing outstanding support and to colleagues working in these studies for their valuable help. In addition, we thank the following state cancer registries for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming.

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INVITED COMMENTARY

Holy Cow! What's Good for You Is Good for Our Planet

Is red meat bad for you? In a word, yes. In this issue, Pan et al[1] describe the outcomes from more than 37 000 men from the Harvard Health Professionals Follow-Up Study and more than 83 000 women from the Harvard Nurses Health Study who were followed up for almost 3 million person-years.

This is the first large-scale prospective longitudinal study showing that consumption of both processed and unprocessed red meat is associated with an increased risk of premature mortality from all causes as well as from cardiovascular disease and cancer. In a related study by Pan et al,[2] red meat consumption was also associated with an increased risk of type 2 diabetes mellitus.

Substitution of red meat with fish, poultry, nuts, legumes, low-fat dairy products, and whole grains was associated with a significantly lower risk of mortality. We have a spectrum of choices; it's not all or nothing.[3]

Plant-based foods are rich in phytochemicals, bioflavonoids, and other substances that are protective. In other words, what we *include* in our diet is as important as what we *exclude*, so substituting healthier foods for red meat provides a double benefit to our health.

Pan et al[1] reported that adjustment for saturated fat, dietary cholesterol, and heme iron accounted for some but not all of the risk of eating red meat. Thus, other mechanisms such as nontraditional risk factors may be involved.

For example, a recent study by Smith[4] found that high-fat, high-protein, low-carbohydrate (HPLC) diets (which are usually high in red meat, such as the Atkins and Paleolithic diets) may accelerate atherosclerosis through mechanisms that are unrelated to the classic cardiovascular risk factors. Mice that were fed an HPLC diet had almost twice the level of arterial plaque as mice that were fed a Western diet even though the classic risk factors were not significantly different between groups. The mice that were fed the HPLC diet had markedly fewer circulating endothelial progenitor cells and higher levels of nonesterified fatty acids (promoting inflammation) than mice that were fed the Western diet.[5]

Therefore, studies of HPLC diets that only examine their effects on changes in weight, blood pressure, and lipid levels may not adequately reflect the negative influence of HPLC diets on health outcomes, such as morbidity and mortality.

There is an emerging consensus among most nutrition experts about what constitutes a healthy way of eating:

- little or no red meat;
- high in "good carbs" (including vegetables, fruits, whole grains, legumes, and soy products in their natural forms);
- low in "bad carbs" (simple and refined carbohydrates, such as sugar, high-fructose corn syrup, and white flour);
- high in "good fats" (ω-3 fatty acids found in fish oil, flax oil, and plankton-based oils);
- low in "bad fats" (trans fats, saturated fats, and hydrogenated fats);