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Red meat consumption and risk of heart failure in male physicians

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Abstract

Background and Aims—Heart failure (HF) remains a major public health issue. Red meat and dietary heme iron have been associated with an increased risk of coronary heart disease and hypertension, two major risk factors for HF. However, it is not known whether red meat intake influences the risk of HF. We therefore examined the association between red meat consumption and incident HF.

Methods and Results—We prospectively studied 21,120 apparently healthy men (mean age 54.6 y) from the Physicians' Health Study (1982–2008). Red meat was assessed by an abbreviated food questionnaire and incident HF was ascertained through annual follow-up questionnaires. We used Cox proportional hazard models to estimate hazard ratios. In a multivariable model, there was a positive and graded relation between red meat consumption and HF [hazard ratio (95% CI) of 1.0 (reference), 1.02 (0.85–1.22), 1.08 (0.90–1.30), 1.17 (0.97–1.41), and 1.24 (1.03–1.48) from the lowest to the highest quintile of red meat, respectively (p for trend 0.007)]. This association was observed for HF with (p for trend 0.035) and without (p for trend 0.038) antecedent myocardial infarction.

Conclusion—Our data suggest that higher intake of red meat is associated with an increased risk of HF.

Keywords

Epidemiology; diet; red meat; heart failure

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None to disclose

Introduction

Heart failure (HF) is a condition that could result from heterogeneous factors, including myocardial damage, heart valve pathology, dysregulation in volume homeostasis, hormonal changes, etc. The lifetime risk of HF is estimated at 20% (1 in 5) for both men and women aged 40 years[1]. HF is the leading cause of hospitalization among elderly people in the United States[2]. About 4.9 million Americans are affected with this condition and HF costs were estimated at 27.9 billion dollars for 2005 in the US[3]. Once diagnosed, mortality after onset of HF is very high[4–6], ranging from 20% to 50%[7–10]. Given the poor prognosis after onset of HF, it is important to identify preventable determinants of this condition. To this end, dietary factors may play an important role. While previous studies have reported detrimental effects of dietary heme iron and red meat on coronary heart disease[11], hypertension[12–14], or type 2 diabetes[15], no previous study has examined whether intake of red meat is associated with an increased risk of HF in a large population. Red meat is an integral part of the Western diet ranging from hotdogs, steak, to other meat dishes. Besides iron, red meat is a source of cholesterol and saturated fatty acids which have been shown to promote atherosclerosis and subsequent cardiovascular diseases. Therefore, we are hypothesizing that frequent consumption of red meat will be associated with an increased risk of HF in general and independent of antecedent myocardial infarction. In the current paper, we used data from the Physicians' Health Study to test above hypotheses.

Methods

Study population

We used data from the Physicians' Health Study (PHS) 1- a completed randomized, double blind, placebo-controlled trial designed to study low-dose aspirin and beta-carotene for the primary prevention of cardiovascular disease and cancer among US male physicians. A detailed description of the PHS I has been published[16]. Of the total 22,071 participants, we excluded 488 subjects with missing data on red meat consumption obtained 1 year after randomization, 27 cases of prevalent HF, and 436 subjects with missing covariates or loss of follow-up before 12 months. Thus, a final sample of 21,120 participants was used for the current analyses. Each participant gave written and informed consent and the institutional Review Board at Brigham and Women's Hospital approved the study protocol.

Red Meat Consumption

Information on red meat consumption was self-reported using a simple abbreviated semi-quantitative food frequency questionnaire (19 items) at 12 months after randomization (1983–1985). Participants were asked to report how often on average over the past 12 months they have consumed beef, pork, or lamb as main dish (steak, roast, ham, etc); beef, pork, or lamb as a sandwich or mixed dish; and hot dogs. Pre-specified responses were “rarely/never”, “1–2/month”, “1/week”, “2–4/week”, “5–6/week”, “daily”, and “2+/day”. We summed up the responses provided on above 3 items to create a red meat score for each subject.

Ascertainment of Incident heart failure in the PHS

Ascertainment of outcomes in PHS including HF, has been obtained through yearly questionnaires, and has been previously described[17]. Specifically, a questionnaire was mailed to each participant every 6 months during the first year and annually thereafter. In a subset of these physicians, the HF diagnoses had been previously confirmed with the use of the Framingham criteria[18]. In addition, we also assessed the validity of self-reported incident HF by reviewing medical records of subjects with a diagnosis of HF that occurred up to 30 days before a hospitalization for myocardial infarction or stroke. Two physicians

(one general internist and a cardiologist) independently reviewed 55 charts that met the above criteria. A diagnosis of HF was made if there was sufficient evidence in the chart; this included a) a diagnosis of HF on the discharge summary, b) major signs and symptoms from the Framingham criteria for a HF diagnosis, c) chest X-ray evidence for congestive HF, d) minor signs and symptoms with concomitant treatment for HF (use of diuretics, digoxin in the absence of atrial fibrillation, angiotensin converting-enzyme inhibitors, angiotensin receptor blockers, and beta-blockers). Lastly, assessment of left ventricular function via echocardiography or cardiac catheterization (where available) was used to further substantiate the HF diagnosis. Using all of these criteria, HF was confirmed in 50 out of 55 cases (~91%). There was excellent agreement between the two examiners (kappa=92.3%) in that only 1 case of self-reported HF was confirmed by 1 of the 2 physicians. The latter case was then re-reviewed by both physicians who concluded that there was sufficient evidence for the HF diagnosis (a discharge summary indicating prevalent HF).

Other variables

At baseline, information on demographic variables, cigarette smoking, parental history of myocardial infarction, exercise, alcohol consumption, and anthropometric data was obtained through a questionnaire. Ascertainment of incident diabetes, hypertension, atrial fibrillation, valvular heart disease, diabetes mellitus, coronary heart disease (angina pectoris, myocardial infarction, coronary angioplasty, and coronary bypass surgery) was obtained through annual follow-up questionnaires. Information on selected foods including breakfast cereal, and fruits and vegetables has been collected at baseline and infrequently throughout follow up. For current analyses, any disease (i.e. diabetes, hypertension, atrial fibrillation, coronary disease, etc) occurred up to 12 months post-randomization was considered as prevalent disease and used in the multivariable analyses.

Statistical analyses

We created quintile of red meat intake and 4 indicator variables for the regression analyses. We computed person-time of follow up from exposure assessment (12 months post-randomization) until the first occurrence of (a) heart failure, (b) death, or (c) censoring date-date of receipt of last follow-up questionnaire. We used Cox proportional hazard models to compute multivariable adjusted hazard ratios with corresponding 95% confidence intervals using subjects in the lowest category as the comparison group. We controlled for confounding by established risk factors for heart failure or factors shown to be associated with heart failure in this cohort (i.e. breakfast cereal and alcohol intake). In the initial model, we adjusted only for age (continuous). A multivariable model also controlled for aspirin assignment, smoking, (never, past, current), alcohol consumption (<1, 1–4, 5–7, >7 drinks/week), cereal consumption (none, ≤ 1, 2–6, 7+/week), exercise (none, ≤ 1, 2–4, 5+/week), body mass index (< 25.0, 25.0–29.9, 30+ kg/m²), and parental history of MI prior to age 60 y. Lastly, we included possible intermediate factors such as type 2 diabetes, atrial fibrillation, hypertension, and coronary heart disease in the multivariable model. Assumptions for proportional hazard models, were tested (by including main effects and product terms of covariates and log-transformed time factor) and were met (all probability values >0.05). We computed p value for linear trend by creating a new variable that assigned the median intake of red meat in each quintile and then modeling the new variable in the multivariable Cox regression.

In secondary analyses, we examined the association between red meat consumption and HF with and without antecedent myocardial infarction using tertiles of red meat consumption for stable estimates. We also modeled red meat intake as continuous variable. Lastly, we excluded four subjects with reported meat consumption of more than 28 servings/week in a sensitivity analysis. We conducted sensitivity analysis restricting to subjects without

diabetes, hypertension, atrial fibrillation, coronary heart disease, or parental history of myocardial infarction (on exclusion at a time) and obtained similar results (data not shown). All analyses were completed with the 9.1 version of SAS (SAS Institute, Cary, NC). Significance level was set at 0.05.

Results

Characteristics of the 21,120 US male physicians obtained 12 months after randomization are presented in Table 1 according to red meat consumption. The mean age of study participants was 54.6 y at the time of red meat assessment. The median consumption of red meat was 4.5 servings per week in the population. (interquartile range 3.0 to 6.5 servings/week, 99th percentile 14.5 serving per week). During an average follow-up of 19.9 years, 1,204 (5.7%) new cases of HF occurred. From the lowest to highest category of red meat consumption, crude incidence rates of HF were 2.77, 2.73, 2.78, 2.82, and 3.30 cases per 1,000 person-years, respectively. Frequent red meat consumption was associated with higher body mass index, higher proportion of current smokers and diabetes, and lower proportion of angina pectoris.

In a multivariable Cox proportional hazard model, hazard ratio (95% CI) for HF were 1.0 (reference), 1.02 (0.85 to 1.22), 1.08 (0.90 to 1.30), 1.17 (0.97 to 1.41), and 1.24 (1.03 to 1.48), from the lowest to highest quintile of red meat intake, respectively, after adjustment for age, aspirin assignment, body mass index, smoking, exercise, alcohol intake, breakfast cereal, parental history of myocardial infarction, coronary heart disease, type 2 diabetes, hypertension, and atrial fibrillation (P for trend = 0.007, Table 2). When modeled as a continuous variable, there was a positive association between red meat consumption and incident HF [multivariable adjusted hazard ratio (95% CI): 1.02 (1.01–1.04), $p=0.006$]. Exclusion of 4 subjects with extreme values of red meat intake (> 28 servings/week) did not alter the results. We observed similar associations between red meat intake and HF with antecedent myocardial infarction (Table 3). Red meat intake was not associated with a meaningful increased (albeit statistically significant) risk of HF without antecedent myocardial infarction (Table 3).

Discussion

In this prospective cohort, we observed that red meat consumption was associated with an increased risk of HF among male physicians after adjustment for potential confounding factors. In addition we found similar relation between red meat intake and HF risk with antecedent myocardial infarction and only weak evidence for HF without prior myocardial infarction. To the best of our knowledge, this is the first study to evaluate the relationship between red meat consumption and HF risk in a large cohort.

While little is known about the relation between red meat intake and HF, previous studies have reported a positive relation between red meat consumption or heme iron and predictors of HF. In a prospective study of US female health professionals, Wang and colleagues[12] reported a positive and graded association between red meat intake and incident hypertension, a major risk factor for HF. Furthermore, prospective data from the CARDIA study reported a positive and graded relation between red meat intake and the risk of hypertension[19]. Other investigators have reported a positive association between red meat and hypertension[13;14;20] In addition, both heme iron and red meat have been associated with an increased risk of fatal coronary disease, coronary revascularization, and total coronary heart disease in subjects with diabetes[11]. Among men, a dietary pattern characterized by high intake of red meat, processed meat, refined cereals, high-fat dairy products was associated with an increased risk of coronary heart disease[21]. Data from the

Women's Health Study reported a positive association between red meat consumption and the risk of type 2 diabetes[15]. These findings on the relation between red meat and diabetes have been supported by other investigators[22–24].

As a source of saturated fat and dietary cholesterol, red meat may lead to the development of atherosclerosis and subsequent hypertension and coronary disease, two major risk factors for HF. In addition, dietary cholesterol has been shown to increase the risk of type 2 diabetes[25], suggesting that the relation between red meat and incident HF could also be partially mediated through abnormal glucose metabolism leading to diabetes. Of note is that diabetes is associated with two-to three-fold increased risk of HF[3;26;27]. Taken together, it is possible that the development of hypertension, coronary heart disease, and type 2 diabetes could be in the causal path between red meat consumption and incident HF. Such hypothesis would help to explain the observed relation between red meat consumption and HF risk.

Our study has some limitations. First, we can not eliminate residual confounding by unmeasured factors as alternative explanation of observed relations in the absence of random allocation of red meat. Second, we had only one exposure assessment and were not able to account for possible changes in red meat consumption patterns over time. Third, we did not have nutrient data and energy to further adjust for those potential confounders. Fourth, although food frequency questionnaire has been shown to be a reasonable tool to assess diet[28], we can not exclude reporting bias in our data. However, since red meat assessment preceded HF diagnosis, it is likely that such bias would have been non-differential and had led to an attenuation of the true effect. We did not have data on medications (i.e. diuretics or angiotensin-converting enzyme inhibitors) to control for treatment over time. Lastly, our subjects were male and mostly Caucasian physicians, thereby limiting the generalizability of our findings. Nevertheless, the large sample size, a valid ascertainment of HF cases, the availability of numerous confounding factors, and then long follow-up time are strengths of the current paper. If confirmed in other cohorts and general population, the implications of our data could include recommendation to reduce red meat intake as an additional dietary component of a healthy diet designed to prevent HF.

In conclusion, our data suggest that increased consumption of red meat is associated with a higher risk of incident HF among US male physicians. Further examination underlying mechanisms and of the relationship between red meat consumption and incident heart failure in the general population is warranted.

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Table 1

Characteristics of the 21,120 US male physicians at 12 months post-randomization according to quintile of red meat consumption.

Characteristics	Quintiles of red meat intake				
	Q1 (low) (N=4056)	Q2 (N=4659)	Q3 (N=4599)	Q4 (N=3980)	Q5 (high) (N=3826)
	Median* (Range) (0-2.0)	3.5 (2.5-4.0)	5.0 (4.5-6.0)	6.5 (6.5-7.0)	9.5 (7.5-42)†
Age (years)	55.5 ± 9.6	55.2 ± 9.7	54.5 ± 9.4	53.4 ± 9.1	54.4 ± 9.3
Body mass index (kg/m ²)	24.3 ± 2.6	24.6 ± 2.6	24.8 ± 2.8	25.0 ± 2.8	25.1 ± 3.0
Intake of breakfast cereal (%)	67.2	66.8	68.4	69.9	64.4
Current use of alcohol (%)	80.8	87.4	86.4	86.6	84.1
Current smokers (%)	7.0	10.1	11.2	12.4	14.6
Current exercise (%)	86.7	86.1	87.2	87.6	85.1
Myocardial infarction (%)	0.4	0.4	0.3	0.2	0.2
Parental history of MI (%)	10.0	9.5	9.2	9.4	8.5
Angina pectoris (%)	3.2	2.5	2.4	1.8	1.4
Coronary heart disease (%)	3.4	2.7	2.5	1.9	1.5
Hypertension (%)	24.1	24.8	23.6	22.5	25.3
Aspirin arm (%)	51.5	49.8	50.1	48.8	50.0
Atrial fibrillation (%)	1.8	1.7	1.7	1.8	1.8
Left ventricular hypertrophy (%)	0.4	0.1	0.2	0.2	0.4
Valvular heart disease (%)	0.3	0.4	0.3	0.3	0.3
Diabetes mellitus (%)	2.9	3.2	2.6	2.8	4.3

Data are presented as mean ± standard deviation or percentages; MI = myocardial infarction.

* Servings/week

Table 2

Incidence rate and hazard ratios (95% CI) of heart failure according to quintile of red meat consumption.

Quintile of red meat intake	Cases	Crude incidence rate (cases/1,000 PY)	Hazard Ratio (95% CI)		
			Model 1 [*]	Model 2 [†]	Model 3 [‡]
Q1 (low)	221	2.77	1.0	1.0	1.0
Q2	252	2.73	1.01 (0.85 – 1.22)	0.99 (0.82 – 1.19)	1.02 (0.85 – 1.22)
Q3	255	2.78	1.12 (0.93 – 1.34)	1.06 (0.89 – 1.27)	1.08 (0.90 – 1.30)
Q4	227	2.82	1.22 (1.01 – 1.47)	1.15 (0.95 – 1.39)	1.17 (0.97 – 1.41)
Q5 (high)	249	3.30	1.37 (1.14 – 1.64)	1.22 (1.02 – 1.47)	1.24 (1.03 – 1.48)
P for linear trend			<0.0001	0.008	0.007

^{*} Adjusted for age (continuous);

[†] Adjusted for age, aspirin assignment, smoking, (never, past, current), alcohol consumption (<1, 1–4, 5–7, >7 drinks/week), cereal consumption (none, ≤ 1, 2–6, 7+/week), parental history of MI prior to age 60 y, exercise (none, ≤ 1, 2–4, 5+/week) and body mass index (< 25.0, 25.0–29.9, 30+ kg/m²).

[‡] Adjusted for age, aspirin assignment, smoking, (never, past, current), alcohol consumption (<1, 1–4, 5–7, >7 drinks/week), cereal consumption (none, ≤ 1, 2–6, 7+/week), parental history of MI prior to age 60 y, exercise (none, ≤ 1, 2–4, 5+/week) and body mass index (< 25.0, 25.0–29.9, 30+ kg/m²), and prevalent diabetes, coronary heart disease, atrial fibrillation, and hypertension at 12 months post randomization.

Table 3

Hazard ratio (95% CI) of heart failure with/without antecedent myocardial infarction according to tertiles of red meat intake

Quintile of red meat intake	Heart failure with antecedent myocardial infarction		Heart failure without prior myocardial infarction	
	Cases	Hazard Ratio (95% CI) [*]	Cases	Hazard Ratio (95% CI) [†]
Q1 (low)	51	1.0	301	1.0
Q2	62	1.30 (0.89 – 1.88)	314	1.05 (0.90 – 1.23)
Q3 (high)	79	1.47 (1.03 – 2.10)	397	1.17 (1.01 – 1.36)
P for linear trend		0.035		0.038

* Adjusted for age (continuous);

[†] Adjusted for age, aspirin assignment, smoking, (never, past, current), alcohol consumption (<1, 1–4, 5–7, >7 drinks/week), cereal consumption (none, ≤ 1, 2–6, 7+/week), exercise (none, ≤ 1, 2–4, 5+/week), body mass index (< 25.0, 25.0–29.9, 30+ kg/m²), parental history of MI prior to age 60 y, and prevalence of diabetes mellitus, coronary heart disease, atrial fibrillation, and hypertension at the time of red meat assessment.