Differences in survival associated with processed and with nonprocessed red meat consumption[1–3]

Andrea Bellavia, Susanna C Larsson, Matteo Bottai, Alicja Wolk, and Nicola Orsini

ABSTRACT

Background: High red meat consumption is associated with an increased mortality risk. This association is partly explained by the negative effect of processed meat consumption, which is widely established. The role of nonprocessed meat is unclear.

Objective: The objective was to examine the combined association of processed and nonprocessed meat consumption with survival in a Swedish large prospective cohort.

Design: In a population-based cohort of 74,645 Swedish men (40,089) and women (34,556), red meat consumption was assessed through a self-administered questionnaire. We estimated differences in survival [15th percentile differences (PDs), differences in the time by which the first 15% of the cohort died] according to levels of total red meat and combined levels of processed and nonprocessed red meat consumption.

Results: During 15 y of follow-up (January 1998 to December 2012), we documented 16,683 deaths (6948 women; 9735 men). Compared with no consumption, consumption of red meat >100 g/d was progressively associated with shorter survival—up to 2 y for participants consuming an average of 300 g/d (15th PD: –21 mo; 95% CI: –31, –10). Compared with no consumption, high consumption of processed red meat (100 g/d) was associated with shorter survival (15th PD: –9 mo; 95% CI: –16, –2). High and moderate intakes of nonprocessed red meat were associated with shorter survival only when accompanied by a high intake of processed red meat.

Conclusions: We found that high total red meat consumption was associated with progressively shorter survival, largely because of the consumption of processed red meat. Consumption of nonprocessed red meat alone was not associated with shorter survival. The Swedish Mammography Cohort and the Cohort of Swedish Men were registered at clinicaltrials.gov as NCT01127698 and NCT01127711, respectively. *Am J Clin Nutr* 2014;100:924–9.

INTRODUCTION

High red meat consumption is associated with an increased risk of various chronic diseases, such as cardiovascular disease (CVD) (1–4), certain cancers (2, 4–7), and diabetes (1). In recent years, large population-based studies have also documented an association between red meat consumption and mortality for all causes (2, 4, 8, 9), which was summarized in a recent meta-analysis (10).

The total intake of red meat is usually analyzed by dividing meat into processed and nonprocessed (fresh) meat consumption, which might have a different biological effect on health. Whereas the negative influence of processed meat consumption is well established (11), the role of nonprocessed meat is unclear. Recent studies have suggested that fresh meat consumption might be associated with higher mortality (2, 4, 9), whereas other have reported no association (8, 10, 12). These studies present the association between nonprocessed meat and mortality, eventually adjusting for processed meat consumption. To the best of our knowledge, no studies have evaluated the joint association of processed and nonprocessed meat consumption in predicting mortality.

The association between red meat consumption and mortality has been solidly established in terms of mortality risk or rate (10). A further contribution to current knowledge may be obtained by evaluating the association between meat consumption and mortality in terms of time by which a certain fraction of the general population dies. This approach is notably interesting in evaluating mortality, because it expresses results directly in terms of survival percentiles, facilitating both interpretation and communication of results (13). In a large population cohort of Swedish men and women, we evaluated differences in survival across levels of total red meat consumption and combined levels of processed and nonprocessed meat consumption.

SUBJECTS AND METHODS

Study population

This study incorporated participants from the population-based Swedish Mammography Cohort and the Cohort of Swedish Men. The Swedish Mammography Cohort was established between 1987 and 1990 in Västmanland and Uppsala counties (central Sweden). All women born between 1918 and 1948 received an invitation to participate in the study, together with a self-administrated questionnaire consisting of questions regarding diet, alcohol consumption, education, body weight, and

[1] From the Unit of Nutritional Epidemiology (AB, SCL, AW, and NO) and the Unit of Biostatistics (AB, MB, and NO), Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

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[3] Address correspondence to A Bellavia, Institute of Environmental Medicine, Karolinska Institutet, PO Box, SE-171 77, Stockholm, Sweden. E-mail: andrea.bellavia@ki.se.

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height. In the late fall of 1997, a second questionnaire was sent to all alive participants still residing in the study area. This second questionnaire included all previous items together with additional questions regarding smoking status, physical activity, and other lifestyle factors. The 39,227 women who returned this second questionnaire were included in the current study. The Cohort of Swedish Men recruited participants residing in Västmanland and Örebro counties (central Sweden) in 1997. All men were invited to participate in the study and received a self-administrated questionnaire with questions regarding diet, alcohol consumption, education, body weight, height, physical activity, smoking habits, and other lifestyle factors. A total of 48,850 men returned the questionnaire.

In this study we excluded participants who reported incorrect national personal identification numbers or did not report their personal number on the questionnaire (n = 540), those who died before the start of follow-up (n = 97), and those with any history of CVD (n = 6994) or cancer (n = 4390). We also excluded participants who reported an unlikely extreme value of total energy intake (3 SDs from the $\log_e$-transformed mean energy intake, n = 709) and those with unlikely high daily red meat consumption (>300 g/d; n = 305) or missing information on red meat consumption (n = 397). After these exclusions, a total of 74,645 participants (40,089 men and 34,556 women) were included in the study. This study was approved by the Regional Research Ethics Board at Karolinska Institutet, and all participants gave their informed consent.

Red meat consumption assessment

Diet was assessed with a 96-item food-frequency questionnaire. Total red meat intake (in g/d) was calculated by combining information on amount and frequency of consumption of different types of red meat. The relations between a certain portion size and the relative amount in grams were different according to the type of red meat and the participant's age. Participants were asked to report how often, on average, they had consumed various types of processed and nonprocessed red meat items over the previous year, with 8 predefined frequency categories ranging from "never" to "3 or more times per day." Nonprocessed red meat included fresh and minced pork, beef, and veal. Processed red meat included sausages, hot dogs, salami, ham, processed meat cuts, liver pâté, and blood sausage.

Case ascertainment and follow-up

During 15 y of follow-up, between 1 January 1998 and 31 December 2012, we documented 16,683 deaths (6948 women and 9735 men). Deaths were assessed through linkage to the Swedish Cause of Death Register at the National Board of Health and Welfare. In Sweden, 93% of deaths are reported within 10 d, and 100% are reported within 1 mo (14).

Statistical analysis

The association between red meat consumption and mortality was evaluated in terms of survival percentile differences (PDs) (13). Survival time was defined as the time between entry into the study and either death or the end of follow-up, whichever came first. During 15 y of follow-up, 20% of the study population died. To limit data extrapolation in the multivariable analyses, we focused our main analysis on the 15th survival percentile (ie, the time by which the first 15% of the population has died) and evaluated differences in survival (15th PD) according to levels of red meat consumption. Multivariable adjusted differences in survival percentiles were estimated with Laplace regression (13, 15, 16).

We adjusted our multivariable models for baseline age (<50, 50–54, 55–59, 60–64, 65–69, 70–74, and ≥75 y), sex (male or female), BMI (in kg/m^2; <25, 25–29, or ≥30), total physical activity (metabolic equivalent hours/d, quartiles), smoking status (current ≥40, current 20–39, current <20, former ≥40, former 20–39, former <20, or never), alcohol consumption (never drinker or <5, 5–10, 10.1–20, or >20 g/d), energy intake (continuous variable; kcal/d), educational level (primary school, high school, or university), fruit consumption (servings/d, quartiles), vegetables consumption (servings/d, quartiles), fish consumption (g/d, quartiles), and prevalence of diabetes (yes or no). In multivariable analyses, missing data were handled by performing a complete case analysis.

We evaluated baseline age-standardized characteristics of the study population by 5 equally sized groups of total red meat consumption. To evaluate the possible dose-response association between our exposures and the 15th survival percentile, we introduced red meat consumption as a continuous predictor by means of restricted cubic splines, with 3 kn placed at fixed percentiles of the distribution (31, 77, and 140.5 g/d). No consumption of red meat was used as a referent value for all analyses. Linearity of the dose-response association was evaluated by testing the null hypothesis that the coefficient of the second spline is equal to zero (17).

To allow comparison with previous studies on red meat consumption in relation to mortality, we also estimated HRs of death according to levels of total red meat consumption. HRs were estimated by using Cox proportional-hazards regression models with the same splines variables and confounders as included in the Laplace model. Assumption of proportionality of the hazards was tested by calculating Schoenfeld residuals, regressed against survival time, and tested for a nonzero slope. We found no evidence of departure from this assumption.

Our main model was next replicated in the following series of sensitivity analyses. To evaluate whether results were influenced by the choice of the 15th percentiles, we repeated the analysis estimating differences in the 5th and 10th percentiles. To reduce the potential effect of undiagnosed diseases on meat consumption, we evaluated the main analysis excluding those participants who died in the first 3 y of follow-up (n = 1411). To evaluate any sex difference in the dose-response association, we performed our main analysis separately for men and women. Another sensitivity analysis was to further adjust for family history of chronic diseases (ie, cancer or CVD events for parents or siblings), included as a dichotomous variable. Furthermore, we redefined the continuous exposure of total red meat excluding the consumption of liver pâté and blood sausage, which are based on blood rather than muscles and might have a different nutrient effect.

We next evaluated, in a mutually adjusted model, the 2 continuous variables of processed and nonprocessed red meat consumption, and presented the marginal dose-response of the 2 exposures. Both variables were flexibly modeled with restricted cubic splines with 3 kn of the distribution (at 8.5, 30.5, and 62.5 g/d

for processed meat and at 14, 44, and 88.5 g/d for nonprocessed meat).

To evaluate the joint association of processed and nonprocessed meat consumption in predicting survival, we included in the model the interaction terms of the 2 exposures. An overall *P* value for statistical interaction was obtained by testing the 4 regression coefficients of the interaction terms between splines (2 cubic splines for processed meat multiplied by 2 cubic splines for nonprocessed meat) jointly equal to 0. In this analysis, to maximize the number of subjects in the comparison group, participants with a median consumption of processed and nonprocessed red meat (30.6 and 44.5 g/d, respectively) were used as reference groups. Tabular presentation of 15th PDs and 95% CIs according to different levels of the exposures (25th, 50th, 75th, and 95th percentiles of the 2 distributions) was reported.

Cox regression models were also estimated for the separate exposures of processed and nonprocessed red meat and the combined model. The observed results were consistent with the results presented in terms of survival and are available under "Supplemental data" in the online issue. Statistical analyses were performed with Stata (version 13; StataCorp). All statistical tests were 2-sided, and *P* values <0.05 were considered statistically significant.

RESULTS

Age-standardized baseline characteristics of the study population by quintiles of red meat consumption are shown in **Table 1**. Men had a considerably higher consumption of red meat. Participants in the lowest quintile of red meat consumption were on average older, had lower fish consumption, and had lower energy intakes. Prevalence of diabetes was slightly higher among those in the highest group of red meat consumption. BMI, physical activity, smoking status, alcohol consumption, education, and fruit and vegetable consumption were similar across red meat consumption groups.

We flexibly modeled the dose-response association between total red meat consumption and the 15th survival percentile by evaluating the exposure as continuous and using restricted cubic splines (**Figure 1**). This analysis was also performed for mortality rates, and a tabular presentation of HRs and PDs according to levels of total red meat consumption is reported in **Table 2**. We observed a significant departure from linearity (*P* value $<$ 0.001). Compared with participants who never consumed red meat, moderate consumption up to 100 g/d was not significantly associated with shorter or longer survival. A red meat intake $>$100 g/d was progressively associated with shorter survival and a higher mortality rate. Compared with participants who never consumed red meat, those consuming 200 g/d lived about 1 y less (15th PD: −10 mo; 95% CI: −18, −3) and had a higher mortality rate (HR: 1.26; 95% CI: 1.14, 1.40). Increased consumption up to 300 g/d was associated with a shorter survival of almost 2 y (15th PD: −21 mo; 95% CI: −31, −10) and a 50% increased mortality rate (HR: 1.49; 95% CI: 1.27, 1.75).

We assessed whether our results were influenced by the choice of the 15th percentile by replicating the main analysis at the 5th and 10th percentiles. Differences in the fifth survival percentile, which reflect early deaths, were slightly attenuated and presented higher variability (200 compared with 0 g total red meat/d: 15th PD: –7 mo; 95% CI: –17, 2). Instead, the results for the 10th percentile were similar to those for the 15th percentile (200 g/d compared with 0 g total red meat/d: 15th PD: −10 mo; 95% CI: −18, −2). In the second sensitivity analysis, we repeated the main analysis excluding cases occurring in the first 3 y of follow-up. No changes in the estimates were observed, showing that results are unlikely influenced by potential residual

TABLE 1
Age-standardized baseline characteristics by quintiles of red meat consumption in 45- to 79-y-old Swedish men and 48- to 83-y-old Swedish women

	Quintiles of daily red meat consumption (g/d)[2]				
Characteristics[1]	<46 (31)	46.1–67.0 (57)	67.1–88.0 (77)	88.1–117.0 (101)	>117 (140)
No. of subjects	14,932	14,928	14,928	14,944	14,913
Female (%)	70	66	55	29	12
Mean age at baseline (y)	63.6	62.1	60.2	58.5	57.0
Mean BMI (kg/m^2)	25.0	25.2	25.3	25.5	25.7
Total physical activity (MET[3])	42.3	42.2	42.0	41.8	41.8
Smoking status (%)					
Current	24	23	22	24	25
Former	27	29	30	33	36
Never	49	48	48	43	39
Alcohol consumption (%)					
Current	82	86	87	89	89
Former	6	4	4	3	3
Never	12	10	9	8	8
Education (%)					
High school/university	29	27	27	28	28
Diabetes (%)	4	4	5	5	7
Fruit and vegetable consumption (servings/d)	4	5	5	4	5
Fish consumption (g/d)	17	19	21	22	25
Energy intake (kcal/d)	1745	1929	2155	2471	2873

[1] All factors except age were directly standardized to the age distribution of the entire study cohort (n = 74,645).
[2] Medians in parentheses.
[3] MET, metabolic equivalent.

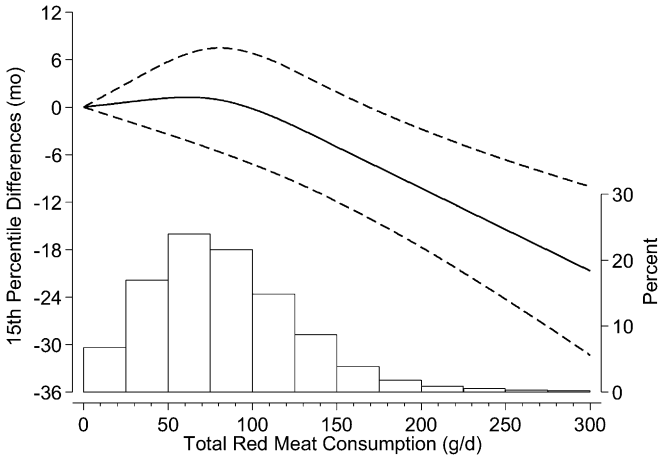

FIGURE 1. Fifteenth percentile differences (differences in months by which 15% of the cohort has died, with 95% CIs) as a function of total red meat consumption. Estimates were obtained by fitting a multivariable Laplace regression and adjusting for baseline age, sex, BMI, total physical activity, smoking status, alcohol consumption, energy intake, educational level, fruit consumption, vegetable consumption, fish consumption, and prevalence of diabetes. Significant divergence from linearity was observed ($P < 0.001$), and red meat consumption was associated with shorter survival for an intake >100 g/d. The histogram shows the percentage of population participants consuming each level of red meat consumption.

confounding due to undiagnosed diseases (200 compared with 0 g total red meat/d: 15th PD: –9 mo; 95% CI: –15, –2). The shape of the dose response was remarkably similar between men and women. Inclusion of family history of chronic diseases among the predictors did not affect the main results (200 compared with 0 g total red meat/d: 15th PD: –10 mo; 95% CI: –17, –3). No substantial differences were finally observed when excluding liver pâté and blood sausage consumption from the main exposure of total red meat (200 compared with 0 g/d: 15th PD: –12 mo; 95% CI: –12, –4).

We next divided total red meat consumption into processed and nonprocessed and estimated differences in survival according to levels of consumption of the 2 different exposures, evaluated as continuous variables and flexibly modeled with restricted cubic splines (**Figure 2**; *see* Supplemental Table 1 under "Supplemental data" in the online issue). Increased consumption of processed red meat was associated with progressively shorter survival. Compared with participants with no consumption, 100 g processed red meat/d intake was associated with 9 mo of shorter survival (15th PD: –9 mo; 95% CI: –16, –2) (Figure 2A). We did not observe significant differences in survival across the distribution of nonprocessed red meat consumption (Figure 2B).

We finally investigated the joint effect of processed and nonprocessed meat in predicting survival (**Table 3**; *see* Supplemental Figure 1 under "Supplemental data" in the online issue). Although the interaction between the 2 exposures was not statistically significant (P-interaction = 0.6), the association between nonprocessed red meat consumption and survival was substantially different across levels of processed red meat intake. In comparison with those with a median consumption of processed and nonprocessed meat, a higher intake of nonprocessed meat was associated with shorter survival only if combined with a higher consumption of processed meat (when consuming 100 g/d of both processed and nonprocessed meat: 15th PD: –19 mo; 95% CI: –37, –2). High processed meat consumption was instead associated with shorter survival regardless of the consumption of nonprocessed meat. The same analysis performed in terms of Cox regression showed consistent results (*see* Supplemental Table 2 under "Supplemental data" in the online issue).

TABLE 2
Multivariable-adjusted 15th survival PDs and HRs with 95% CIs according to levels of total red meat consumption in Swedish men and women[1]

Red meat consumption[2]	15th PD[3]	95% CI	HR	95% CI
	mo			
0 g/d	Reference		Reference	
30 g/d	1	(−2, 4)	1.01	(0.98, 1.05)
50 g/d	1	(−3, 6)	1.02	(0.96, 1.08)
100 g/d	0	(−7, 7)	1.07	(0.98, 1.17)
150 g/d	−5	(−12, 2)	1.16	(1.06, 1.27)
200 g/d	−10	(−18, −3)	1.26	(1.14, 1.40)
250 g/d	−15	(−24, −7)	1.37	(1.21, 1.56)
300 g/d	−21	(−31, −10)	1.49	(1.27, 1.75)

[1] PD, percentile difference (defined as the difference in months by which 15% of the cohort has died in 15 y of follow-up).
[2] Tabular estimates for specific values of total red meat consumption are from a spline dose-response model.
[3] Differences in the 15th survival PDs and HRs were adjusted for baseline age, sex, BMI, total physical activity, smoking status, alcohol consumption, energy intake, educational level, fruit consumption, vegetable consumption, fish consumption, and prevalence of diabetes.

DISCUSSION

In a population-based cohort of Swedish men and women, we found that high levels of total red meat consumption were associated with progressively shorter survival. The association between total red meat and mortality was largely attributable to the consumption of processed meat. The evaluation of the combined consumption of processed and nonprocessed meat showed that consumption of nonprocessed meat alone was not associated with shorter survival.

Epidemiologic studies have consistently shown an association between high levels of red meat consumption and an increased risk of the major chronic diseases, such as CVD (1–4), cancer (2, 4–7), and diabetes (1). Recent results from large population-based studies have also shown that high levels of red meat consumption are significantly associated with an increased mortality risk (2, 4, 8, 9). These findings were summarized in a recently published meta-analysis (10).

Total red meat consumption is usually classified between processed meat and fresh (nonprocessed) red meat. It is reasonable to assume that processed and nonprocessed meat might have different biological mechanisms, resulting in different effects on mortality. Red meat is a rich source of zinc and dietary protein, which might be responsible for the positive effect of red meat consumption (18–21). On the other hand, meat processing involves different potentially adverse components that could counteract the positive effects of the beneficial nutrients in meat (22–26). Whereas the adverse health effects of processed meat consumption are widely accepted (11), the role of nonprocessed red meat is less clear (8, 10, 12).

Intakes of processed and nonprocessed meat are usually evaluated in a mutually adjusted model, and only the marginal estimates for the exposures effects are presented. A substantial contribution to the current understanding of the role of processed

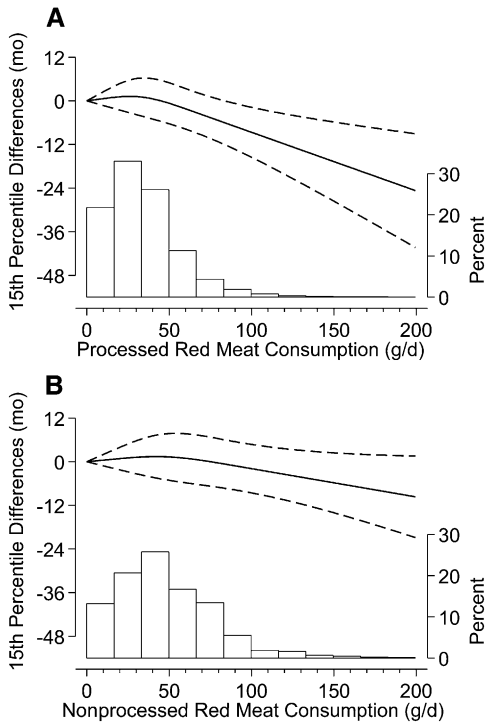

FIGURE 2. Fifteenth percentile differences (differences in months by which 15% of the cohort has died, with 95% CIs) as a function of processed (A) and nonprocessed (B) red meat consumption. Estimates were obtained by fitting a multivariable Laplace regression and adjusting for baseline age, sex, BMI, total physical activity, smoking status, alcohol consumption, energy intake, educational level, fruit consumption, vegetable consumption, fish consumption, and prevalence of diabetes. Processed and nonprocessed red meat consumptions were mutually adjusted in the same model. Nonlinear associations were observed in both situations ($P < 0.001$), with a significant (A) and nonsignificant (B) reduction in survival for high levels of consumption. The histograms show the percentage of population participants consuming each level of processed (A) and nonprocessed (B) red meat consumption.

and nonprocessed meat consumption in predicting mortality is to evaluate the combined effect of the 2 exposures, presenting the association between nonprocessed meat and mortality for each level of processed meat intake and vice versa. To the best of our knowledge, the current study was the first to evaluate the joint association of processed and nonprocessed red meat consumption and mortality. Our results show that nonprocessed meat consumption is associated with shorter survival only when processed meat intake is high, which suggests that the negative effects of red meat consumption might be largely due to processed meat. This finding can partly explain the conflict between previous results.

We presented our findings in terms of survival time. The evaluation of differences in survival according to levels of the exposure provides a measure of association that is directly interpreted in terms of time (eg, days, months, years), which improves interpretation of the results and facilitates the communication of the risks of hazardous behaviors (13, 27, 28). Presenting results in terms of time could more easily convince the general public to make healthy choices and eventually change their lifestyles. In particular, we focused our analysis on the 15th survival percentile—the time by which the first 15% of the cohort has died. This percentile was chosen to rely only on those participants who have experienced the event of interest during the follow-up period, minimizing data extrapolation. In our cohort, 20% of the participants died in 15 y of follow-up; thus, any estimation of higher percentiles, such as the median survival (50th percentile), would require data extrapolation beyond the observed range of data. Our sensitivity analysis showed that the results were not affected by the choice of this percentile but are extendable to a wide range of observed percentiles. Longer follow-up would result in a higher proportion of cases allowing the estimation of higher survival percentiles, but the results reported in this study would not change. Commonly used approaches for the analysis of time-to-event data—including Cox regression—do not share these properties, but provide relative measures of association that are strongly dependent on follow-up time and background risk (29).

Survival percentiles can be indirectly derived from nonparametric (eg, Kaplan-Meier), semiparametric (eg, Cox), and parametric methods [eg, accelerated failure time (30) and flexible parametric models (31)]. The required postestimation calculations, however, may not be straightforward, and some of these methods may require assumptions (eg proportional hazards). Laplace regression, the approach we used for statistical analysis, directly models the survival percentiles while allowing for inclusion of multiple covariates and interaction terms, modeling multiple

TABLE 3
Multivariable-adjusted 15th survival percentile differences (and 95% CIs) according to specific joint levels of processed and nonprocessed red meat consumption[1]

	Processed red meat consumption[2]				
Nonprocessed red meat consumption[2]	0 g/d	18 g/d	30.5 g/d	44.5 g/d	75 g/d
0 g/d	−3.5 (–13, 6)	2 (–6, 9)	3 (–7, 12)	−4 (–16, 6)	−30 (–62, 2)
26.5 g/d	−5 (–11, 1)	−1 (–4, 3)	1 (–2, 4)	−2 (–6, 2)	−15 (–27, –4)
44.5 g/d	−5 (–13, 3)	−2 (–4, 1)	0 (reference)	−1 (–3, 1)	−8 (–15, –1)
64 g/d	−3 (–11, 5)	−1 (–5, 2)	−1 (–3, 2)	−2 (–5, 1)	−8 (–14, –1)
100 g/d	3.5 (–18, 25)	1 (–9, 11)	−2 (–10, 7)	−5 (–13, 3)	−19 (–37, –2)

[1] Percentile differences were adjusted for baseline age, sex, BMI, total physical activity, smoking status, alcohol consumption, energy intake, educational level, fruit consumption, vegetable consumption, fish consumption, and prevalence of diabetes. The model includes the interaction terms between processed and nonprocessed meat. *P*-interaction = 0.6. Tabular estimates for specific values of processed and nonprocessed meat consumption are from a spline model. The median consumptions of 44.5 g nonprocessed meat/d and 30.5 g processed meat/d were used as the referent.

[2] The values shown are estimates for the 25th, 50th, 75th, and 95th percentiles of the distribution of processed meat and nonprocessed meat consumption.

percentiles simultaneously, and testing regression coefficients within and between survival percentiles (13, 15, 16).

Different features, such as the large size of the cohort, its population-based and prospective design, the large number of cases, and the completeness of case ascertainment through the National Register, can increase the generalizability of our study findings. The main limitation of this study was that meat consumption was self-reported. A certain degree of exposure misclassification is therefore unavoidable. Because our study population included middle-aged and elderly men and women, the results from the current study might not be generalizable to younger populations. Moreover, health or lifestyle factors that could influence our results, such as self-reported health status, were not present in both questionnaires. A certain degree of residual confounding from unmeasured risk factors cannot be excluded. In the current study, we focused on red meat consumption and evaluated the different effects of processed and nonprocessed red meat. Future studies might evaluate the effect of different nutrients, such as zinc and protein, and their role in the observed association.

In conclusion, we evaluated differences in survival according to levels of total red meat consumption and to combined levels of nonprocessed and processed red meat consumption. High intake of total red meat was associated with progressively shorter survival, largely due to the consumption of processed red meat. Consumption of nonprocessed red meat alone was not associated with shorter survival.

The authors' responsibilities were as follows—AB, SCL, MB, AW, and NO: participated in the study design and in writing the manuscript; AW: participated in the data collection; AB: analyzed the data and wrote the manuscript under the supervision of NO; SCL, MB, and AW: interpreted the results and critically reviewed the manuscript; and MB: revised the statistical method. All authors read and approved the final manuscript. None of the authors had any personal or financial conflict of interest. The funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

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