Consumption of dietary fat and meat and risk of ovarian cancer in the Netherlands Cohort Study

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ABSTRACT

Background: Evidence that links dietary factors to ovarian cancer is conflicting, but several epidemiologic studies suggested that consumption of dietary fat and meat may increase risk of ovarian cancer.

Objective: We studied associations of intakes of total fat and sources and subtypes of fat, fresh meat, processed meat, and fish with ovarian cancer risk within the Netherlands Cohort Study (NLCS).

Design: The NLCS includes 62,573 postmenopausal women, aged 55–69 y at baseline, who completed a baseline questionnaire on dietary habits and other risk factors for cancer in 1986. After 16.3 y of follow-up, 340 ovarian cancer cases and 2161 subcohort members were available for a case-cohort analysis. Multivariable rate ratios (RRs) were adjusted for age at baseline, total energy intake, oral contraceptive use, and parity.

Results: There were no clear associations between intakes of total fat, saturated fat, mono- and polyunsaturated fats, animal fat, plant-based fat, dairy fat, other fat sources, fresh meat, processed meat, and fish and ovarian cancer risk. There was a positive association between consumption of *trans* unsaturated fatty acids and ovarian cancer risk. The multivariable RR for women in the highest compared with the lowest quintiles of intake was 1.51 (95% CI: 1.04, 2.20; P for trend = 0.01). Although no significant interactions by oral contraceptive use or parity were shown, effect sizes were generally more pronounced and significant in women who never used oral contraceptives and in parous women.

Conclusion: This prospective study suggests that *trans* unsaturated fatty acids, but no other types of fat or meat, are associated with increased ovarian cancer risk. *Am J Clin Nutr* 2011;93:118–26.

INTRODUCTION

Research has suggested that the cause of ovarian cancer is predominantly related to hormones and reproduction; the strongest known protective factors are oral contraceptive use and parity (1, 2). In contrast, evidence linking dietary factors to ovarian cancer is inconsistent and limited, although several epidemiologic studies have suggested that consumption of dietary fat and meat may increase risk of ovarian cancer.

Ecologic and migrant studies were the first to provide epidemiologic support for a direct association between the intake of dietary fat, particularly animal fat, and meat and ovarian cancer mortality (3, 4). Since then, numerous case-control studies (5–17), but only a few prospective cohort studies (18–22), have published on total, animal, or saturated fat intake or meat consumption and ovarian carcinogenesis at the individual level. Nonetheless, a recent expert panel report concluded that these epidemiologic data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached (23).

Dietary fat and meat were hypothesized to affect ovarian carcinogenesis primarily via hormone related mechanisms. A high intake of dietary fat was suggested to expose the ovarian epithelium to high concentrations of endogenous circulating estrogens that may, through cell damage and proliferation, increase the likelihood of cancer development (24–26). Although this mechanism was not supported by all studies (27–29), a meta-analysis of dietary intervention studies to lower total fat intake observed significant reductions in serum estradiol levels (30), and research showed higher urinary estrogen excretion concentrations in omnivore compared with vegetarian postmenopausal women (31). Likewise, meat consumption was suggested to increase ovarian carcinogenesis either via its relatively high fat content or alternatively through the cancerous effect of meat-specific mutagens; *N*-nitroso compounds, heterocyclic amines, and polycyclic aromatic hydrocarbons can be derived from natural food or during the process of food preservation and preparation (32).

Nevertheless, little is known concerning the association of ovarian cancer risk and different sources and types of fat and meat. Therefore, the objective of the current study was to test the hypothesis that dietary intake of fat and specific sources of fat and intakes of fresh meat, processed meat, and fish are associated with subsequent risk of ovarian cancer in postmenopausal women in a large prospective cohort study that includes extensive quantitative food frequency and lifestyle information and a large number of ovarian cancer cases in the Netherlands. Because the effect of fat and meat intake may vary according to parity and oral contraceptive use, we also examined whether the associations

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differed by these well-established protective factors of ovarian cancer.

SUBJECTS AND METHODS

Study population and cancer follow-up

The Netherlands Cohort Study (NCLS) was initiated in September 1986 and includes 62,573 women, aged 55–69 y at baseline, who originated from 204 municipalities with computerized population registries. Full details of the study design have been described elsewhere (33). At the start of the study, participants completed a self-administered questionnaire on dietary habits, lifestyle characteristics, medical histories, and other potential risk factors for cancer. The case-cohort approach was used for reasons of efficiency in questionnaire processing and follow-up. Case subjects were enumerated from the entire cohort, whereas the accumulated person-years of the entire cohort were estimated from a random subcohort of 2589 women who were chosen immediately after baseline. The entire cohort is being monitored for cancer occurrence by an annual record linkage to the Netherlands Cancer Registry and the Netherlands Pathology, which, together, provide nearly 100% coverage (34). None of the female subcohort members were lost to follow-up.

For cases and subcohort members, all prevalent cancer cases at baseline other than nonmelanoma skin cancer were excluded. After 16.3 y of follow-up (until December 2002), 421 incident, microscopically confirmed, primary ovarian carcinomas were detected. After the exclusion of nonepithelial tumors (n = 13), borderline invasive tumors (n = 14), and cases with incomplete or inconsistent dietary data (35) (n = 42), 352 cases remained eligible for analyses. In the subcohort, women who had reported at baseline to have undergone an oophorectomy (n = 32) and women with incomplete or inconsistent dietary data (n = 190) were excluded, which left 2216 subcohort members (including 16 ovarian cancer cases) for analysis. The NLCS was approved by the institutional review boards of the TNO Quality of Life research institute (Zeist, Netherlands) and Maastricht University (Maastricht, Netherlands).

Questionnaire

All participants completed a 150-item semiquantitative food-frequency questionnaire (FFQ) at baseline that estimated the average frequency and amounts of foods and beverages consumed over the previous 12 mo. Daily mean nutrient intakes were calculated from the FFQ dietary data by summing the multiplied frequencies and number of serving sizes of all food items with their tabulated nutrient contents from the Dutch food-composition table (36).

Intakes of specific fatty acids were based on a separate database with specific fatty acids derived from the TRANSFAIR study (37). In the database, total fat included triglycerides and other lipids, such as phospholipids and sterols. The percentage of triglycerides in total fat was assumed to be 93% on average, but it varies across food sources. The concentrations of fatty acids were based on the concentrations before 1995 when changes in the *trans* content of manufactured products, such as margarines, led to a substantial decrease in the intake of *trans* unsaturated fatty acids (TFAs).

The coding of fresh meat items was based on raw weights to take into account the amount of fat originally present in the meat but eventually ending up in the gravy, which is usually consumed as well. Processed meat was defined as meat items that had undergone some form of preservation (mostly treatment with nitrate salt and sometimes smoked or fermented).

The FFQ has been validated and tested for reproducibility (35, 38). Crude Pearson's r (energy- and sex-adjusted values between parentheses) between the questionnaire and the 9-d diet record (kept over 3-d periods, 4–5 mo apart) was 0.74 for energy, 0.72 (0.52) for total fat, 0.73 (0.58) for saturated fatty acids (SFAs), and 0.73 (0.75) for polyunsaturated fatty acids (PUFAs). Spearman's r for fresh meat, processed meat, and fish were 0.46, 0.54, and 0.53, respectively (35).

Statistical analyses

The comprehensive set of exposure variables in our analyses included intakes (in g/d) of the following nutrients: total fat, fat from plant foods, fat from animal products (ie, milk, eggs, meat, and fish), the ratio of plant-based fat to animal fat, fat from meat, dairy fat, fat from margarines, SFAs, monounsaturated fatty acids (MUFAs), PUFAs, and TFAs.

Fat from plant foods covered fat that is naturally present in all plant foods (including vegetable oils) but excluded (partly hydrogenated) vegetable fat from margarine. Fat from meat referred to fat from fresh meats and fat from processed meats. Fat from fish was not analyzed separately because fish intake was measured with limited accuracy only (no differentiation between oily fish and whitefish), whereas fat from margarines was assessed comprehensively in the NLCS. We intentionally included TFAs in analyses; TFAs were characterized by part hydrogenation of plant-based oils, which were hypothesized to have distinct carcinogenic effects. Intakes of fat items were all adjusted for energy intakes by the residual method (39). Also, the following food groups and foods were selected (in g/d): fresh meat (ie, beef, pork, minced meat, chicken, and liver), processed meat, fish, fresh red meat (ie, fresh meat without chicken), and beef, pork, minced meat, chicken, and liver as separate items.

Age- and energy-adjusted and multivariable adjusted incidence rate ratios (RRs) and their corresponding 95% CIs were estimated by using Cox proportional hazards models. The total person-years at risk, which were estimated from the subcohort, were used in analyses (40). SEs were estimated by using the robust Huber-White sandwich estimator to account for additional variance introduced by sampling from the cohort (41). The proportional hazards assumption was tested by using the scaled Schoenfeld residuals; in case of violation, the follow-up period was stratified into 3 categories ($<$5, 5–10, and $>$10 y of follow-up), a test for interaction between the determinant and time was calculated, and time-stratified results were estimated.

The covariates included in the multivariate analyses were either a priori–selected risk factors of ovarian cancer or variables that changed risk estimates for total fat or total fresh meat intakes by $\geq$10%. The latter criterion was not met for any covariate other than the predefined covariates, which resulted in a final model that included age (in y), use of oral contraceptives (ever compared with never), and number of children (n). Total energy intake (in kcal/d) was included in the age and multivariable-adjusted models. RRs for energy-adjusted total fat and fatty

acids were interpreted as the effect of an increase in these variables relative to a decrease of an equivalent amount of energy from other energy-delivering nutrients (ie, substituting these exposure nutrients for other energy-delivering nutrients). In addition, to assess the independent contribution of SFAs, MUFAs, PUFAs, and TFAs, total fat intake was also included in the respective multivariable adjusted models. To further explore our data, we ran an additional model that included all fatty acids together (SFAs, MUFAs, PUFAs, and TFAs) to investigate the relative contribution of each fatty acid. The independent contribution of the individual meat categories (ie, total fresh meat, fresh red meat, beef, pork, minced meat, chicken, and liver) was examined by creating a model in which the complementary meat items were also included in the respective multivariable adjusted models.

Subjects were classified into quintiles of consumption (with the lowest quintile regarded as the reference group) and as continuous variables. The latter were reported in a 1-SD increase of consumption for the fat and fatty acid items, an increase of 0.2 in the ratio of plant-based fat to animal fat, and a 25-g/d increase for all meat items and fish. For some variables, categories were used instead of quintiles. For liver intake, there was a nonconsumption and consumption group (>0 g liver/d). For chicken and fish, nonconsumption and 3 consumption categories (0 to <13.2, ≥13.2 to <22.8, and ≥22.8 g chicken/d; 0 to <10, ≥10 to <20, and ≥20 g fish/d) were defined.

To enable comparison, the age- and energy-adjusted analyses were restricted to subjects included in multivariable-adjusted analyses (eg, with no missing values on confounding variables), which left 2161 subcohort members and 340 ovarian cancer cases for analyses. For each analysis, trends were evaluated with the Wald test by assigning participants the median value for each level of the categorical exposure variables among the subcohort members, and this variable was entered as a continuous term in the Cox regression model.

The interaction of meat and fat intake by use of oral contraceptives or parity was tested by using cross-product terms between continuous variables of meat or fat intake and oral contraceptive use and parity as a dichotomous variable [categories were ever and never oral contraceptive use; nulliparous (0 children) and parous (≥1 child)].

All analyses were performed with STATA Statistical Software (Intercooled STATA, version 10; StataCorp LP, College Station, TX). All tests were 2-tailed, and differences were regarded as statistically significant at $P < 0.05$.

RESULTS

After 16.3 y of follow-up in 62,573 women, 394 invasive epithelial ovarian cancer cases occurred, 340 cases of which were in women with complete and consistent dietary data. The baseline characteristics for cases and subcohort members of which the greater part did not differ between ovarian cancer cases and subcohort members are shown in **Table 1**. However, the percentage of women who reported ever use of oral contraceptives and the percentage of current smokers were higher in subcohort members than in cases. Fewer cases reported to have undergone a hysterectomy, and cases had a smaller number of children than subcohort members. No striking differences between cases and subcohort members were observed regarding baseline dietary intakes of exposures of interest.

TABLE 1
Baseline characteristics and dietary intakes of exposures of interest of ovarian cancer cases and subcohort members within the Netherlands Cohort Study, 1986–2002

Characteristics	Ovarian cancer cases	Subcohort
n	340	2161
Age (y)	61.8 ± 4.3[1]	61.4 ± 4.3
Current smokers (%)	17.6	21.2
Years of smoking	26.8 ± 12.4	27.8 ± 12.5
BMI (kg/m^2)	25.1 ± 3.5	25.1 ± 3.5
Physical activity, nonoccupational (%)		
<30 min/d	27.1	24.2
30–60 min/d	31.5	30.7
60–90 min/d	23.2	22.6
>90 min/d	17.1	21.2
Level of education (%)		
Low	58.8	56.7
Medium	33.2	34.5
High	8.0	8.8
Reproductive and hormonal factors		
Age at menarche (y)	13.7 ± 1.8	13.7 ± 1.8
Age at menopause (y)	49.2 ± 4.0	48.7 ± 4.5
Use of oral contraceptives (% ever)	18.5	24.9
Hysterectomy (% yes)	7.4	14.2
Use of postmenopausal hormones (% ever)	12.1	12.4
Parity (%)		
0 children	23.2	18.0
1 child	9.7	8.2
2 children	25.6	21.7
>2 children	41.5	52.1
Age at first birth (y)	21.1 ± 12.2	22.1 ± 11.0
Family history of ovarian cancer (%)	0.6	0.0
Family history of breast cancer (%)	7.9	8.7
Dietary factors (daily intake) (g)		
Total fat and specific fatty acids[2]		
Total fat	74.1 ± 9.9	73.9 ± 10.3
Fat from plant-based products	8.5 ± 6.4	9.0 ± 6.8
Fat from animal sources, total	40.1 ± 13.6	38.6 ± 13.1
Fat from meat fat	15.6 ± 6.6	15.9 ± 7.1
Fat from dairy products	20.4 ± 13.7	18.5 ± 12.6
Fat from margarines	25.5 ± 13.0	26.3 ± 13.2
Saturated fatty acids	30.6 ± 6.3	29.7 ± 5.8
Monounsaturated fatty acids	27.5 ± 4.8	27.5 ± 5.0
Polyunsaturated fatty acids	14.5 ± 6.3	15.0 ± 6.1
trans Unsaturated fatty acids	2.6 ± 1.0	2.5 ± 0.9
Types of fresh meat, processed meat, fish, and eggs[3]		
Total fresh meat	92.0 ± 34.4	93.4 ± 40.0
Fresh red meat	80.0 ± 33.4	80.7 ± 38.6
Beef	26.0 ± 21.6	24.2 ± 21.7
Pork	34.0 ± 24.6	35.5 ± 28.4
Minced meat	16.0 ± 14.2	16.9 ± 15.5
Liver	1.7 ± 4.1	1.7 ± 4.0
Chicken	12.9 ± 14.2	13.4 ± 15.6
Other meat (eg, horsemeat and lamb)	2.2 ± 6.5	2.4 ± 7.0
Processed meat	10.4 ± 11.3	10.5 ± 11.8
Fish	10.9 ± 11.8	11.7 ± 13.5
Eggs	15.3 ± 10.3	14.8 ± 9.8

[1] Mean ± SD (all such values).
[2] Energy-adjusted intake.
[3] Intakes of fresh meat items were based on raw-meat weights.

No association was shown when the relation was examined between risk of ovarian cancer and the dietary intake of total fat, fat from meat, fat from animal products, fat from margarines, SFAs, MUFAs, and PUFAs in the multivariable model (**Table 2**). Regarding fat from plant foods, an inverse association was observed, which showed a significant decreased risk of ovarian cancer for all quintiles compared with the lowest quintile (multivariable RRs: 1.00, 0.58, 0.67, 0.67, and 0.64, respectively; *P* for trend = 0.05) (Table 2). A significant increased ovarian cancer risk per 1-SD intake of dairy fat intake as a continuous variable was observed (multivariable RR: 1.13; 95% CI: 1.01, 1.27), but no evidence of a linear trend was shown (Table 2). For TFAs, a significant increased risk of ovarian cancer for the highest compared with the lowest quintiles of TFA intake (multivariable RR: 1.51; 95% CI: 1.04, 2.20) was observed. Also, a dose-response relation was observed (*P* for trend = 0.01), and a significant increased ovarian cancer risk per 1-SD intake of TFA intake as a continuous variable was reported (multivariable RR: 1.14; 95% CI: 1.03, 2.28) (Table 2). When all fatty acids were included together in one model, the association between SFAs, MUFAs, PUFAs and TFAs and ovarian cancer risk attenuated slightly, but the direction of the association did not change appreciably (results not shown). A significant inverse trend across all quintiles of MUFA intake and ovarian cancer was observed (*P* for trend = 0.03), but the RR for a 1-SD increase was similar (RR: 0.84; 95% CI: 0.88, 1.14) (results not shown).

Intakes of total fresh meat and fresh red meat did not show a clear monotonic increasing relation with ovarian cancer risk but RRs did significantly increase in women in the intermediate quintiles of intakes (ie, quintiles 2–4; multivariable RRs for total fresh meat: 1.00, 1.45, 1.54, 1.48, and 0.97, respectively; multivariable RRs for fresh red meat: 1.00, 1.58, 1.47, 1.78, and 0.93, respectively) (**Table 3**). After adjustment for age and energy, no association was shown between intakes of beef, pork, minced meat, liver, chicken, processed meat, and fish separately and risk of ovarian cancer (Table 3). These findings remained after the inclusion of the confounding variables in the multivariable model. Additional adjustment for the complementary meat items in the multivariable models did not change the results notably (results not shown). For beef and pork consumption, the proportional hazards assumption was violated. We observed a significant interaction with time for beef (*P* for interaction = 0.022) but not for pork (*P* for interaction = 0.092). When the follow-up period was stratified into 3 categories (data not shown), only during the first 5 y of follow-up was a statistical significantly increased risk of ovarian cancer observed in quintiles 3–5 compared with in the lowest quintile of beef intake (RRs: 1.00, 0.99, 2.30, 2.04, and 3.02, respectively), which indicated that the association between beef intake and ovarian cancer risk attenuates over time.

When we tested for interactions by the use of oral contraceptives or parity, we observed no significant interaction (results not shown). Stratified analyses (*see* supplemental Table 1 under "Supplemental data" in the online issue) showed significant positive associations with ovarian cancer only in parous women and those who never used oral contraceptives as regards to animal fat, dairy fat, TFA, and SFA intakes, whereas an inverse association with PUFA intake was observed in parous women only. Stratified analyses regarding meat consumption yielded similar results compared with the overall assessment (results not shown). Because of the limited use of postmenopausal hormone-replacement therapy in our cohort, we were not able to test this interaction.

DISCUSSION

In this large, prospective cohort study, a comprehensive set of different sources and subtypes of fat and meat was examined in relation to ovarian cancer risk. Results showed a significant positive association between the dietary intake of TFAs and risk of epithelial ovarian cancer.

Previously, a meta-analysis of predominantly case-control studies (42) showed an increased risk of ovarian cancer for the highest compared with the lowest intakes of total fat, animal fat and saturated fat (RRs: 1.24, 1.20 and 1.70, respectively). Nevertheless, incidence of ovarian cancer was not associated with total fat or any subtype of dietary fat intake according the Iowa Women's Health Study (20) and the Nurses' Health Study (19), whereas case control studies yielded mixed results (8, 13–17). Although comparable with previous studies, the range of energy intake from total fat in the current study was small (varied from 32% in the lowest quintile to 46% in the fifth quintile), which might have contributed to the lack of association observed. Moreover, habitual fat intake of $<$30% of energy is considered to be difficult to achieve in Western populations. However, recent results from the Women's Health Initiative Dietary Modification Trial suggested that a low-fat dietary pattern (24.3% compared with 35.1% of energy from fat after 1 y from baseline for the intervention and control groups, respectively) may reduce the incidence of ovarian cancer in healthy postmenopausal women (RR: 0.60; low-fat diet compared with a regular diet after 4–8 y of follow-up) (43).

Thus far, epidemiologic evidence that links TFAs to any type of cancer is limited (44); both the Nurses' Health Study (19) and a pooled analysis (45) that included data from 4 cohort studies showed no evidence of an association between the intake of TFAs and ovarian cancer risk. In contrast, we showed a positive association between the dietary intake of TFAs and risk of ovarian cancer. After the substantial reduction of TFAs in margarines in Europe in 1995 (46), the remaining TFAs in the diet are mainly consumed from fast food products, cakes, and biscuits (47). Although these specific dietary sources are likely to be closely related to other lifestyle factors or food specific chemicals such as acrylamide, the adjustment for these did not substantially attenuate the association between TFAs and ovarian cancer risk (results not shown). Although a considerable latency period may exist between fat intake and cancer risk, we did not observe a significant interaction with time of follow-up (*P* for interaction = 0.46), which suggested that the strength of the association did not follow the decline in TFA exposure.

The consumption of fat from plant foods was not associated with ovarian cancer risk in 2 case-control studies (8, 12) or in 2 prospective cohort studies in the United States (19, 20) and a pooled analysis of 9 cohort studies (45). Conversely, the current results suggested an inverse association between plant-based fat consumption and ovarian cancer risk above the threshold of 4.5 g plant-based fat/d. However, the direction of the association depends on the choice of the reference category; changing this to a higher category would show an increased risk for individuals with the lowest intake. Nevertheless, previous studies often do

TABLE 2
Ovarian cancer according to quintile (Q) of intake of total fat, fat sources, and specific fatty acids within the Netherlands Cohort Study, 1986–2002[1]

Food item	Median intake in subcohort	Person-years	No. of cases	Total ovarian cancer cases	
				RR (95% CI)[2]	RR (95% CI)[3]
Total fat (g/d)[4]					
Q1	61.0	6399	70	1.00	1.00
Q2	69.1	6462	60	0.86 (0.59, 1.24)	0.86 (0.59, 1.25)
Q3	73.9	6388	74	1.08 (0.75, 1.54)	1.07 (0.75, 1.53)
Q4	78.9	6408	61	0.88 (0.61, 1.27)	0.87 (0.60, 1.26)
Q5	86.5	6466	75	1.06 (0.74, 1.50)	1.04 (0.73, 1.49)
P for trend	—	—	—	0.73	0.80
Continuous 1 SD	—	—	—	1.02 (0.91, 1.13)	1.01 (0.90, 1.13)
Fat from plant sources (g/d)[4]					
Q1	2.8	6324	95	1.00	1.00
Q2	5.8	6495	56	0.57 (0.40, 0.83)	0.58 (0.40, 0.84)
Q3	8.0	6365	64	0.67 (0.46, 0.96)	0.67 (0.46, 0.96)
Q4	10.6	6421	64	0.68 (0.47, 0.97)	0.67 (0.47, 0.96)
Q5	15.9	6519	61	0.63 (0.45, 0.90)	0.64 (0.45, 0.91)
P for trend	—	—	—	0.06	0.05
Continuous 1 SD				0.93 (0.81, 1.06)	0.93 (0.81, 1.07)
Fat from animal sources (g/d)[4]					
Q1	23.9	6436	71	1.00	1.00
Q2	31.4	6407	61	0.85 (0.59, 1.23)	0.84 (0.58, 1.22)
Q3	36.7	6511	58	0.81 (0.56, 1.17)	0.81 (0.56, 1.18)
Q4	43.6	6442	56	0.78 (0.53, 1.13)	0.78 (0.53, 1.13)
Q5	56.6	6327	94	1.31 (0.94, 1.84)	1.30 (0.93, 1.83)
P for trend	—	—	—	0.19	0.19
Continuous 1 SD	—	—	—	1.12 (0.88, 1.25)	1.11 (0.99, 1.25)
Ratio of plant-based to animal fat					
Q1	0.06	6302	76	1.00	1.00
Q2	0.13	6430	69	0.89 (0.63, 1.27)	0.92 (0.65, 1.31)
Q3	0.20	6462	76	0.99 (0.70, 1.40)	1.00 (0.70, 1.41)
Q4	0.30	6364	66	0.88 (0.61, 1.26)	0.90 (0.63, 1.29)
Q5	0.53	6550	53	0.69 (0.47, 1.01)	0.70 (0.48, 1.02)
P for trend	—	—	—	0.08	0.09
Continuous 1 SD	—	—	—	0.95 (0.86, 1.05)	0.95 (0.86, 1.06)
Fat from fresh and processed meats (g/d)[4]					
Q1	7.6	6633	75	1.00	1.00
Q2	12.2	6558	67	0.91 (0.64, 1.31)	0.93 (0.65, 1.34)
Q3	15.2	6456	70	0.97 (0.68, 1.38)	0.96 (0.67, 1.36)
Q4	18.8	6652	64	0.86 (0.60, 1.23)	0.88 (0.61, 1.26)
Q5	24.6	6653	64	0.87 (0.60, 1.24)	0.90 (0.62, 1.29)
P for trend	—	—	—	0.39	0.50
Continuous 1 SD	—	—	—	0.96 (0.86, 1.07)	0.98 (0.87, 1.09)
Fat from dairy products (g/d)[4]					
Q1	5.3	6627	70	1.00	1.00
Q2	11.0	6434	62	0.90 (0.62, 1.30)	0.89 (0.62, 1.29)
Q3	15.6	6457	51	0.74 (0.50, 1.08)	0.72 (0.49, 1.06)
Q4	22.6	6325	64	0.92 (0.64, 1.33)	0.90 (0.62, 1.30)
Q5	36.2	6381	93	1.33 (0.95, 1.87)	1.28 (0.91, 1.80)
P for trend	—	—	—	0.11	0.17
Continuous 1 SD	—	—	—	1.15 (1.03, 1.28)	1.13 (1.01, 1.27)
Fat from margarines (g/d)[4]					
Q1	9.7	6424	80	1.00	1.00
Q2	19.3	6368	61	0.78 (0.54, 1.12)	0.77 (0.54, 1.11)
Q3	26.0	6456	69	0.87 (0.61, 1.23)	0.87 (0.61, 1.23)
Q4	32.7	6519	60	0.76 (0.53, 1.09)	0.75 (0.52, 1.08)
Q5	42.5	6357	70	0.88 (0.62, 1.25)	0.87 (0.61, 1.23)
P for trend	—	—	—	0.49	0.42
Continuous 1 SD	—	—	—	0.94 (0.84, 1.05)	0.93 (0.83, 1.05)
Saturated fatty acids (g/d)[4,5]					
Q1	23.1	6401	68	1.00	1.00
Q2	26.7	6427	64	0.98 (0.66, 1.46)	0.98 (0.66, 1.46)

(Continued)

TABLE 2 (*Continued*)

Food item	Median intake in subcohort	Person-years	No. of cases	Total ovarian cancer cases	
				RR (95% CI)[2]	RR (95% CI)[3]
Q3	29.2	6530	57	0.88 (0.58, 1.35)	0.90 (0.59, 1.37)
Q4	32.3	6403	57	0.89 (0.57, 1.41)	0.89 (0.56, 1.40)
Q5	37.5	6363	94	1.50 (0.95, 2.38)	1.48 (0.94, 2.34)
P for trend	—	—	—	0.12	0.14
Continuous 1 SD	—	—	—	1.23 (1.05, 1.43)	1.21 (1.04, 1.41)
Monounsaturated fatty acids (g/d)[4,5]					
Q1	21.7	6410	66	1.00	1.00
Q2	25.1	6418	78	1.12 (0.78, 1.64)	1.16 (0.80, 1.68)
Q3	27.4	6381	65	0.95 (0.63, 1.42)	1.00 (0.66, 1.51)
Q4	29.8	6436	66	0.92 (0.60, 1.41)	0.97 (0.63, 1.49)
Q5	33.5	6479	65	0.84 (0.52, 1.37)	0.90 (0.55, 1.46)
P for trend	—	—	—	0.29	0.44
Continuous 1 SD	—	—	—	0.92 (0.78, 1.09)	0.85 (0.80, 1.12)
Polyunsaturated fatty acids (g/d)[4,5]					
Q1	8.0	6381	86	1.00	1.00
Q2	11.4	6412	54	0.63 (0.44, 0.91)	0.65 (0.44, 0.94)
Q3	14.1	6473	62	0.73 (0.50, 1.05)	0.78 (0.54, 1.14)
Q4	17.6	6411	78	0.91 (0.64, 1.29)	0.93 (0.66, 1.32)
Q5	23.2	6446	60	0.68 (0.47, 0.99)	0.89 (0.47, 1.01)
P for trend	—	—		0.30	0.33
Continuous 1 SD	—	—		0.90 (0.79, 1.03)	0.90 (0.79, 1.03)
trans Unsaturated fatty acids (g/d)[4,5]					
Q1	1.5	6435	63	1.00	1.00
Q2	2.1	6446	55	0.92 (0.62, 1.35)	0.91 (0.62, 1.35)
Q3	2.4	6407	59	0.99 (0.67, 1.47)	0.99 (0.67, 1.47)
Q4	2.8	6420	77	1.31 (0.90, 1.91)	1.33 (0.91, 1.94)
Q5	3.5	5417	86	1.49 (1.03, 2.16)	1.51 (1.04, 2.20)
P for trend	—	—	—	0.01	0.01
Continuous 1 SD	—	—	—	1.14 (1.02, 1.26)	1.14 (1.03, 1.28)

[1] RR, rate ratio. Q1 was the reference category. RRs were derived from Cox regression analyses.
[2] Adjusted for age (y) and total energy intake (kcal).
[3] Adjusted for age (y), total energy intake (kcal), parity (number of children), and use of oral contraceptives (ever or never).
[4] Energy-adjusted intake.
[5] Additionally adjusted for total energy-adjusted fat intake.

not specify whether hydrogenated vegetable oils, which are characteristically more comparable with animal fat, are included in this fat source, which makes comparisons between studies difficult. In the current analyses, plant-based fat accounted, on average, for only 12% of total fat intake. However, the intake was greatly dispersed and likely to reflect a dietary pattern in the extremes. Regarding this, factor analyses previously identified 5 stable dietary patterns in women in the NLCS (48). Although consumption of fat from plant foods was inversely correlated with the "fat dairy pattern" ($r = 0.28$, $P < 0.001$) (high loadings of potatoes, nonfermented whole milk, margarine, and sweet sandwich spread), adjustment for this pattern did not noticeably change the results (results not shown). Moreover, a borderline significant trend toward a protective effect of ovarian cancer for higher intakes of plant-based fat relative to animal fat (P for trend = 0.086) was observed in the current study.

We observed a higher ovarian cancer risk per 1-SD increase in dairy fat intake, but because there was no increasing trend through all quintiles, we are prudent when interpreting these findings. More studies are warranted to further examine this association particularly because longitudinal epidemiologic evidence is limited and conflicting (18, 19).

A direct association between meat consumption and ovarian cancer risk has been proposed by several (5–9) but not all (10–13, 19, 20, 22) case-control studies. Two prospective cohort studies that included a large proportion of vegetarians or low-meat consumers were indicative of a positive association between total meat consumption and ovarian cancer risk (18, 49). In contrast, 4 other cohort studies (19–22) and a recent meta-analysis (50) with smaller numbers of low- or no-meat consumers showed no clear evidence for an association with total or red meat consumption. However, our results suggested that women at the extremes of the total fresh-meat and fresh red-meat consumption spectrum may be at lower risk of developing ovarian cancer compared with women with intermediate consumption. To our knowledge, such an association has not previously been reported and may reflect a specific dietary and lifestyle pattern that is high in fresh-meat consumption. Nevertheless, a negligible attenuation in the association with ovarian cancer was observed after adjustment for the dietary pattern that correlated most strongly with total fresh-meat consumption ("pork, processed meat, and potatoes pattern") (48) ($r = 0.29$, $P < 0.001$) or when adjusting for other potential covariates. Although our reference category was characterized by a considerable wide range of total fresh-meat consumption

TABLE 3
Ovarian cancer according to quintile (Q) and category of intake of fresh meat, types of fresh meat, and processed meat within the Netherlands Cohort Study, 1986–2002[1]

Food item	Median intake in subcohort	Person-years	No. of cases	Total ovarian cancer cases	
				RR (95% CI)[2]	RR (95% CI)[3]
Total fresh meat (g/d)[4]					
Q1	45.2	6300	52	1.00	1.00
Q2	74.4	6500	77	1.44 (0.99, 2.09)	1.45 (1.00, 2.13)
Q3	92.0	6367	80	1.51 (1.04, 2.20)	1.54 (1.06, 2.42)
Q4	107.5	6519	80	1.48 (1.02, 2.15)	1.49 (1.03, 2.17)
Q5	145.8	6438	51	0.94 (0.62, 1.42)	0.97 (0.63, 1.47)
P for trend				0.86	0.96
Continuous (25-g/d intake increment)				0.97 (0.91, 1.04)	0.98 (0.91, 1.04)
Fresh red meat (g/d)[5]					
Q1	36.2	6491	51	1.00	1.00
Q2	61.3	6314	77	1.54 (1.06, 2.25)	1.58 (1.08, 2.30)
Q3	77.9	6389	73	1.45 (0.99, 2.12)	1.47 (1.00, 2.16)
Q4	95.6	6477	92	1.77 (1.23, 2.56)	1.78 (1.23, 2.58)
Q5	129.6	6453	47	0.91 (0.60, 1.38)	0.93 (0.61, 1.42)
P for trend				0.90	0.85
Continuous (25-g/d intake increment)				0.98 (0.92, 1.05)	0.98 (0.92, 1.05)
Beef (g/d)					
Q1	2.2	6445	68	1.00	1.00
Q2	10.7	6471	53	0.77 (0.53, 1.13)	0.77 (0.52, 1.13)
Q3	18.9	6478	58	0.98 (0.68, 1.41)	0.98 (0.68, 1.42)
Q4	30.7	6391	67	0.97 (0.67, 1.40)	0.95 (0.66, 1.38)
Q5	50.4	6339	84	1.21 (0.86, 1.72)	1.15 (0.81, 1.64)
P for trend				0.14	0.23
Continuous (25-g/d intake increment)				1.09 (0.97, 1.22)	1.07 (0.95, 1.20)
Pork (g/d)					
Q1	3.5	6489	62	1.00	1.00
Q2	18.3	6335	74	1.23 (0.85, 1.76)	1.26 (0.87, 1.81)
Q3	31.1	6417	71	1.18 (0.81, 1.69)	1.21 (0.84, 1.76)
Q4	44.7	6410	67	1.09 (0.75, 1.58)	1.14 (0.78, 1.66)
Q5	71.2	6472	66	1.07 (0.73, 1.55)	1.08 (0.75, 1.59)
P for trend				0.99	0.88
Continuous (25-g/d intake increment)				0.95 (0.86, 1.04)	0.96 (0.87, 1.05)
Minced meat (g/d)[6]					
Q1	0	6357	66	1.00	1.00
Q2	7.6	6281	67	1.02 (0.71, 1.47)	1.06 (0.73, 1.53)
Q3	13.4	6722	83	1.19 (0.84, 1.68)	1.26 (0.89, 1.80)
Q4	21.4	6366	69	1.05 (0.73, 1.52)	1.13 (0.78, 1.63)
Q5	36.6	6398	55	0.82 (0.56, 1.21)	0.86 (0.59, 1.27)
P for trend				0.43	0.64
Continuous (25-g/d intake increment)				0.89 (0.74, 1.07)	0.91 (0.76, 1.09)
Liver (g/d)[7]					
Q1	0	21,519	227	1.00	1.00
Q2	3.3	10,604	113	1.04 (0.81, 1.33)	1.07 (0.84, 1.38)
Continuous (25-g/d intake increment)				1.15 (0.59, 2.25)	1.29 (0.66, 2.52)
Chicken (g/d)[7]					
Q1	0	7530	76	1.00	1.00
Q2	5.3	8304	95	1.15 (0.83, 1.59)	1.18 (0.85, 1.64)
Q3	13.2	7436	79	1.07 (0.76, 1.51)	1.14 (0.81, 1.61)
Q4	22.8	8853	90	1.01 (0.73, 1.41)	1.06 (0.76, 1.48)
P for trend				0.93	0.83
Continuous (25-g/d intake increment)				0.94 (0.78, 1.13)	0.96 (0.80, 1.14)
Processed meat (g/d)					
Q1	0	6725	80	1.00	1.00
Q2	2.7	6268	53	0.71 (0.49, 1.03)	0.71 (0.49, 1.03)
Q3	6.8	6436	70	0.91 (0.65, 1.29)	0.91 (0.64, 1.29)
Q4	13.0	9227	70	0.93 (0.66, 1.32)	0.93 (0.65, 1.31)
Q5	25.6	6466	67	0.85 (0.60, 1.21)	0.83 (0.59, 1.20)
P for trend				0.80	0.74
Continuous (25-g/d intake increment)				0.97 (0.75, 1.25)	0.96 (0.75, 1.23)

(Continued)

TABLE 3 (*Continued*)

Food item	Median intake in subcohort	Person-years	No. of cases	Total ovarian cancer cases	
				RR (95% CI)[2]	RR (95% CI)[3]
Fish (g/d)[7]					
Q1	0	9879	102	1.00	1.00
Q2	4.6	7057	82	1.14 (0.83, 1.57)	1.15 (0.84, 1.58)
Q3	15.5	9729	101	1.00 (0.75, 1.36)	1.02 (0.76, 1.38)
Q4	28.2	5458	55	0.98 (0.69, 1.39)	1.01 (0.71, 1.43)
P for trend				0.81	0.94
Continuous (25-g/d intake increment)				0.90 (0.73, 1.10)	0.91 (0.74, 1.12)

[1] RR, rate ratio. Q1 was the reference category. RRs were derived from Cox regression analyses.
[2] Adjusted for age (y) and total energy intake (kcal).
[3] Adjusted for age (y), total energy intake (kcal), parity (number of children), and use of oral contraceptives (ever or never).
[4] Includes all types of meat (except processed meat) and chicken.
[5] Includes beef, pork, minced meat, liver, and other meat.
[6] Includes beef and pork.
[7] Categorical cutoffs were as follows—for liver: 0 and >0 g/d; for chicken: 0, 0 to <13.2, ≥13.2 to <22.8, and ≥22.8 g/d; and for fish: 0, 0 to <10, ≥10 to <20, and ≥20 g/d.

(0–62.5 g fresh meat/d; 0–7 d/wk), changing this to a smaller, more extreme category did not change the results appreciably.

In accordance with the one study (45) that previously examined effect modification by hormonal and reproductive factors on the association between dietary fat and meat intakes and ovarian cancer, we observed null results (possibly because of small numbers). However, the effect sizes regarding fat exposures were generally more pronounced in women who never used oral contraceptives and parous women, which suggested that hormonal pathways may be of significance in the cause of ovarian cancer. However; in our cohort, relatively few women were nulliparous, and women who reported oral contraceptive use were significantly younger than women who did not use oral contraceptives.

Our analyses were performed by using baseline FFQ data, which resulted in an inability to assess and account for changes in intakes and food compositions over time (eg, TFA content). However, the validity of the FFQ has been tested and shown to be representative for dietary habits over a period of at least 5 y (35). The prospective design reduced the potential for recall bias, and the nearly complete follow-up of cases and subcohort members made selection bias unlikely. The detailed information on diet and potential risk factors of ovarian cancer enabled us to control for most known ovarian cancer risk factors, although misclassification of exposure may have occurred. Regression parameters proved to be robust estimators because adjustment for potential covariates did not change them appreciably.

In conclusion, this prospective study suggests that TFAs, but no other types of fat or meat, may be associated with increased ovarian cancer risk in this population of postmenopausal women. The risk attributable to different sources and types of fats and interactions by oral contraceptive use and parity warrant further investigation.

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