Meat Intake and Mortality

A Prospective Study of Over Half a Million People

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Background: High intakes of red or processed meat may increase the risk of mortality. Our objective was to determine the relations of red, white, and processed meat intakes to risk for total and cause-specific mortality.

Methods: The study population included the National Institutes of Health–AARP (formerly known as the American Association of Retired Persons) Diet and Health Study cohort of half a million people aged 50 to 71 years at baseline. Meat intake was estimated from a food frequency questionnaire administered at baseline. Cox proportional hazards regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) within quintiles of meat intake. The covariates included in the models were age, education, marital status, family history of cancer (yes/no) (cancer mortality only), race, body mass index, 31-level smoking history, physical activity, energy intake, alcohol intake, vitamin supplement use, fruit consumption, vegetable consumption, and menopausal hormone therapy among women. Main outcome measures included total mortality and deaths due to cancer, cardiovascular disease, injuries and sudden deaths, and all other causes.

Results: There were 47 976 male deaths and 23 276 female deaths during 10 years of follow-up. Men and women in the highest vs lowest quintile of red (HR, 1.31 [95% CI, 1.27-1.35], and HR, 1.36 [95% CI, 1.30-1.43], respectively) and processed meat (HR, 1.16 [95% CI, 1.12-1.20], and HR, 1.25 [95% CI, 1.20-1.31], respectively) intakes had elevated risks for overall mortality. Regarding cause-specific mortality, men and women had elevated risks for cancer mortality for red (HR, 1.22 [95% CI, 1.16-1.29], and HR, 1.20 [95% CI, 1.12-1.30], respectively) and processed meat (HR, 1.12 [95% CI, 1.06-1.19], and HR, 1.11 [95% CI 1.04-1.19], respectively) intakes. Furthermore, cardiovascular disease risk was elevated for men and women in the highest quintile of red (HR, 1.27 [95% CI, 1.20-1.35], and HR, 1.50 [95% CI, 1.37-1.65], respectively) and processed meat (HR, 1.09 [95% CI, 1.03-1.15], and HR, 1.38 [95% CI, 1.26-1.51], respectively) intakes. When comparing the highest with the lowest quintile of white meat intake, there was an inverse association for total mortality and cancer mortality, as well as all other deaths for both men and women.

Conclusion: Red and processed meat intakes were associated with modest increases in total mortality, cancer mortality, and cardiovascular disease mortality.

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MEAT INTAKE VARIES SUBstantially around the world, but the impact of consuming higher levels of meat in relation to chronic disease mortality is ambiguous.[1-6] To increase sample size, pooled analyses of meat intake have been carried out in Seventh-Day Adventists in the United States[1,2] and other vegetarian populations in Europe.[3-6] Vegetarian diets differ from nonvegetarian diets in several respects. The main sources of protein in a vegetarian diet are legumes, grains, and nuts. Vegetarian diets also include higher intakes of vegetables, unsaturated fats, dietary fiber, and antioxidants (carotenoids and vitamins C and E), although they contain lower amounts of iron, zinc, and vitamin B_{12}. Furthermore, other lifestyle factors, such as smoking, physical activity, and alcohol consumption among vegetarians and members of select religious groups can differ substantially from the general population.

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We prospectively investigated red, white, and processed meat intakes as risk factors for total mortality, as well as cause-specific mortality, including cancer and cardiovascular disease (CVD) mortality in a cohort of approximately half a million men

and women enrolled in the National Institutes of Health (NIH)–AARP (formerly known as the American Association of Retired Persons) Diet and Health Study.[7] This large prospective study facilitated the investigation of a wide range of meat intakes with chronic disease mortality.

METHODS

STUDY POPULATION

Individuals aged 50 to 71 years were recruited from 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) to form a large prospective cohort, the NIH-AARP Diet and Health Study. Questionnaires on demographic and lifestyle characteristics, including dietary habits, were mailed to 3.5 million members of AARP in 1995, as described in detail elsewhere.[7] The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute. Completion of the baseline questionnaire was considered to imply informed consent.

DIETARY ASSESSMENT

A 124-item food frequency questionnaire (http://riskfactor.cancer.gov/DHQ/forms/files/shared/dhq1.2002.sample.pdf) was completed at baseline. The food frequency questionnaire collected information on the usual consumption of foods and drinks and portion sizes over the last 12 months. The validity of the food frequency questionnaire was estimated using two 24-hour recalls,[8] and the estimated energy-adjusted correlations ranged from 0.36 to 0.76 for various nutrients and attenuation factors ranged from 0.24 to 0.68. Red meat intake was calculated using the frequency of consumption and portion size information of all types of beef and pork and included bacon, beef, cold cuts, ham, hamburger, hotdogs, liver, pork, sausage, steak, and meats in foods such as pizza, chili, lasagna, and stew. White meat included chicken, turkey, and fish and included poultry cold cuts, chicken mixtures, canned tuna, and low-fat sausages and low-fat hotdogs made from poultry. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hotdogs and low-fat hotdogs made from poultry. The components constituting red or white and processed meats can overlap because both can include meats such as bacon, sausage, and ham, while processed meat can also included smoked turkey and chicken. However, these meat groups are not used in the same models; thus, they are not duplicated in any one analysis.

To investigate whether the overall composition of meat intake was associated with mortality, we created 3 diet types: high-, medium-, and low-risk meat diet. To form these diet variables, red and white meat consumption was energy adjusted and split into 2 groups using the median values as cut points. Individuals with red meat consumption in the upper half and white meat consumption in the lower half got a score of 1 (high-risk meat diet), those with both red and white meat consumption in the same half got a score of 2 (medium-risk meat diet), and those with red meat consumption in the lower half and white meat consumption in the upper half got a score of 3 (low-risk meat diet).

COHORT FOLLOW-UP AND CASE ASCERTAINMENT

Cohort members were followed-up from the date the baseline questionnaire was returned (beginning 1995) through December 31, 2005, by annual linkage of the cohort to the National Change of Address database maintained by the US Postal Service and through processing of undeliverable mail, other address change update services, and directly from cohort members' notifications. For matching purposes, we have virtually complete data on first and last name, address history, sex, and date of birth. Follow-up for vital status is performed by annual linkage of the cohort to the Social Security Administration Death Master File in the US verification of vital status, and cause of death information is provided by follow-up searches of the National Death Index (NDI) Plus with the current follow-up for mortality covered until 2005.

CAUSE-SPECIFIC CASE ASCERTAINMENT

Cancer (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 140-239 and *International Statistical Classification of Diseases, 10th Revision* [*ICD-10*] codes C00-C44, C45.0, C45.1, C45.7, C45.9, C48-C97, and D12-D48) mortality included deaths due to cancers of the oral cavity and pharynx, digestive tract, respiratory tract, soft tissue (including heart), skin (excluding basal and squamous cell carcinoma), female genital system and breast, male genital system, urinary tract, endocrine system, lymphoma, leukemia, and other miscellaneous cancers.

Cardiovascular disease (*ICD-9* codes 390-398, 401-404, 410-438, and 440-448 and *ICD-10* codes I00-I09, I10-I13, I20-I51, and I60-I78) mortality was from a combination of diseases of the heart; hypertension without heart disease; cerebrovascular diseases; atherosclerosis; aortic aneurysm and dissection; and other diseases of the arteries, arterioles, and capillaries.

Mortality from injuries and sudden deaths (*ICD-9* codes 800-978 and *ICD-10* codes U01-U03, V01-Y09, Y35, Y85-Y86, Y87.0, Y87.1, and Y89.0) included deaths due to unintentional injury, adverse effects, suicide, self-inflicted injury, homicide, and legal intervention.

All others deaths included mortality from tuberculosis, human immunodeficiency virus, other infectious and parasitic diseases, septicemia, diabetes mellitus, Alzheimer disease, stomach and duodenal ulcers, pneumonia and influenza, chronic obstructive pulmonary disease and allied conditions, chronic liver disease and cirrhosis, nephritis, nephrotic syndrome and nephrosis, congenital anomalies, certain conditions originating in the perinatal period, ill-defined conditions, and unknown causes of death.

Total mortality is a combination of all of the aforementioned causes of deaths.

STATISTICAL ANALYSIS

A total of 617 119 persons returned the baseline questionnaire; of these, we excluded individuals who moved out of the 8 study areas before returning the baseline questionnaire (n = 321), requested to be withdrawn from the study (n = 829), died before study entry (n = 261), had duplicate records (n = 179), indicated that they were not the intended respondent and did not complete the questionnaire (n = 13 442), provided no information on gender (n = 6), and did not answer substantial portions of the questionnaire or had more than 10 recording errors (n = 35 679). After these exclusions, we further removed individuals whose questionnaire was filled in by someone else on their behalf (n = 15 760). We excluded 4849 subjects reporting extreme daily total energy intake defined as more than 2 interquartile ranges above the 75th percentile or below the 25th percentile and 140 people who had zero person-years of follow-up. After all exclusions, our analytic cohort comprised 322 263 men and 223 390 women.

We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) with time since entry into the study as the underlying time metric using Cox proportional hazards regression models. Quintile cut points were based on the entire cohort, and multivariate-adjusted HRs are reported using the lowest quintile as the referent category. The violation of the proportional hazard assumption was investigated by testing an interaction between a time-dependent binary covariate, which indicated if follow-up was in the first 5 years or in the second 5 years, and the quintile terms for meat consumption. Dietary variables were energy adjusted using the nutrient density method, and meat variables in each model added up to total meat (addition model). For example, one model contained both red and white meat, while the processed meat model also contained a nonprocessed meat variable.

To address confounding, we used forward stepwise variable selection to include covariates to develop the fully adjusted model. Smoking was the largest confounder of the association between meat intake and mortality. Physical activity and education were also important covariates, but not to the same degree as smoking. The final model included age (continuous); education (<8 years or unknown, 8-11 years, 12 years [high school], some college, or college graduate); marital status (married: yes/no); family history of cancer (yes/no) (cancer mortality only); race (non-Hispanic white, non-Hispanic black, Hispanic/Asian/Pacific Islander/American Indian/Alaskan native, or unknown); body mass index (18.5 to <25, 25 to <30, 30 to <35, ≥35 [calculated as weight in kilograms divided by height in meters squared]); 31-level smoking history using smoking status (never, former, or current), time since quitting for former smokers and smoking dose; frequency of vigorous physical activity (never/rarely, 1-3 times/mo, 1-2 times/wk, 3-4 times/wk, ≥5 times/wk); total energy intake (continuous); alcohol intake (none, 0 to <5, 5 to <15, 15 to <30, ≥30 g/d); vitamin supplement user (≥1 supplement/mo); fruit consumption (0 to <0.7, 0.7 to <1.2, 1.2 to <1.7, 1.7 to <2.5, ≥2.5 servings/1000 kcal); vegetable consumption (0 to <1.3, 1.3 to <1.8, 1.8 to <2.2, 2.2 to <3.0, ≥3.0 servings/1000 kcal); and menopausal hormone therapy among women in the multivariate models.

In subanalyses, we investigated the relation between meat intake and mortality by smoking status. We used median values of each quintile to test for linear trend with 2-sided *P* values. We also calculated population-attributable risks as an estimate of the percentage of mortality that could be prevented if individuals adopted intake levels of participants within the first quintile. This was computed as 1 minus the ratio consisting of the sum of the estimated HR (derived from the Cox proportional hazard regression models) of each member of the cohort divided by the sum of the estimated HR for which meat exposure was assigned to the lowest or highest quintile, depending on which quintile was the ideal level of meat consumption. The population-attributable risk was multiplied by 100 to convert them to a percentage. All statistical analyses were carried out using Statistical Analytic Systems (SAS) software (SAS Institute Inc, Cary, North Carolina).

RESULTS

During 10 years of follow-up, there were 47 976 male deaths and 23 276 female deaths. In general, those in the highest quintile of red meat intake tended to consume a slightly lower amount of white meat but a higher amount of processed meat compared with those in the lowest quintile. Subjects who consumed more red meat tended to be married, more likely of non-Hispanic white ethnicity, more likely a current smoker, have a higher body mass index, and have a higher daily intake of energy, total fat, and saturated fat, and they tended to have lower education and physical activity levels and lower fruit, vegetable, fiber, and vitamin supplement intakes (**Table 1**).

RED MEAT

There was an overall increased risk of total, cancer, and CVD mortality, as well as all other deaths in both men (**Table 2**) and women (**Table 3**) in the highest compared with the lowest quintile of red meat intake in the fully adjusted model. There was an increased risk associated with death from injuries and sudden death with higher consumption of red meat in men but not in women.

WHITE MEAT

When comparing the highest with the lowest quintile of white meat intake, there was an inverse association for total mortality and cancer mortality, as well as all other deaths for both men (Table 2) and women (Table 3). In contrast, there was a small increase in risk for CVD mortality in men with higher intake of white meat. There was no association between white meat consumption and death from injuries and sudden death in men or women.

PROCESSED MEAT

There was an overall increased risk of total, cancer, and CVD mortality, as well as all other deaths in both men (Table 2) and women (Table 3) in the highest compared with the lowest quintile of processed meat intake. In contrast, there was no association for processed meat intake and death from injuries and sudden death in either sex.

A lag analysis, excluding deaths occurring in the first 2 years of follow-up, produced results consistent with the main findings in Table 2 and Table 3. For example, the HRs for total mortality in men for red meat was as follows: second quintile HR, 1.05 (95% CI, 1.01-1.09); third quintile HR, 1.13 (95% CI, 1.09-1.17); fourth quintile HR, 1.20 (95% CI, 1.16-1.24); and fifth quintile HR, 1.30 (95% CI, 1.26-1.35). For women, the HRs were as follows: second quintile HR, 1.07 (95% CI, 1.02-1.12); third quintile HR, 1.15 (95% CI, 1.11-1.21); fourth quintile HR, 1.27 (95% CI, 1.21-1.33); and fifth quintile HR, 1.35 (95% CI, 1.28-1.42). Furthermore, we investigated our models for a violation of the proportional hazard assumption. Proportional hazard assumption was not rejected for all analyses except one, the model with red and white meat among the women for total mortality ($P = .008$). On further examination in that model of the relative HR between the first 5 years of follow-up and the second 5 years of follow-up, the red meat results were consistent between the 2 follow-up periods. However, for white meat, the second 5-year period showed less of an inverse trend compared with the first 5-year period (data not shown).

We investigated whether people who consumed a high-risk meat diet had mortality risk profiles that were different from people who consumed a low-risk meat diet. Both men and women who consumed a low-risk meat diet had statistically significant lower HRs compared with

Table 1. Selected Age-Adjusted Characteristics of the National Institutes of Health–AARP Cohort by Red Meat Quintile Category[a]

Characteristic	Red Meat Intake Quintile, g/1000 kcal				
	Q1	Q2	Q3	Q4	Q5
Men (n=322 263)					
Meat intake					
Red meat, g/1000 kcal	9.3	21.4	31.5	43.1	68.1
White meat, g/1000 kcal	36.6	32.2	30.7	30.4	30.9
Processed meat, g/1000 kcal	5.1	7.8	10.3	13.3	19.4
Age, y	62.8	62.8	62.5	62.3	61.7
Race, %					
Non-Hispanic white	88.6	91.8	93.1	94.0	94.1
Non-Hispanic black	4.2	3.2	2.7	2.2	1.9
Hispanic/Asian/Pacific Islander/American Indian/Alaskan native/unknown	7.2	5.0	4.2	3.8	4.0
Positive family history of cancer,%	47.0	47.7	48.4	48.6	47.8
Currently married, %	80.8	84.4	86.1	86.7	85.6
BMI	25.9	26.7	27.1	27.6	28.3
Smoking history, %[b]					
Never smoker	34.4	30.5	28.8	27.6	25.4
Former smoker	56.5	58.1	57.5	57.1	55.8
Current smoker or having quit <1 y prior	4.9	7.6	9.9	11.4	14.8
Education, college graduate or postgraduate, %	53.0	47.3	45.1	42.3	39.1
Vigorous physical activity ≥5 times/wk, %	30.7	23.6	20.5	18.6	16.3
Dietary intake					
Energy, kcal/d	1899	1955	1998	2038	2116
Fruit, servings/1000 kcal	2.3	1.8	1.6	1.4	1.1
Vegetables, servings/1000 kcal	2.4	2.1	2.0	2.0	1.9
Alcohol, g/d	20.2	20.4	17.6	15.3	12.5
Total fat, g/1000 kcal	25.8	30.5	33.5	35.9	39.4
Saturated fat, g/1000 kcal	7.6	9.4	10.5	11.3	12.7
Fiber, g/1000 kcal	13.2	11.0	10.2	9.6	8.8
Vitamin supplement use ≥1/mo	67.3	62.1	59.1	55.8	52.0
Women (n=223 390)					
Meat intake					
Red meat, g/1000 kcal	9.1	21.2	31.2	42.8	65.9
White meat, g/1000 kcal	37.4	35.6	34.9	35.1	35.3
Processed meat, g/1000 kcal	3.8	6.4	8.7	11.3	16.0
Age, y	62.2	62.2	62.0	61.7	61.3
Race, %					
Non-Hispanic white	86.2	89.9	91.0	91.8	91.4
Non-Hispanic black	7.5	5.5	4.8	4.1	3.8
Hispanic/Asian/Pacific Islander/American Indian/Alaskan native/unknown	6.3	4.5	4.3	4.1	4.9
Positive family history of cancer, %	51.4	53.0	52.9	52.4	51.5
Currently married, %	37.2	42.4	46.3	48.8	50.7
BMI	25.6	26.6	27.1	27.7	28.4
Never received HT (women only)	46.6	463	47.1	48.1	50.5
Smoking history, %[b]					
Never smoker	45.5	44.3	43.23	42.2	40.0
Former smoker	41.8	39.5	38.1	37.0	35.4
Current smoker or having quit <1 y prior	8.8	12.7	15.3	17.7	21.2
Education, college graduate or postgraduate, %	37.1	30.7	27.7	25.6	22.7
Vigorous physical activity ≥5 times/wk, %	22.5	16.3	13.9	12.0	11.0
Dietary intake, %					
Energy, kcal/d	1526	1539	1584	1613	1646
Fruit, servings/1000 kcal	2.5	2.0	1.8	1.5	1.3
Vegetables, servings/1000 kcal	2.8	2.5	2.4	2.3	2.3
Alcohol, g/d	5.8	6.3	6.2	5.7	5.1
Total fat, g/1000 kcal	27.7	32.1	34.7	37.0	40.1
Saturated fat, g/1000 kcal	8.3	9.9	10.8	11.6	12.7
Fiber, g/1000 kcal	13.8	11.7	10.9	10.3	9.5
Vitamin supplement use ≥1/mo	72.2	68.4	66.1	63.7	58.8

Abbreviations: AARP, formerly the American Association of Retired Persons; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HT, hormone therapy; Q, quintile.

[a] Data are given as mean value or percentage of participants (N = 545 653). Generalized linear models were used to estimate mean values for the continuous variables and frequencies for dichotomous proportions within each red meat intake quintile.

[b] A total of 12 597 men (3.9%) and 7885 women (3.5%) had missing smoking history data.

Table 2. Multivariate Analysis for Red, White, and Processed Meat Intake and Total and Cause-Specific Mortality in Men in the National Institutes of Health–AARP Diet and Health Study[a]

Mortality in Men (n=322 263)	Quintile					*P* Value for Trend
	Q1	Q2	Q3	Q4	Q5	
Red Meat Intake[b]						
All mortality						
Deaths	6437	7835	9366	10 988	13 350	
Basic model[c]	1 [Reference]	1.07 (1.03-1.10)	1.17 (1.13-1.21)	1.27 (1.23-1.31)	1.48 (1.43-1.52)	<.001
Adjusted model[d]	1 [Reference]	1.06 (1.03-1.10)	1.14 (1.10-1.18)	1.21 (1.17-1.25)	1.31 (1.27-1.35)	<.001
Cancer mortality						
Deaths	2136	2701	3309	3839	4448	
Basic model[c]	1 [Reference]	1.10 (1.04-1.17)	1.23 (1.16-1.29)	1.31 (1.24-1.39)	1.44 (1.37-1.52)	<.001
Adjusted model[d]	1 [Reference]	1.05 (0.99-1.11)	1.13 (1.07-1.20)	1.18 (1.12-1.25)	1.22 (1.16-1.29)	<.001
CVD mortality						
Deaths	1997	2304	2703	3256	3961	
Basic model[c]	1 [Reference]	1.02 (0.96-1.08)	1.10 (1.04-1.17)	1.24 (1.17-1.31)	1.44 (1.37-1.52)	<.001
Adjusted model[d]	1 [Reference]	0.99 (0.96-1.09)	1.08 (1.02-1.15)	1.18 (1.12-1.26)	1.27 (1.20-1.35)	<.001
Mortality from injuries and sudden deaths						
Deaths	184	216	228	280	343	
Basic model[c]	1 [Reference]	1.02 (0.84-1.24)	0.97 (0.80-1.18)	1.09 (0.90-1.31)	1.24 (1.03-1.49)	.01
Adjusted model[d]	1 [Reference]	1.06 (0.86-1.29)	1.01 (0.83-1.24)	1.14 (0.94-1.39)	1.26 (1.04-1.54)	.008
All other deaths						
Deaths	1268	1636	1971	2239	2962	
Basic model[c]	1 [Reference]	1.13 (1.05-1.22)	1.25 (1.17-1.35)	1.33 (1.24-1.42)	1.68 (1.57-1.80)	<.001
Adjusted model[d]	1 [Reference]	1.17 (1.09-1.26)	1.28 (1.19-1.38)	1.34 (1.25-1.44)	1.58 (1.47-1.70)	<.001
White Meat Intake[e]						
All mortality						
Deaths	12 521	10 442	9359	8444	7210	
Basic model[c]	1 [Reference]	0.83 (0.81-0.85)	0.77 (0.75-0.79)	0.74 (0.72-0.76)	0.74 (0.72-0.76)	<.001
Adjusted model[d]	1 [Reference]	0.92 (0.90-0.95)	0.90 (0.88-0.93)	0.90 (0.88-0.93)	0.92 (0.89-0.94)	<.001
Cancer mortality						
Deaths	4424	3647	3203	2830	2329	
Basic model[c]	1 [Reference]	0.82 (0.79-0.86)	0.74 (0.71-0.78)	0.71 (0.67-0.74)	0.68 (0.65-0.72)	<.001
Adjusted model[d]	1 [Reference]	0.91 (0.87-0.95)	0.87 (0.83-0.91)	0.85 (0.81-0.90)	0.84 (0.80-0.88)	<.001
CVD mortality						
Deaths	3521	3015	2771	2578	2336	
Basic model[c]	1 [Reference]	0.85 (0.81-0.89)	0.81 (0.77-0.85)	0.81 (0.77-0.85)	0.86 (0.81-0.90)	<.001
Adjusted model[d]	1 [Reference]	0.96 (0.91-1.00)	0.96 (0.91-1.01)	0.99 (0.94-1.04)	1.05 (1.00-1.11)	.009
Mortality from injuries and sudden deaths						
Deaths	333	266	249	219	184	
Basic model[c]	1 [Reference]	0.81 (0.69-0.95)	0.78 (0.66-0.93)	0.73 (0.62-0.87)	0.71 (0.59-0.85)	<.001
Adjusted model[d]	1 [Reference]	0.89 (0.76-1.05)	0.90 (0.76-1.06)	0.86 (0.72-1.03)	0.85 (0.70-1.02)	.11
All other deaths						
Deaths	2775	2206	1948	1722	1425	
Basic model[c]	1 [Reference]	0.79 (0.75-0.83)	0.72 (0.68-0.76)	0.68 (0.64-0.73)	0.67 (0.63-0.72)	<.001
Adjusted model[d]	1 [Reference]	0.90 (0.85-0.95)	0.88 (0.83-0.93)	0.86 (0.81-0.92)	0.86 (0.80-0.92)	<.001

(continued)

people who consumed a high-risk meat diet for all-cause, cancer, and CVD mortality, as well as all other deaths; for example, for all-cause mortality, the HR for a low-risk meat diet was 0.92 (95% CI, 0.80-0.94) for men and 0.80 (95% CI, 0.78-0.84) for women.

To further explore possible confounding by smoking, we analyzed meat intake and mortality in 2 subgroups—never smokers (15 413 deaths among 190 135 never smokers) and former/current smokers (n=52 754 deaths among 335 036 former/current smokers). For men, the risks in the fifth quintile of red meat intake for never and former/current smokers were as follows: for total mortality, HR, 1.28 (95% CI, 1.19-1.38), and HR, 1.25 (95% CI, 1.20-1.30), respectively; for cancer mortality, HR, 1.16 (95% CI, 1.02-1.33), and HR, 1.17 (95% CI, 1.09-1.24), respectively; and for CVD mortality, HR, 1.43 (95% CI, 1.25-1.63), and HR, 1.17 (95% CI, 1.10-1.26), respectively. In women, the risks in the fifth quintile of red meat intake for never and former/current smokers were as follows: for total mortality, HR, 1.36 (95% CI, 1.25-1.48), and HR, 1.28 (95% CI, 1.21-1.35), respectively; for cancer mortality, HR, 1.10 (95% CI, 0.95-1.27), and HR, 1.16 (95% CI, 1.06-1.27), respectively; and for CVD mortality, HR, 1.63 (95% CI, 1.38-1.93), and HR, 1.34 (95% CI, 1.18-1.51), respectively. Risks were similar for the 2 smoking categories in most instances for processed meat except for cancer mortality, for which we found a null relation for both sexes in never smokers (men: HR, 1.01 [95% CI, 0.88-1.15]; women: HR, 1.02

Table 2. Multivariate Analysis for Red, White, and Processed Meat Intake and Total and Cause-Specific Mortality in Men in the National Institutes of Health–AARP Diet and Health Study[a] (continued)

Mortality in Men (n=322 263)	Quintile					*P* Value for Trend
	Q1	Q2	Q3	Q4	Q5	
Processed Meat Intake[f]						
Deaths	6235	7738	9435	11 249	13 319	
Basic model[c]	1 [Reference]	1.04 (1.01-1.08)	1.13 (1.09-1.16)	1.20 (1.16-1.24)	1.30 (1.26-1.34)	<.001
Adjusted model[d]	1 [Reference]	1.01 (0.98-1.04)	1.07 (1.04-1.11)	1.12 (1.08-1.16)	1.16 (1.12-1.20)	<.001
Cancer mortality						
Deaths	2032	2784	3334	3906	4377	
Basic model[c]	1 [Reference]	1.15 (1.08-1.22)	1.22 (1.15-1.29)	1.28 (1.21-1.35)	1.32 (1.25-1.39)	<.001
Adjusted model[d]	1 [Reference]	1.07 (1.01-1.14)	1.11 (1.05-1.17)	1.14 (1.07-1.20)	1.12 (1.06-1.19)	.001
CVD mortality						
Deaths	1977	2225	2752	3255	4012	
Basic model[c]	1 [Reference]	0.94 (0.88-1.00)	1.02 (0.96-1.09)	1.08 (1.02-1.14)	1.22 (1.15-1.29)	<.001
Adjusted model[d]	1 [Reference]	0.92 (0.87-0.98)	0.99 (0.93-1.05)	1.02 (0.96-1.08)	1.09 (1.03-1.15)	<.001
Mortality from injuries and sudden deaths						
Deaths	190	201	257	273	330	
Basic model[c]	1 [Reference]	0.87 (0.72-1.07)	0.98 (0.81-1.19)	0.93 (0.77-1.13)	1.04 (0.86-1.25)	.24
Adjusted model[d]	1 [Reference]	0.88 (0.72-1.08)	0.99 (0.81-1.20)	0.93 (0.76-1.13)	1.00 (0.83-1.21)	.48
All other deaths						
Deaths	1259	1548	1896	2430	2943	
Basic model[c]	1 [Reference]	1.05 (0.97-1.13)	1.15 (1.07-1.23)	1.31 (1.22-1.41)	1.46 (1.36-1.56)	<.001
Adjusted model[d]	1 [Reference]	1.05 (0.97-1.13)	1.14 (1.06-1.23)	1.28 (1.19-1.38)	1.33 (1.24-1.43)	<.001

Abbreviations: AARP, formerly the American Association of Retired Persons; CVD, cardiovascular disease.

[a] Data are given as hazard ratio (95% confidence interval) unless otherwise specified.

[b] Median red meat intake based on men and women (g/1000 kcal): Q1, 9.8; Q2, 21.4; Q3, 31.3; Q4, 42.8; and Q5, 62.5.

[c] Basic model: age (continuous); race (non-Hispanic white, non-Hispanic black, Hispanic/Asian/Pacific Islander/American Indian/Alaskan native, or unknown); and total energy intake (continuous).

[d] Adjusted model: basic model plus education (<8 years or unknown, 8-11 years, 12 years [high school], some college, or college graduate); marital status (married: yes/no); family history of cancer (yes/no) (cancer mortality only); body mass index (18.5 to <25, 25 to <30, 30 to <35, ≥35 [calculated as weight in kilograms divided by height in meters squared]); 31-level smoking history using smoking status (never, former, current), time since quitting for former smokers, and smoking dose; frequency of vigorous physical activity (never/rarely, 1-3 times/mo, 1-2 times/wk, 3-4 times/wk, ≥5 times/wk); alcohol intake (none, 0 to <5, 5 to <15, 15 to <30, ≥30 servings/1000 kcal), vitamin supplement user (≥1 supplement/mo); fruit consumption (0 to <0.7, 0.7 to <1.2, 1.2 to <1.7, 1.7 to <2.5, ≥2.5 servings/1000 kcal); and vegetable consumption (0 to <1.3, 1.3 to <1.8, 1.8 to <2.2, 2.2 to <3.0, ≥3.0 serving/1000 kcal).

[e] Median white meat intake based on men and women (g/1000 kcal): Q1, 9.5; Q2, 18.4; Q3, 27.4; Q4, 39.4; and Q5, 64.6.

[f] Median processed meat intake based on men and women (g/1000 kcal): Q1, 1.6; Q2, 4.4; Q3, 7.4; Q4, 12.2; and Q5, 22.6.

[95% CI, 0.89-1.17]), but in former/current smokers we found higher risks (men: HR, 1.12 [95% CI, 1.05-1.19]; women: HR, 1.11 [95% CI, 1.02-1.21]). Intriguingly, there was increased risk with higher intake of white meat for CVD mortality in never smokers (men: HR, 1.24 [95% CI, 1.10-1.40]; women: HR, 1.20 [95% CI, 1.03-1.41]).

We calculated the population attributable risks, representing the percentage of deaths that could be prevented if individuals adopted red or processed meat intake levels of participants within the first quintile. For overall mortality, 11% of deaths in men and 16% of deaths in women could be prevented if people decreased their red meat consumption to the level of intake in the first quintile. The impact on CVD mortality was an 11% decrease in men and a 21% decrease in women if the red meat consumption was decreased to the amount consumed by individuals in the first quintile. The median red meat consumption based on men and women in the first quintile was 9.8 g/1000 kcal/d compared with 62.5 g/1000 kcal/d in the fifth quintile. For women eating processed meat at the first quintile level, the decrease in CVD mortality was approximately 20%. The median processed meat consumption based on men and women in the first quintile was 1.6 g/1000 kcal/d compared with 22.6 g/1000 kcal/d in the fifth quintile.

COMMENT

We examined total and cause-specific mortality in relation to meat consumption in a large prospective study. We found modest increases in risk for total mortality, as well as cancer and CVD mortality, with higher intakes of red and processed meat in both men and women. In contrast, higher white meat consumption was associated with a small decrease in total and cancer mortality in men and women.

The principal strength of this study is the large size of the cohort, which provided us the ability to investigate the relationship of many deaths (47 976 male deaths and 23 276 female deaths) within the context of a single study with a standardized protocol and a wide range of meat consumption. In contrast, other reports investigating meat intake in relation to mortality have pooled data from different studies conducted in California, the United Kingdom, and Germany because the numbers of events were limited in each study.[1-6,9-14] The protocols and questionnaires in these studies were different, as were the populations: Seventh-Day Adventists in California and vegetarians and nonvegetarians in Europe. Pooled analyses of specialized populations with distinct healthy lifestyles are subject to unmeasured confounding. Further-

Table 3. Multivariate Analysis Red, White, and Processed Meat Intake and Total and Cause-Specific Mortality in Women in the National Institutes of Health–AARP Diet and Health Study[a]

Mortality in Women (n=223 390)	Quintile					*P* Value for Trend
	Q1	Q2	Q3	Q4	Q5	
Red Meat Intake[b]						
All mortality						
Deaths	5314	5081	4734	4395	3752	
Basic model[c]	1 [Reference]	1.11 (1.07-1.16)	1.24 (1.20-1.29)	1.43 (1.38-1.49)	1.63 (1.56-1.70)	<.001
Adjusted model[d,e]	1 [Reference]	1.08 (1.03-1.12)	1.17 (1.12-1.22)	1.28 (1.23-1.34)	1.36 (1.30-1.43)	<.001
Cancer mortality						
Deaths	2134	1976	1784	1687	1348	
Basic model[c]	1 [Reference]	1.07 (1.01-1.14)	1.15 (1.08-1.23)	1.34 (1.26-1.43)	1.42 (1.33-1.52)	<.001
Adjusted model[d,e]	1 [Reference]	1.02 (0.96-1.09)	1.06 (1.00-1.14)	1.20 (1.12-1.28)	1.20 (1.12-1.30)	<.001
CVD mortality						
Deaths	1173	1155	1101	1027	900	
Basic model[c]	1 [Reference]	1.15 (1.06-1.25)	1.32 (1.22-1.44)	1.54 (1.41-1.68)	1.82 (1.66-1.98)	<.001
Adjusted model[d,e]	1 [Reference]	1.13 (1.04-1.23)	1.26 (1.16-1.37)	1.39 (1.27-1.52)	1.50 (1.37-1.65)	<.001
Mortality from injuries and sudden deaths						
Deaths	129	97	74	76	61	
Basic model[c]	1 [Reference]	0.86 (0.66-1.12)	0.77 (0.58-1.03)	0.96 (0.72-1.28)	1.01 (0.74-1.37)	.88
Adjusted model[d,e]	1 [Reference]	0.85 (0.65-1.12)	0.75 (0.56-1.02)	0.92 (0.68-1.25)	0.94 (0.68-1.31)	.88
All other deaths						
Deaths	1178	1187	1181	1058	961	
Basic model[c]	1 [Reference]	1.18 (1.09-1.28)	1.41 (1.30-1.53)	1.58 (1.45-1.72)	1.91 (1.76-2.09)	<.001
Adjusted model[d,e]	1 [Reference]	1.16 (1.07-1.26)	1.35 (1.24-1.47)	1.44 (1.32-1.57)	1.61 (1.46-1.76)	<.001
White Meat Intake[f]						
All Mortality						
Deaths	5006	4606	4469	4520	4675	
Basic model[c]	1 [Reference]	0.87 (0.84-0.91)	0.81 (0.78-0.84)	0.78 (0.75-0.81)	0.76 (0.73-0.79)	<.001
Adjusted model[d,e]	1 [Reference]	0.96 (0.92-1.00)	0.94 (0.90-0.98)	0.95 (0.91-0.99)	0.92 (0.88-0.96)	<.001
Cancer mortality						
Deaths	1887	1757	1728	1735	1822	
Basic model[c]	1 [Reference]	0.89 (0.83-0.95)	0.84 (0.78-0.90)	0.80 (0.75-0.85)	0.78 (0.73-0.83)	<.001
Adjusted model[d,e]	1 [Reference]	0.94 (0.88-1.01)	0.92 (0.86-0.99)	0.92 (0.86-0.98)	0.89 (0.83-0.95)	.001
CVD mortality						
Deaths	1107	1007	1090	1049	1103	
Basic model[c]	1 [Reference]	0.86 (0.79-0.93)	0.89 (0.82-0.97)	0.82 (0.75-0.89)	0.81 (0.75-0.88)	<.001
Adjusted model[d,e]	1 [Reference]	0.97 (0.89-1.06)	1.07 (0.98-1.17)	1.05 (0.96-1.14)	1.04 (0.96-1.14)	.19
Mortality from injuries and sudden deaths						
Deaths	89	81	92	86	89	
Basic model[c]	1 [Reference]	0.92 (0.68-1.25)	1.01 (0.75-1.35)	0.89 (0.66-1.20)	0.82 (0.61-1.10)	.17
Adjusted model[d,e]	1 [Reference]	0.96 (0.71-1.31)	1.09 (0.81-1.47)	0.99 (0.73-1.34)	0.91 (0.67-1.24)	.52
All other deaths						
Deaths	1319	1155	1016	1055	1020	
Basic model[c]	1 [Reference]	0.82 (0.76-0.89)	0.69 (0.64-0.75)	0.68 (0.63-0.74)	0.63 (0.58-0.68)	<.001
Adjusted model[d,e]	1 [Reference]	0.93 (0.86-1.01)	0.84 (0.77-0.91)	0.88 (0.82-0.96)	0.82 (0.75-0.89)	<.001

(continued)

more, recall bias and reverse causality were minimized in our study because diet was assessed prior to the diagnosis of the conditions that led to death.

There is a possibility that some residual confounding by smoking may remain; however, we used a detailed 31-level smoking history variable and repeated the analyses within smoking status strata. Within smoking subgroups, we found consistent results for red, white, and processed meat intakes; however, there were some intriguing differences that could be further investigated. We found a positive association for processed meat intake and cancer mortality among former/current smokers but not among never smokers. This may be because we were still not able to fully statistically adjust for residual confounding of smoking because people who eat processed meat may also smoke. An additional reason could be that in addition to being exposed to *N*-nitroso compounds from processed meats, smokers inhale carcinogenic chemicals. The possible reason why there was an increased risk with white meat consumption among never smokers is not readily apparent.

Because our cohort was predominantly non-Hispanic white, more educated, consumed less fat and red meat and more fiber and fruits and vegetables, and had fewer current smokers than similarly aged adults in the US population, caution should be applied when attempting to generalize our findings to other populations,[7] although this caution is somewhat tempered because it is unlikely that the mechanisms relating meat to mortality differ quantitatively between our study population and other white populations older than 50 years.

Table 3. Multivariate Analysis Red, White, and Processed Meat Intake and Total and Cause-Specific Mortality in Women in the National Institutes of Health–AARP Diet and Health Study[a] (continued)

Mortality in Women (n=223 390)	Quintile					*P* Value for Trend
	Q1	Q2	Q3	Q4	Q5	
Processed Meat Intake[g]						
All mortality						
Deaths	5624	5133	4525	4181	3813	
Basic model[c]	1 [Reference]	1.13 (1.09-1.17)	1.20 (1.15-1.25)	1.35 (1.29-1.40)	1.49 (1.43-1.56)	<.001
Adjusted model[d,e]	1 [Reference]	1.07 (1.03-1.12)	1.11 (1.06-1.15)	1.20 (1.15-1.25)	1.25 (1.20-1.31)	<.001
Cancer mortality						
Deaths	2283	2035	1722	1550	1339	
Basic model[c]	1 [Reference]	1.08 (1.02-1.15)	1.10 (1.04-1.18)	1.21 (1.13-1.30)	1.28 (1.19-1.37)	<.001
Adjusted model[d,e]	1 [Reference]	1.03 (0.97-1.10)	1.02 (0.96-1.09)	1.10 (1.02-1.17)	1.11 (1.04-1.19)	.001
CVD mortality						
Deaths	1245	1132	1039	973	967	
Basic model[c]	1 [Reference]	1.13 (1.04-1.22)	1.25 (1.14-1.35)	1.41 (1.29-1.54)	1.69 (1.55-1.84)	<.001
Adjusted model[d,e]	1 [Reference]	1.08 (0.99-1.17)	1.15 (1.05-1.25)	1.24 (1.13-1.35)	1.38 (1.26-1.51)	<.001
Mortality from injuries and sudden deaths						
Deaths	118	115	71	71	62	
Basic model[c]	1 [Reference]	1.22 (0.94-1.59)	0.91 (0.67-1.23)	1.10 (0.82-1.50)	1.18 (0.86-1.62)	.52
Adjusted model[d,e]	1 [Reference]	1.21 (0.93-1.57)	0.89 (0.65-1.21)	1.06 (0.78-1.45)	1.10 (0.80-1.53)	.83
All other deaths						
Deaths	1265	1174	1101	1055	970	
Basic model[c]	1 [Reference]	1.16 (1.07-1.26)	1.32 (1.22-1.44)	1.54 (1.42-1.68)	1.72 (1.58-1.87)	<.001
Adjusted model[d,e]	1 [Reference]	1.11 (1.02-1.20)	1.22 (1.12-1.32)	1.35 (1.24-1.47)	1.39 (1.27-1.51)	<.001

Abbreviations: AARP, formerly the American Association of Retired Persons; CVD, cardiovascular disease.

[a] Data are given as hazard ratio (95% confidence interval) unless otherwise specified.

[b] Median red meat intake based on men and women (g/1000 kcal): Q1, 9.8; Q2, 21.4; Q3, 31.3; Q4, 42.8; and Q5, 62.5.

[c] Basic model: age (continuous); race (non-Hispanic white, non-Hispanic black, Hispanic/Asian/Pacific Islander/American Indian/Alaskan native, or unknown); and total energy intake (continuous).

[d] Adjusted model: basic model plus education (<8 years or unknown, 8-11 years, 12 years [high school], some college, or college graduate); marital status (married: yes/no); family history of cancer (yes/no) (cancer mortality only); body mass index (18.5 to <25, 25 to <30, 30 to <35, ≥35 [calculated as weight in kilograms divided by height in meters squared]); 31-level smoking history using smoking status (never, former, current), time since quitting for former smokers, and smoking dose; frequency of vigorous physical activity (never/rarely, 1-3 times/mo, 1-2 times/wk, 3-4 times/wk, ≥5 times/wk); alcohol intake (none, 0 to <5, 5 to <15, 15 to <30, ≥30 servings/1000 kcal), vitamin supplement user (≥1 supplement/mo); fruit consumption (0 to <0.7, 0.7 to <1.2, 1.2 to <1.7, 1.7 to <2.5, ≥2.5 servings/1000 kcal); and vegetable consumption (0 to <1.3, 1.3 to <1.8, 1.8 to <2.2, 2.2 to <3.0, ≥3.0 serving/1000 kcal).

[e] Hormone therapy included in models for women.

[f] Median white meat intake based on men and women (g/1000 kcal): Q1, 9.5; Q2, 18.4; Q3, 27.4; Q4, 39.4; and Q5, 64.6.

[g] Median processed meat intake based on men and women (g/1000 kcal): Q1, 1.6; Q2, 4.4; Q3, 7.4; Q4, 12.2; and Q5, 22.6.

Furthermore, the population-attributable risks in our cohort may be conservative estimates because red and processed meat consumption may be higher in the general population than in our cohort.

The inherent limitations of measurement error in this study are similar to those of any nutritional epidemiologic study that is based on recall of usual intake over a given period. We attempted to reduce measurement error by adjusting our models for reported energy intake.[15] The correlations for red meat consumption assessed from the food frequency questionnaire compared with two 24-hour recall diaries were 0.62 for men and 0.70 for women, as reported previously by Schatzkin et al.[7] The problem of residual confounding may still exist and could explain the relatively small associations found throughout this study despite the care taken to adjust for known confounders.

Overall, we did not find statistically significant association between meat consumption and deaths from injury and sudden deaths in most instances. The relative HRs of meat consumption with the other causes of death (total, cancer, and CVD mortality) were similar in magnitude in some cases to those of deaths from injury and sudden deaths; however, the number of deaths from injury and sudden deaths was less than the other causes of deaths, and thus the HRs were generally not statistically significant. We observed a higher risk with the category that included "all other deaths"; this is a broad category with many heterogeneous conditions (eg, diabetes mellitus, Alzheimer disease, stomach and duodenal ulcers, chronic liver disease, cirrhosis, nephritis, nephrotic syndrome, and nephrosis), some of which may be positively related to meat intake.

There are various mechanisms by which meat may be related to mortality. In relation to cancer, meat is a source of several multisite carcinogens, including heterocyclic amines and polycyclic aromatic hydrocarbons,[16-21] which are both formed during high-temperature cooking of meat, as well as *N*-nitroso compounds.[22,23] Iron in red meat may increase oxidative damage and increase the formation of *N*-nitroso compounds.[24-27] Furthermore, meat is a major source of saturated fat, which has been positively associated with breast[28-30] and colorectal cancer.[31]

In relation to CVD, elevated blood pressure has been shown to be positively associated with higher intakes of red and processed meat, even though the mechanism is unclear, except that possibly meat may substitute for other beneficial foods such as grains, fruits, or vegetables.[32] Mean

plasma total cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and triglyceride levels were found to be decreased in subjects who substituted red meat with fish.[33,34] Vegetarians have lower arachidonic, eicosapentaenoic, and docosahexaenoic acid levels and higher linoleate and antioxidant levels in platelet phospholipids; such a biochemical profile may be related to decreased atherogenesis and thrombogenesis.[34-36]

Red and processed meat intakes, as well as a high-risk meat diet, were associated with a modest increase in risk of total mortality, cancer, and CVD mortality in both men and women. In contrast, high white meat intake and a low-risk meat diet was associated with a small decrease in total and cancer mortality. These results complement the recommendations by the American Institute for Cancer Research and the World Cancer Research Fund to reduce red and processed meat intake to decrease cancer incidence.[31] Future research should investigate the relation between subtypes of meat and specific causes of mortality.

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Correction

Error in Text. In the Original Investigation titled "Oregonians' Reasons for Requesting Physician Aid in Dying" by Ganzini et al, published in the March 9 issue of the *Archives* (2009;169[5]:489-492), an error occurred in the text on page 490. In the first paragraph of the "Results" section, the last sentence should have appeared as follows: "At death, 18 (44%) had received a prescription for medication under the ODDA, and 9 (22%) died by lethal ingestion." Online versions of this article on the *Archives of Internal Medicine* Web site were corrected on March 9, 2009.