

# Processed and Unprocessed Red Meat Consumption and Incident Type 2 Diabetes Among French Women

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**OBJECTIVE**—To evaluate the relation of processed and unprocessed red meat and incident type 2 diabetes.

**RESEARCH DESIGN AND METHODS**—We conducted a prospective study among 66,118 disease-free French women with dietary information from a validated questionnaire. Between 1993 and 2007, we identified 1,369 cases of incident diabetes. Multivariate analyses were adjusted for age, education, region, smoking, BMI, hypertension, hypercholesterolemia, physical activity, parental history of diabetes, menopause, hormone replacement therapy, alcohol, calories, n-3 fatty acids, carbohydrates, coffee, fiber, and fruits and vegetables.

**RESULTS**—Comparing the highest category of processed meat intake,  $\geq 5$  servings/week (median, 48 g/day), to the lowest,  $< 1$  serving/week (median, 5 g/day), processed meat was significantly associated with incident diabetes (hazard ratio 1.30 [95% CI 1.07–1.59],  $P$  trend = 0.0007; for 1 serving/day, 1.29 [1.14–1.45]). Unprocessed red meat was not associated with diabetes.

**CONCLUSIONS**—In this large prospective cohort of French women, a direct association was observed only for processed red meat and type 2 diabetes.

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Despite consistent epidemiologic evidence linking processed red meats with type 2 diabetes (1,2), evidence for the underlying mechanism is tenuous at best. Evaluating this relation in different populations may be useful to exclude the possibility that results can be explained by difficulties in accounting for diabetes risk factors that are associated with diet. Therefore, we evaluated the relation of processed and unprocessed red meat and type 2 diabetes in a prospective cohort of French women.

**RESEARCH DESIGN AND METHODS**—The E3N study (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education

Nationale) started in 1990 when 98,995 middle-aged French women responded to a mailed reproductive, lifestyle, and medical questionnaire (3). Participants have periodically responded to similar questionnaires. Average follow-up has been 83% in each questionnaire cycle and loss to follow-up  $< 3\%$ . In 1993, 74,531 participants responded to a validated self-administered dietary questionnaire (4). After excluding participants with unrealistic diet ( $n = 1,499$ ) (5), no follow-up ( $n = 1,753$ ), prevalent diabetes ( $n = 431$ ), and cancer or cardiovascular disease ( $n = 4,730$ ), the final study population was 66,118.

Unprocessed red meat was defined as beef, pork, veal, horse, and sheep, whereas

processed red meat was defined as sausage, salami, bacon, and ham. In our validation study, the correlation coefficients between this dietary questionnaire and 12 recalls (24 h) were 0.52 for unprocessed and 0.39 for processed meat (4). BMI, smoking, treated hypertension and hypercholesterolemia, menopause, hormone replacement therapy, physical activity (6), and alcohol were based on self-reports.

For case identification, we used self-reports, supplementary questionnaires, and drug reimbursement information (7). Between 1993 and 2007, a total of 2,657 self-reported cases were confirmed through a supplementary questionnaire or reimbursement claims for diabetes medications. We identified 839 additional cases through the drug reimbursement database and used the supplementary questionnaire for confirmation. This analysis is based on 1,369 incident cases for which dietary information was available.

Nutrients and foods were energy adjusted using the residual method (8). Unprocessed and processed red meat were categorized in servings per week (1 serving unprocessed meat = 100 g; 1 serving processed meat = 50 g) and evaluated as indicator categories with the lowest category as the referent. The median value for each category was used as a continuous variable to test for trend. Servings per day were evaluated continuously. Person-time was calculated from the date of completion of the dietary questionnaire to the date of diagnosis, death, or June 2007, whichever occurred first. Cox regression models with age as the time scale were fit to estimate hazard ratios (HRs) and 95% CIs (SAS Institute Inc., Cary, NC). We stratified by BMI ( $< 25$  and  $\geq 25$  kg/m<sup>2</sup>) and smoking status (never, past, and current) and tested for statistical interaction using log-likelihood tests to compare models with and without a cross-product term.

**RESULTS**—Mean processed red meat consumption was 3.4 servings/week (SD 2.5), and mean unprocessed red meat intake was 3.0 servings/week (SD 2.7). Processed meat intake was directly associated

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**Table 1—Age-adjusted and multivariate-adjusted HRs (95% CIs) of type 2 diabetes according to servings per week of processed and unprocessed red meat**

|                            | Servings per week |                  |                  |                  | P trend | HR (95% CI)<br>serving per day |
|----------------------------|-------------------|------------------|------------------|------------------|---------|--------------------------------|
|                            | <1                | 1–2.9            | 3–4.9            | ≥5               |         |                                |
| <b>Processed meat</b>      |                   |                  |                  |                  |         |                                |
| Median intake (g/day)      | 5                 | 13               | 26               | 48               |         |                                |
| Cases (n)                  | 143               | 448              | 389              | 389              |         |                                |
| Person-years               | 109,151           | 331,116          | 234,478          | 163,352          |         |                                |
| Age adjusted               | Ref.              | 1.06 (0.87–1.27) | 1.35 (1.12–1.64) | 1.99 (1.64–2.41) | <0.0001 | 1.97 (1.77–2.21)               |
| Multivariate*              | Ref.              | 1.04 (0.86–1.26) | 1.18 (0.97–1.44) | 1.39 (1.15–1.69) | <0.0001 | 1.36 (0.76–0.99)               |
| + Diet†                    | Ref.              | 1.03 (0.85–1.25) | 1.14 (0.94–1.39) | 1.30 (1.06–1.59) | 0.0006  | 1.29 (1.14–1.45)               |
| + Diet† + unprocessed meat | Ref.              | 1.03 (0.85–1.25) | 1.15 (0.94–1.40) | 1.30 (1.07–1.59) | 0.0007  | 1.29 (1.14–1.45)               |
| <b>Unprocessed meat</b>    |                   |                  |                  |                  |         |                                |
| Median intake (g/day)      | 0                 | 30               | 55               | 90               |         |                                |
| Cases (n)                  | 435               | 255              | 333              | 346              |         |                                |
| Person-years               | 237,425           | 196,342          | 220,847          | 183,483          |         |                                |
| Age adjusted               | Ref.              | 0.72 (0.61–0.83) | 0.85 (0.74–0.98) | 1.08 (0.93–1.24) | 0.29    | 1.18 (1.03–1.36)               |
| Multivariate*              | Ref.              | 0.82 (0.70–0.96) | 0.88 (0.76–1.01) | 0.96 (0.83–1.11) | 0.59    | 1.03 (0.90–1.17)               |
| + Diet†                    | Ref.              | 0.83 (0.71–0.97) | 0.88 (0.76–1.01) | 0.93 (0.81–1.08) | 0.36    | 1.00 (0.87–1.14)               |
| + Diet† + processed meat   | Ref.              | 0.83 (0.71–0.97) | 0.88 (0.76–1.02) | 0.95 (0.82–1.10) | 0.45    | 1.02 (0.89–1.17)               |

Ref., referent. \*Adjusted for education, residence in the Mediterranean, BMI (<22, 22–25, 35–30, and >30), smoking (never, past, and current), parental history of diabetes, physical activity METs/week (quartiles), hormone replacement therapy (premenopausal, ever, and never), hypertension, and hypercholesterolemia. †Additional adjustment for n-3 polyunsaturated fatty acid (quartiles), carbohydrates (quartiles), fiber (quartiles), coffee (quartiles), and fruits and vegetables (quartiles).

with smoking. Both types of meat were associated with higher alcohol intake and BMI and inversely related to physical activity (Supplementary Table 1).

After multivariate adjustment, there was a significant 30% higher rate of diabetes among individuals consuming ≥5 servings/week of processed red meat compared with those consuming <1 serving/week (HR 1.30 [95% CI 1.07–1.59], *P* trend = 0.0007; for 1 serving/day, 1.29 [1.14–1.45]) (Table 1). This association did not differ by BMI (*P* = 0.81), but we observed statistical evidence of heterogeneity (*P* = 0.04) for smoking status. Among nonsmokers, the HR was ~20% higher in high consumers compared with low consumers of processed meat. Conversely, among current smokers, the HR was 1.95 (1.08–3.54; *P* trend = 0.002) (Supplementary Table 2). For unprocessed red meat, no overall association was observed.

**CONCLUSIONS**—In a prospective study of French women with a median follow-up of 13.8 years, we observed a direct association between processed red meat and type 2 diabetes. We found no association between unprocessed meat and type 2 diabetes.

One explanation for these results is that added nitrates and salt in processed red meat may have a biological effect on

glucose metabolism (1). However, consistent evidence from cell and animal models is still lacking. Another explanation is confounding by unmeasured risk factors for diabetes. In our analysis, smoking intensity was unavailable. We observed a stronger association among current smokers as compared with nonsmokers, which may be indicative of residual confounding by smoking intensity. Nevertheless, only 13% of participants were smokers, and there was an indication that the association was still present among nonsmokers. In addition, it is unlikely that unmeasured risk factors for diabetes could explain the null result observed for unprocessed red meat. Our results are somewhat consistent with two recent meta-analyses (1,2). In contrast with one of these studies, we observed no association between unprocessed red meat and diabetes risk (2). We cannot exclude the possibility of measurement error; however, in our validation study, the correlation coefficient was higher for unprocessed compared with processed red meat.

The strengths of the present analysis include prospective design, limited loss to follow-up, use of a validated dietary questionnaire, and a study population that differs in the distribution of lifestyle factors from previous reports. The main limitation for this analysis is absence of a

biological mechanism. In addition, because diet was assessed only once, measurement error is likely. However, the error introduced is independent of the outcome and may have attenuated the association toward the null. Asymptomatic diabetes cases were probably missed; however, assuming very high specificity, nondifferential misclassification probably had no measurable effect on our estimates. We cannot rule out the possibility of confounding by unmeasured factors such as red meat intake (or other dietary factors) prior to baseline. Therefore, we had to assume, as is usually done in dietary analyses, that baseline assessment represents lifetime diet and that prior diet is not an independent risk factor for diabetes.

Our results suggest that habitual consumption of processed red meat may be associated with a higher incidence of type 2 diabetes and that consumption of unprocessed red meat may not. In the absence of a clear biological mechanism, the consistency of the epidemiologic evidence calls for a thorough investigation of the constituents found in processed red meats that may disrupt glucose metabolism.

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M.L. planned the analysis and wrote the manuscript. L.T. analyzed data. G.F. reviewed and edited the manuscript. B.d.L.-G. validated cases and reviewed and edited the manuscript. M.-C.B.-R. reviewed and edited the manuscript.

F.C.-C. reviewed the analysis plan, secured funding, and reviewed and edited the manuscript. M.L. had full access to all data in the study and takes responsibility for the integrity of data and the accuracy of the data analysis.

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