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High processed meat consumption is a risk factor of type 2 diabetes in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study

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Relatively small lifestyle modifications related to weight reduction, physical activity and diet have been shown to decrease the risk of type 2 diabetes. Connected with diet, low consumption of meat has been suggested as a protective factor of diabetes. The aim of the present study was to examine the association between the consumption of total meat or the specific types of meats and the risk of type 2 diabetes. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort included middle-aged male smokers. Up to 12 years of follow-up, 1098 incident cases of diabetes were diagnosed from 24 845 participants through the nationwide register. Food consumption was assessed by a validated FFQ. In the age- and intervention group-adjusted model, high total meat consumption was a risk factor of type 2 diabetes (relative risk (RR) 1·50, 95 % CI 1·23, 1·82, highest *v.* lowest quintile). The result was similar after adjustment for environmental factors and foods related to diabetes and meat consumption. The RR of type 2 diabetes was 1·37 for processed meat (95 % CI 1·11, 1·71) in the multivariate model. The results were explained more by intakes of Na than by intakes of SFA, protein, cholesterol, haeme Fe, Mg and nitrate, and were not modified by obesity. No association was found between red meat, poultry and the risk of type 2 diabetes. In conclusion, reduction of the consumption of processed meat may help prevent the global epidemic of type 2 diabetes. It seems like Na of processed meat may explain the association.

Cohort studies: Epidemiology: Meat: Processed meat: Diabetes

It has been predicted that the number of adults with diabetes will double during the next two decades, being 300 million worldwide in the year 2025[1]. Because of the long-term serious complications and indirect mortality of diabetes, all established preventive factors against the disease are valuable. From lifestyle factors, obesity and physical inactivity have consistently been associated with an increased risk of type 2 diabetes[2,3]. The intervention studies have also shown the possibility to reduce the risk of type 2 diabetes by relatively small lifestyle modifications in weight control, physical activity and diet[4,5].

Three cohort studies from the United States have shown that high consumption of meat, particularly processed meat, may increase the risk of type 2 diabetes in men[6] and women[7,8]. The only cohort study outside the United States found that especially high consumption of processed meat increased the risk of type 2 diabetes among overweight and obese Chinese women[9]. The mechanisms behind the observed relationship are unclear.

The prospective data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study (ATBC study) were used to examine the relationship between the consumption of total meat and specific types of meats (red meat, processed meat and poultry) and the risk of type 2 diabetes in Finnish middle-aged male smokers. Furthermore, the explanatory factors related to meat and whole diet (alcohol, fruits, vegetables, rye, milk, coffee, SFA, protein, cholesterol, haeme Fe, Mg, Na, nitrate and energy) were examined.

Methods

The ATBC Study was a randomised, double-blinded, placebo-controlled clinical trial undertaken to determine the effects of antioxidant supplements on cancer among male smokers aged 50–69 years and living in Southwestern Finland (*n* 29 133)[10,11]. At baseline, men were excluded if they smoked fewer than five cigarettes a day and had a previous history of cancer, severe angina on exertion, chronic renal insufficiency, liver cirrhosis, alcoholism or other medical conditions limiting long-term participation. Furthermore, men who received anticoagulant therapy or used vitamin E, vitamin A or β-carotene supplements in excess of predefined doses were excluded. The recruitment was carried out between 1985 and 1988, and the trial intervention continued until April 1993. The trial cohort had been followed up through national registers thereafter.

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Institutional Review Boards of the National Public Health

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; RR, relative risk.

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Institute (currently the National Institute for Health and Welfare), Finland, and the National Cancer Institute, USA. Written informed consent was obtained from all the subjects.

Ascertainment of diabetes

In Finland, patients needing medical treatment for diabetes are entitled to reimbursement of their medication expenses according to the sickness insurance legislation. This requires a medical certificate from the attending physician. The certificate of every case is verified to fulfil the diagnostic criteria (blood glucose permanently 7·0 mmol/l or higher after dietary treatment) for diabetes at the Social Insurance Institution which maintains a central register of all the persons receiving drug reimbursement. The participants of the ATBC study were linked to the register through the unique personal identity number assigned to each Finnish citizen.

At baseline, 1272 participants had a history of diabetes diagnosed by a physician. Furthermore, 1918 participants were excluded because of an incompletely filled-in FFQ. After the exclusions, the final cohort for the present study comprised 25 943 men, among whom 1098 incident cases of diabetes were identified from the drug reimbursement register through December 1997 (followed up to 12 years).

Baseline data collection

At baseline, each man completed questionnaires on general characteristics as well as on medical history, smoking and physical activity. Height and weight were measured, and BMI (kg/m^2) was calculated. Blood pressure was measured using a mercury sphygmomanometer from the right arm, while the subject remained seated. Serum samples were collected and stored at −70°C. Serum glucose was determined by the enzymatic hexokinase method using an Optima analyser (ThermoFischer, Vantaa, Finland). Serum total cholesterol concentrations were determined enzymatically (cholesterol oxidase-*p*-aminophenazone, method; Boehringer Mannheim, Mannheim, Germany). HDL- cholesterol was measured after precipitation with dextran sulphate and $MgCl_2$.

Dietary assessment

Food consumption over the previous 12 months was assessed at baseline with a validated self-administered FFQ developed for the ATBC study[12]. The consumption of 276 food items and mixed dishes (about fifty food items or dishes including meat, sausage or poultry) was recorded by asking the number of times an item was usually consumed per day, week or month. Participants were also allowed to report additional foods consumed frequently but not listed in the FFQ. The portion size was assessed by a picture booklet including 122 colour photographs of food items or dishes. The participants completed the FFQ at home, and returned it during the second baseline visit, where a trained study nurse checked the FFQ thoroughly and modified possible discrepancies during a 30 min interview. Thereafter, a senior nutritionist reviewed all the FFQ for final approval. In all, 93 % of the FFQ were approved. The food data were converted into daily meat consumption (total meat, red meat (beef and pork), processed meat and poultry) and nutrient intakes according to the software and food composition database at the National Public Health Institute in Finland. We did not assess the fish consumption in the present study.

The reproducibility and validity of the dietary questionnaire were tested in a pilot study with 189 men using a 24 d food record (2 × 12 d) as a reference method[12]. For the meat variables, the extended analyses of crude intraclass correlations between the first and second FFQ ranged from 0·56 (pork) to 0·74 (poultry), and the correlation coefficient between the first FFQ and the food records ranged from 0·31 (pork) to 0·50 (processed meat).

Statistical analyses

The associations between quintiles of meat consumption and the incidence of diabetes were calculated by Cox proportional hazards regression, and are expressed as relative risks (RR) and 95 % CI. The proportional hazards assumption was tested with no evidence of non-proportional hazards. Person-years of follow-up were calculated from the date of randomisation to the date of diabetes occurrence, death or the end of follow-up (December 1997), whichever came first.

The first model (Model 1) was adjusted for age and intervention groups (α-tocopherol, β-carotene, both or placebo). Model 2 was further adjusted for BMI, number of cigarettes smoked daily, smoking years, systolic blood pressure, diastolic blood pressure, serum total cholesterol and serum HDL-cholesterol, leisure-time physical activity and intakes of alcohol and energy. Furthermore, the multivariate Model 3 was adjusted for all the variables included in Model 2 plus consumption of foods related to type 2 diabetes (fruits, vegetables, rye, milk and coffee). We also added (Model 4) intakes of SFA, protein, cholesterol, haeme Fe, Mg, Na and nitrate to examine mechanisms/explanatory factors behind the results (data not shown). Nutrient intakes were adjusted for energy according to the residual method[13].

Tests for linearity of the trend across the categories were performed using the Wald test by modelling the median value of each quintile as a continuous variable.

The likelihood ratio test was used to study whether BMI modified the effect of meat consumption on diabetes incidence.

All analyses were carried out with the R statistical program version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria)[14]. All *P* values were two sided, and $P < 0.05$ was considered statistically significant.

Results

On average, men with high consumption of total meat were younger, more obese and physically less active and had more energy in their diet compared with the others (Table 1). The consumption of total meat was 3-fold higher in the highest quintile compared with the lowest quintile. Especially, the consumption of processed meat and poultry was relatively high among those in the highest quintile of total meat consumption. Furthermore, men whose diet was rich in meat tended to have a higher intake of other foods and nutrients as well.

The Pearson coefficients of correlation (adjusted for energy) between the consumption of total meat and specific types of

Table 1. Age-standardised baseline characteristics (medians) by quintiles of total meat consumption among 25 943 men in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, Finland, 1985–97*

	Quintiles of total meat intake				
	1	2	3	4	5
Background characteristics					
n	5189	5188	5189	5188	5189
Age (years)	59	58	57	56	56
BMI (kg/m^2)	25·7	25·7	25·9	26·0	26·2
Cigarettes smoked daily (no.)	20	20	20	20	20
Smoking years	37	36	36	36	37
Systolic blood pressure (mmHg)	140	140	140	140	140
Diastolic blood pressure (mmHg)	88	88	88	88	88
Serum total cholesterol (mmol/l)	6·12	6·16	6·18	6·23	6·19
Serum HDL- cholesterol (mmol/l)	1·14	1·15	1·15	1·16	1·15
Leisure-time physical activity (%) †	59	60	60	58	56
Energy (kJ/d)	8985	10 003	10 836	11 749	13 453
Alcohol (g/d)	8	10	11	12	14
Fruits (g/d)	138	160	176	184	199
Vegetables (g/d)	219	255	282	311	338
Rye (g/d)	77	80	83	83	87
Milk (g/d)	466	499	528	543	595
Coffee (g/d)	550	550	550	600	600
Meat-related characteristics					
Total meat (g/d)	79	111	139	174	244
Red meat (g/d)	40	54	63	74	88
Beef (g/d)	12	18	22	26	30
Pork (g/d)	25	33	38	44	52
Processed meat (g/d)	28	46	62	84	139
Poultry (g/d)	2	8	10	14	14
SFA (g/d)	40	45	49	53	63
Protein (g/d)	74	83	91	100	116
Cholesterol (mg/d)	413	478	533	594	719
Haeme Fe (mg/d)	1·9	2·6	3·1	3·7	4·8
Mg (mg/d)	411	443	465	493	542
Na (mg/d)	3745	4272	4723	5282	6285
Nitrate (mg/d)	40	48	54	60	66

* All differences were statistically significant, except for diastolic blood pressure and leisure-time physical activity.
† Moderate or heavy activity at leisure time.

meats (red meat, processed meat and poultry) were 0·48, 0·82 and 0·27, respectively. Instead, correlations between the consumption of processed meat and the other types of meats (red meat, beef, pork and poultry) ranged from −0·04 to −0·02. Total meat, especially pork and processed meat, correlated positively with energy intake ($r > 0·35$).

In the model adjusted for age and intervention groups, the RR of type 2 diabetes was significantly higher by 50 % for the highest *v.* the lowest quintile of total meat consumption (Table 2). The association did not change after adjustment for confounding factors related to diabetes (RR 1·45; 95 % CI 1·16, 1·81; *P* value, test for trend<0·001) and foods (RR 1·50; 95 % CI 1·19, 1·89; *P* value, test for trend<0·001). Among nutrients, the association between total meat consumption and the risk of diabetes was slightly attenuated by an additional adjustment for Na (RR 1·28; 95 % CI 1·00, 1·64; *P* value, test for trend 0·04).

The RR of type 2 diabetes was 1·46 (95 % CI 1·20, 1·77; *P* value, test for trend<0·001) for the highest quintile compared with the lowest quintile of processed meat consumption. The association was attenuated slightly after adjustment for confounding factors related to type 2 diabetes (RR 1·35; 95 % CI 1·09, 1·68; *P* value, test for trend<0·001) and foods (RR 1·37; 95 % CI 1·11, 1·71; *P* value, test for trend=0·001), but it remained statistically significant. The attenuation of RR was explained more by the intakes of Na than by intakes of other nutrients (RR 1·19; 95 % CI 0·95, 1·49; *P* value, test for trend=0·10). No associations were found between the consumption of red meat (beef and pork), poultry and the risk of type 2 diabetes.

When the diabetes cases diagnosed during the first 5 years of follow-up were excluded (*n* 417) from the analyses, the results between the consumption of total meat as well as of specific types of meats and the risk of type 2 diabetes did not change. For example, the risk of type 2 diabetes (adjusted for risk factors related to diabetes) was 1·52 (95 % CI 1·14, 2·01; *P* value, test for trend<0·001) for the highest quintile of total meat consumption, and was 1·46 (95 % CI 1·11, 1·92; *P* value, test for trend=0·01) for processed meat.

The associations between the consumption of total meat, processed meat and the risk of type 2 diabetes were not modified by BMI (*P* value, test for interaction≥0·30).

Discussion

In the present cohort study of Finnish male smokers followed up to 12 years, the multivariate relative risk (e.g. BMI and energy) of type 2 diabetes was 50 % higher for the highest

Table 2. Risk of diabetes by quintiles of meat consumption among 25 943 men in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, Finland, 1985–97
(Relative risks (RR) and 95 % confidence intervals)

	Quintiles of meat consumption									
	1	2		3		4		5		
	RR	RR	95 % CI	RR	95 % CI	RR	95 % CI	RR	95 % CI	*P* for trend
Total meat										
Median (g/d)	79	111		139		174		244		
Cases (*n*)	181	192		225		220		280		
Age-adjusted*	1·00	1·03	0·83, 1·26	1·19	0·97, 1·46	1·15	0·94, 1·41	1·50	1·23, 1·82	< 0·001
Multivariate†	1·00	1·05	0·85, 1·29	1·22	1·00, 1·50	1·19	0·96, 1·47	1·45	1·16, 1·81	< 0·001
Multivariate‡	1·00	1·06	0·85, 1·31	1·24	1·00, 1·53	1·22	0·98, 1·52	1·50	1·19, 1·89	< 0·001
Red meat										
Median (g/d)	33	47		60		76		106		
Cases (*n*)	189	217		241		219		232		
Age-adjusted*	1·00	1·12	0·92, 1·37	1·22	1·00, 1·48	1·08	0·89, 1·32	1·14	0·93, 1·39	0·33
Multivariate†	1·00	1·23	1·00, 1·50	1·31	1·07, 1·59	1·16	0·94, 1·42	1·19	0·97, 1·47	0·23
Multivariate‡	1·00	1·24	1·01, 1·52	1·33	1·08, 1·63	1·18	0·95, 1·46	1·22	0·97, 1·53	0·21
Beef										
Median (g/d)	6	14		20		29		47		
Cases (*n*)	189	221		222		217		249		
Age-adjusted*	1·00	1·14	0·94, 1·39	1·12	0·92, 1·37	1·09	0·89, 1·33	1·23	1·01, 1·50	0·09
Multivariate†	1·00	1·13	0·93, 1·38	1·19	0·97, 1·45	1·12	0·91, 1·36	1·23	1·01, 1·50	0·08
Multivariate‡	1·00	1·13	0·92, 1·37	1·19	0·98, 1·46	1·11	0·91, 1·37	1·22	0·99, 1·50	0·10
Pork										
Median (g/d)	19	29		37		47		66		
Cases (*n*)	216	200		224		250		208		
Age-adjusted*	1·00	0·89	0·74, 1·09	0·99	0·82, 1·20	1·10	0·91, 1·33	0·90	0·74, 1·09	0·99
Multivariate†	1·00	0·94	0·77, 1·14	1·04	0·85, 1·26	1·14	0·94, 1·38	0·96	0·78, 1·18	0·57
Multivariate‡	1·00	0·94	0·77, 1·15	1·04	0·85, 1·27	1·15	0·95, 1·41	0·97	0·78, 1·20	0·50
Processed meat										
Median (g/d)	22	42		60		86		142		
Cases (*n*)	176	186		236		243		257		
Age-adjusted*	1·00	1·04	0·84, 1·28	1·32	1·08, 1·61	1·35	1·10, 1·64	1·46	1·20, 1·77	< 0·001
Multivariate†	1·00	1·04	0·84, 1·29	1·26	1·03, 1·55	1·19	0·97, 1·46	1·35	1·09, 1·68	< 0·001
Multivariate‡	1·00	1·04	0·84, 1·29	1·26	1·03, 1·54	1·19	0·96, 1·46	1·37	1·11, 1·71	< 0·001
Poultry										
Median (g/d)	0	8		14		17		32		
Cases (*n*)	366	174		179		165		214		
Age-adjusted*	1·00	0·86	0·72, 1·04	1·05	0·88, 1·27	0·89	0·74, 1·07	1·15	0·96, 1·36	0·25
Multivariate†	1·00	0·92	0·77, 1·11	1·00	0·83, 1·20	0·92	0·76, 1·11	1·04	0·87, 1·23	0·88
Multivariate‡	1·00	0·90	0·75, 1·09	0·98	0·82, 1·18	0·89	0·74, 1·08	1·01	0·85, 1·21	0·88

* Adjusted for age and intervention group.
† Adjusted further for BMI, number of cigarettes smoked daily, smoking years, systolic blood pressure, diastolic blood pressure, serum total cholesterol, serum HDL- cholesterol, leisure-time physical activity and intakes of alcohol and energy.
‡ Adjusted further for consumption of fruits, vegetables, rye, milk and coffee.

quintile of total meat consumption compared with the lowest quintile. Especially, high consumption of processed meat was associated with a 35 % increased risk of type 2 diabetes compared with the diet low in processed meat (median consumption on average 22 *v.* 142 g), also after adjustments for environmental and dietary factors. The consumption of red meat (beef and pork) and poultry was not associated with the risk of type 2 diabetes.

A 20–30 % higher risk of type 2 diabetes has been observed for the highest category of frequent red meat consumption compared with the lowest category in the Nurses' Health Study and in the Women's Health Study[7,8], and a 40–90 % higher risk has been observed for the consumption of processed meat at least five times a week compared with the consumption less than once a week in the Nurses' Health Study and in the Health Professionals Follow-up Study[6,15]. Long-term adherence to a diet that included at least weekly meat consumption was associated with a 74 % increased risk of diabetes compared with a vegetarian diet[16]. In a large Chinese female cohort with a very low intake of meat, the consumption of processed meat (> once a month *v.* never) was also slightly associated with the risk of type 2 diabetes[9], especially among the obese women (BMI $\geq$ 30 kg/m^2) whose risk of type 2 diabetes was 3·5-fold higher compared with the women with normal weight. A relatively small cohort study among Japanese-Brazilians found that high meat consumption was related to the risk of the metabolic syndrome[17]. The result, however, attenuated when the model was adjusted for the intake of SFA. Furthermore, two cross-sectional studies have found contradictory results[18,19]. The present study is the first European cohort study on this issue. Furthermore, our male population was totally different from the previous male cohorts, the well-educated health professionals[15] and the participants in the Adventist Health Study. Our population, in general, included lowly educated smokers (about 10 % smokers in the Health Professionals Follow-up Study) whose coffee and alcohol consumption was high (on average 18 and 610 g/d, respectively). In the present study, the range of meat consumption was especially high, between 79 and 244 g/d (median in the lowest and highest quintiles) including mainly red meat and sausages. The results of the present study, however, confirmed the previous findings that the high consumption of processed meat seemed to be a risk factor of type 2 diabetes more than the high total meat consumption. The results were not modified by BMI.

The mechanisms related to the positive associations between red meat or processed meat consumption and type 2 diabetes are unclear. It has been suggested that the associations observed are mediated through high intake of fat, SFA[2], protein[8], haeme Fe[20,21], preservatives used in processed meat (such as nitrates and nitrite)[22], heterocyclic amines and polycyclic aromatic hydrocarbons formed in meat through high heating practice[23,24], or glycation end products formed in meat and high-fat products through heating and processing[25]. These dietary factors have been found to affect insulin resistance[26], oxidative stress[27], inflammation[28] and toxically pancreatic cells[23]. In our data, the attenuation of RR was explained more by the intakes of Na than by intakes of SFA, protein, cholesterol, haeme Fe, Mg, nitrate, energy, alcohol, fruits, vegetables, rye, milk or coffee. The other factors related to preservation or cooking meat at high temperature could not be included in our analyses. The effect of nitrite was difficult to assess because of the very high correlation between nitrite and total meat intakes (r 0·82). On the other hand, high meat consumption may be a biomarker for a general lifestyle related to high risk of type 2 diabetes.

A strength of the present study was the prospective cohort design, which minimises recall and selection biases. We also had large amounts and ranges of the consumption of total meat and the specific types of meats. Although we were able to adjust for main non-dietary risk factors of type 2 diabetes, we cannot entirely rule out the possibility of residual or unmeasured confounding.

The ATBC study included only male smokers, which should be noted when the results are extrapolated to women or non-smokers. Furthermore, the drug reimbursement register was not able to separate the types of diabetes (type 1 and type 2 diabetes). We assumed, however, that the new diabetes cases in the present study had type 2 diabetes based on the age (50–69 years) of the participants at baseline. We were able to identify only patients receiving medication for the treatment of diabetes, not individuals treating their disease with dietary changes. This will attenuate our estimates between meat consumption and diabetes incidence towards unity. Furthermore, we had a single assessment of diet by a FFQ at baseline, and were not able to investigate changes in meat consumption during the follow-up. This may have contributed to the misclassification of exposure, which will also attenuate the observed associations.

Maintenance of normal weight, avoidance of sedentary behaviour and smoking, moderate alcohol consumption and healthy diet are the most potential preventive factors against type 2 diabetes[29]. The present findings confirmed that a diet poor in meat, especially processed meat, may also help to prevent type 2 diabetes.

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