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Long-term meat intake and risk of breast cancer by oestrogen and progesterone receptor status in a cohort of Swedish women

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ABSTRACT

Red meat intake has been postulated to increase the risk of breast cancer but epidemiologic studies have yielded inconsistent results. Data on meat intake in relation to hormone receptor-defined breast cancer are sparse. We examined the association of meat intake with incidence of breast cancer defined by oestrogen receptor (ER) and progesterone receptor (PR) status in the Swedish Mammography Cohort, a population-based cohort of 61,433 women. Dietary intake was assessed at baseline in 1987–1990 and again in 1997. Cox proportional hazards models were used to estimate relative risks for the association between long-term meat intake and breast cancer risk. During a mean follow-up of 17.4 years, 2952 incident cases of invasive breast cancer were ascertained. We found no association of total red meat, fresh red meat or processed meat intake with breast cancer risk. The multivariate relative risks (95% confidence interval) for the highest quintile of total red meat intake (≥ 98 g/d) compared with the lowest quintile (<46 g/d) were 0.98 (0.86–1.12) for overall breast cancer, 1.10 (0.90–1.34) for ER+/PR+ tumours, 0.86 (0.60–1.23) for ER+/PR– tumours and 1.12 (0.70–1.79) for ER–/PR– tumours. Intake of pan-fried meat was positively associated with a risk of ER+/PR– tumours; the multivariate relative risk for the highest compared with the lowest quartile of intake was 1.45 (95% confidence interval 1.03–2.03; $P_{\text{trend}} = 0.03$). These results do not support an association between red meat intake and overall breast cancer risk but suggest that fried meat intake may increase the risk of ER+/PR– breast cancer.

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1. Introduction

Diets high in red meat have been hypothesised to increase the risk of breast cancer. Red meat is an important source of dietary iron and there is evidence that elevated body iron levels and meat-derived haem iron may contribute to the development of breast cancer.^{1,2} Processed red meats, including bacon, sausage and ham, may contain carcinogenic N-nitroso compounds.³ Moreover, meat cooked at high temperatures,

such as pan frying and grilling/barbecuing, is a source of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons that can induce mammary gland cancer in rats.^{4,5} A positive association between intake of well-done meat or HCAs and the risk of breast cancer has been observed in some epidemiologic studies,^{6–9} but not in all.^{10–13} Epidemiologic studies on meat intake in relation to breast cancer risk have yielded inconsistent results, with a positive association observed in a meta-analysis¹⁴ and in some prospective

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studies^{15,16} but not in a pooled analysis of eight prospective studies¹⁷ and in several other prospective studies.^{11,18–20}

Increasing evidence indicates that oestrogen receptor-positive breast tumours are aetiologically different from receptor-negative tumours. Components of red meat, including HCAs in cooked meat and haem iron may influence breast cancer through hormone receptors.^{21,22} Hence, red meat intake may increase the risk specifically of hormone receptor-positive breast cancers. However, there is a paucity of data on red meat intake and risk of breast cancer defined by oestrogen receptor (ER) and progesterone receptor (PR) status of the tumour. In the Nurses' Health Study II, red meat intake was associated with an increased risk of ER+/PR+ breast cancer among premenopausal women.²³

The aim of this study was to examine the association between red meat intake and the risk of breast cancer defined by hormone receptor status in a population-based cohort of Swedish women. We also assessed the relation between pan-fried meat intake and breast cancer risk.

2. Materials and methods

2.1. Study population

The Swedish Mammography Cohort was established in 1987–1989 in Västmanland County and in 1988–1990 in Uppsala County in central Sweden. All women born between 1917 and 1948 in Västmanland County and between 1914 and 1948 in Uppsala County received a mailed invitation to be screened by mammography. Enclosed with the invitation was a six-paged questionnaire regarding diet, body size, reproductive factors, family history of breast cancer and other factors; a total of 66,651 women, representing 74% of the source population returned a completed questionnaire. In the late autumn of 1997, all cohort members who were still alive and residing in the study area ($n = 56,030$ women) received a new questionnaire that was expanded to include about 350 items concerning diet and other lifestyle factors; 39,227 women (70%) completed the second questionnaire.

From the baseline cohort of 66,651 women, we excluded those with an erroneous or a missing national registration number as well as those lacking date on the questionnaire, date of moving out of the study area or date of death. After additional exclusion of women with implausible values for total energy intake (i.e. 3 standard deviations from the mean value for \log_e -transformed energy intake) and those with a cancer diagnosis (except non-melanoma skin cancer) before baseline, the cohort consisted of 61,433 women. For analyses using data from the second questionnaire, 36,664 women were eligible after excluding those with implausible energy intake on the second dietary questionnaire and those with a cancer diagnosis between baseline and January 1998. The study was approved by the ethics committees at the Uppsala University Hospital (Uppsala, Sweden) and the Karolinska Institutet (Stockholm, Sweden).

2.2. Assessment of diet

A food-frequency questionnaire (FFQ) with 67 and 96 food items was used to assess diet at baseline and in 1997, respec-

tively. In these FFQs, participants reported their average intake of each food item over the previous 6th months (baseline FFQ) or previous year (1997 FFQ) with the use of eight prespecified mutually exclusive frequency categories. For this analysis, we grouped meats into red meat, fresh red meat and processed meat. Fresh red meat included all fresh and minced pork, beef and veal. Processed meats included ham, bacon, sausages, salami, processed meat cuts, liver pâté and blood sausages. Total red meat was the sum of fresh red meat and processed meat. Information on intake of pan-fried meats (including beef, pork and sausage) was obtained in the 1997 FFQ.

The baseline FFQ has been validated in a sample of 129 women randomly chosen from the cohort. The Spearman correlation coefficients between the baseline FFQ and the average of four 1-week weighted diet records ranged from 0.3 to 0.7 for red meat and processed meat items (A. Wolk, unpublished data).

2.3. Case ascertainment and follow-up

We ascertained histologically confirmed incident cases of invasive breast cancer by linkage of the study cohort with the national and regional Swedish Cancer registers. The completeness of cancer follow-up was estimated to be almost 100%.²⁴ Information on ER and PR status of breast tumours was obtained by reviewing pathology laboratory work logs stored at Uppsala University Hospital (from 1987 to 1994) and by linkage to the clinical database (the Quality Register) at the Regional Oncology Centre in Uppsala (from January 1992 to December 2007), which was based on the patients' original medical records. ER and PR status was evaluated by using an Abbott immunoassay until 1997 and an immunohistochemical method thereafter. Cases with ≥ 0.1 fmol/ μ g cytosol DNA were considered hormone receptor positive when using the Abbott immunoassay. By the immunohistochemical method, cases were considered as receptor positive when the percentage of positive cells was $\geq 10\%$, and receptor negative when the percentage of positive cells was $<10\%$. The Department of Pathology and Cytology at Uppsala University Hospital and Västerås Central Hospital were involved in this evaluation. Information on dates of death for deceased participants was obtained from the Swedish Death Registry.

2.4. Statistical analysis

Each woman accrued person-time of follow-up from the date of enrolment until the date of breast cancer diagnosis, death from any cause or 31st December 2007, whichever came first. In analyses of hormone receptor status, for women in Västmanland County, person-time of follow-up was calculated from January 1998 because routine evaluation of ER and PR status was implemented in Västmanland County first in the late 1997.

Participants were categorised into quintiles according to their meat intake. In additional analyses, we also grouped participants into deciles of meat intake to examine more extreme levels of meat intake. To account for changes in diet during follow-up and to better represent long-term dietary intake, we used a cumulative average approach.²⁵ Specifically,

the incidence of breast cancer from baseline through 1997 was related to meat intake reported on the baseline dietary questionnaire, and breast cancer incidence from 1998 to December 2007 was related to the average meat intake at baseline and in 1997.

We used Cox proportional hazards models²⁶ to estimate relative risks (RRs) with 95% confidence intervals (CIs). To control as finely as possible for age and calendar time, and any possible two-way interactions between these two time scales, we stratified the models jointly by the age in months at the start of each follow-up period (baseline and 1997) and calendar year of the questionnaire cycle. Multivariate models were further adjusted for education, body mass index (the weight in kilograms divided by the square of height in metres), height, parity and age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of breast cancer and intakes of total energy and alcohol. We tested the proportional hazard assumption using the likelihood ratio test and found no departure from the assumption.

To test for trend, we assigned the median value to each quintile of meat intake and treated this value as a continuous variable in the model. All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC). All P-values were 2-sided.

3. Results

The characteristics of the study population by quintiles of red meat intake in 1997 (roughly the midpoint of the follow-up period) are presented in Table 1. Compared with women with a low intake of red meat, those with a higher intake were, on average, younger and less likely to have a postsecondary education. They also had higher body mass index and energy intake.

During 1,071,164 person-years of follow-up (mean, 17.4 years) of 61,433 women, a total of 2952 incident cases of invasive breast cancer were diagnosed. We had information

on ER and PR status for 2062 cases (for women in Västmanland County, information on ER/PR status was available first in 1997). Among them, 1286 (62.4%) were ER+/PR+, 417 (20.2%) were ER+/PR–, 266 (12.9%) were ER–/PR– and 93 (4.5%) were ER–/PR+.

We found no significant association between total red meat intake and risk of overall or ER/PR-defined breast cancer (Table 2). The lack of association persisted when we categorised participants into deciles of red meat intake. For example, the multivariate RR of overall breast cancer for the highest decile of red meat intake (>118 g/d) compared with the lowest decile (<35 g/d) was 1.06 (95% CI 0.88–1.27). Further adjustment for fish, chicken and total fat intake did not change the results materially. The association between meat intake and breast cancer risk did not differ by the age of the women at breast cancer diagnosis (<55 years and ≥55 years).

In analyses of subgroups of red meats, neither fresh red meat nor processed meat intake showed any significant association with risk of breast cancer. The multivariate RRs of overall breast cancer comparing extreme quintiles of intake were 0.90 (95% CI 0.79–1.03) for fresh red meat and 1.08 (95% CI 0.96–1.22) for processed meat.

We tested the consistency of the results by analysing the association of red meat intake in 1997 with incidence of breast cancer from January 1998 to December 2007. During a mean follow-up of 9.4 years (346,163 person-years), 1008 incident breast cancer cases were diagnosed among 36,664 women. We observed no associations of total red meat, fresh red meat or processed meat intake with risk of breast cancer. For example, the multivariate RR of overall breast cancer comparing extreme quintiles of total red meat intake was 1.13 (95% CI 0.91–1.39). Further adjustment for physical activity did not change the results.

We used data from the 1997 questionnaire to examine the association between pan-fried meat intake and risk of breast cancer. We observed no significant association between pan-fried meat intake and risk of overall breast cancer; the multivariate RR comparing the highest quartile of pan-fried meat

Table 1 – Characteristics according to quintiles of total red meat intake among participants of the Swedish Mammography Cohort^a.

| Characteristic | Quintile of red meat intake, g/d | | | | |
|---|----------------------------------|-------|-------|-------|-------|
| | <46 | 46–61 | 62–76 | 77–97 | ≥98 |
| Age (years) | 64.0 | 62.4 | 60.8 | 59.3 | 60.0 |
| Postsecondary education (%) | 22.0 | 20.1 | 17.4 | 17.0 | 15.6 |
| Body mass index (kg/m ²) | 24.8 | 24.9 | 25.1 | 25.2 | 25.5 |
| Height (cm) | 164.7 | 164.8 | 164.7 | 164.7 | 164.7 |
| Age at menarche (years) | 13.2 | 13.2 | 13.2 | 13.1 | 13.2 |
| Age at menopause (years) | 51.0 | 51.0 | 51.1 | 51.0 | 50.9 |
| Age at first birth (years) ^b | 24.3 | 24.4 | 24.3 | 24.2 | 24.2 |
| Number of children ^b | 2.1 | 2.1 | 2.1 | 2.2 | 2.2 |
| Oral contraceptive use (%) | 57.1 | 57.2 | 58.3 | 58.5 | 56.8 |
| Postmenopausal hormone use (%) | 51.5 | 51.0 | 51.6 | 50.0 | 49.3 |
| Family history of breast cancer (%) | 8.5 | 9.3 | 9.8 | 8.1 | 9.2 |
| Total energy intake (kcal/d) | 1534 | 1666 | 1769 | 1877 | 2178 |
| Alcohol intake (g/d) | 3.8 | 4.2 | 4.3 | 4.3 | 4.3 |

^a Characteristics in 1997, age standardised to the age distribution of the study population in 1997. All values are means if not otherwise indicated.

^b Among parous women.

Table 2 – Relative risks of breast cancer by quintiles of long-term total red meat intake in the Swedish Mammography Cohort, 1987–2007.

| | Quintile of red meat intake, g/d | | | | | P _{trend} ^a |
|---|----------------------------------|------------------|------------------|------------------|------------------|---------------------------------|
| | <46 | 46–61 | 62–76 | 77–97 | ≥98 | |
| Total breast cancer | | | | | | |
| Cases | 604 | 602 | 615 | 577 | 554 | |
| Person-years | 212,007 | 213,214 | 215,062 | 215,487 | 215,394 | |
| Age-adjusted RR (95% confidence interval, CI) | 1.00 | 1.00 (0.90–1.13) | 1.05 (0.93–1.17) | 0.99 (0.88–1.12) | 1.01 (0.89–1.14) | 0.97 |
| Multivariate RR (95% CI) ^b | 1.00 | 0.99 (0.88–1.11) | 1.03 (0.92–1.16) | 0.98 (0.86–1.10) | 0.98 (0.86–1.12) | 0.72 |
| ER+/PR+ tumours | | | | | | |
| Cases | 273 | 263 | 257 | 248 | 245 | |
| Age-adjusted RR (95% CI) | 1.00 | 0.96 (0.80–1.13) | 0.98 (0.83–1.17) | 0.99 (0.83–1.18) | 1.09 (0.91–1.31) | 0.22 |
| Multivariate RR (95% CI) ^b | 1.00 | 0.95 (0.80–1.13) | 0.98 (0.82–1.17) | 1.00 (0.83–1.20) | 1.10 (0.90–1.34) | 0.21 |
| ER+/PR– tumours | | | | | | |
| Cases | 82 | 87 | 92 | 91 | 65 | |
| Age-adjusted RR (95% CI) | 1.00 | 1.00 (0.74–1.36) | 1.04 (0.77–1.41) | 1.03 (0.76–1.40) | 0.83 (0.59–1.16) | 0.24 |
| Multivariate RR (95% CI) ^b | 1.00 | 0.98 (0.72–1.34) | 1.02 (0.75–1.39) | 1.02 (0.74–1.40) | 0.86 (0.60–1.23) | 0.41 |
| ER–/PR– tumours | | | | | | |
| Cases | 43 | 54 | 66 | 61 | 42 | |
| Age-adjusted RR (95% CI) | 1.00 | 1.28 (0.85–1.92) | 1.62 (1.09–2.40) | 1.50 (0.99–2.24) | 1.13 (0.72–1.76) | 0.86 |
| Multivariate RR (95% CI) ^b | 1.00 | 1.26 (0.83–1.90) | 1.62 (1.08–2.42) | 1.49 (0.98–2.26) | 1.12 (0.70–1.79) | 0.91 |

a Test for trend calculated with a median intake of each quintile of red meat intake as a continuous variable.

b Multivariate model stratified by age in months at the start of each follow-up period (baseline and 1997) and calendar year of the questionnaire cycle and simultaneously adjusted for education (primary school, high school and university), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²), height (in cm), parity and age at first birth (nulliparous, parity 1–2 and age at first birth <26 years, parity 1–2 and age at first birth 26–30 years, parity 1–2 and age at first birth ≥31, parity ≥3 and age at first birth <26 years, parity ≥3 and age at first birth 26–30, parity ≥3 and age at first birth ≥31 years), age at menarche (≤12, 13, ≥14 years), age at menopause (<51, ≥51 years), use of oral contraceptives (ever/never), use of postmenopausal hormones (ever/never), family history of breast cancer (yes/no) and intakes of total energy (in kcal/d) and alcohol (non-drinkers, <3.4, 3.4–9.9, ≥10.0 g/d).

a Test for trend calculated with a median intake of each quintile of red meat intake as a continuous variable.

b Multivariate model stratified by age in months at the start of each follow-up period (baseline and 1997) and calendar year of the questionnaire cycle and simultaneously adjusted for education (primary school, high school and university), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²), height (in cm), parity and age at first birth (nulliparous, parity 1–2 and age at first birth <26 years, parity 1–2 and age at first birth 26–30 years, parity 1–2 and age at first birth ≥31, parity ≥3 and age at first birth <26 years, parity ≥3 and age at first birth 26–30, parity ≥3 and age at first birth ≥31 years), age at menarche (≤12, 13, ≥14 years), age at menopause (<51, ≥51 years), use of oral contraceptives (ever/never), use of postmenopausal hormones (ever/never), family history of breast cancer (yes/no) and intakes of total energy (in kcal/d) and alcohol (non-drinkers, <3.4, 3.4–9.9, ≥10.0 g/d).

intake (≥10 times/mo) with the lowest quartile (<4 times/mo) was 1.10 (95% CI 0.93–1.30). Pan-fried meat intake was significantly positively associated with the risk of ER+/PR– breast cancer but not with the risk of ER+/PR+ or ER–/PR– breast cancer. The multivariate RRs of ER+/PR– breast cancer across quartiles of pan-fried meat intake were 1.00 (reference), 1.12 (95% CI 0.79–1.59), 1.12 (95% CI 0.76–1.65) and 1.45 (95% CI 1.03–2.03) (*P*_{trend} = 0.03).

4. Discussion

In this prospective cohort of Swedish women, we observed no association between red meat or processed meat intake and risk of breast cancer overall or by subtypes jointly defined by ER and PR status. A high intake of pan-fried meat was associated with a significant increased risk of ER+/PR– breast cancer but not with other subtypes.

Epidemiologic studies of the association between red meat intake and breast cancer risk have yielded inconsistent findings. A meta-analysis of 22 case-control and nine cohort studies based on the results published in July 2003 showed a significant increased risk of overall breast cancer when comparing the highest and lowest levels of total meat intake in both case-control (summary RR = 1.13; 95% CI, 1.01–1.25) and cohort studies (summary RR = 1.32; 95% CI, 1.12–1.56).¹⁴ Among prospective studies published since that meta-analysis, significant positive associations of red meat and processed meat intakes with overall breast cancer risk were

observed in a Danish nested case-control study (378 cases and 378 controls)¹⁵ and in the UK Women's Cohort Study (678 cases).¹⁶ However, several other prospective studies not included in the meta-analysis^{11,18–20} as well as a pooled analysis of eight prospective studies (*n* = 7379 cases)¹⁷ showed no associations between any types of meats and overall breast cancer risk.

To our knowledge only two previous studies have investigated the association between meat intake and risk of breast cancer stratified by hormone receptor status of the tumour. In the Nurses' Health Study II cohort of premenopausal women, a high intake of red meat intake was associated with a significant increased risk of ER+/PR+ breast cancer but not ER–/PR– breast cancer.²³ In the NIH-AARP Diet and Health Study of postmenopausal women, where information on hormone receptor status was available for only a minority of breast cancer cases, neither red meat nor processed meat intake was associated with any subtype of breast cancer defined by hormone receptor status.¹¹ Our results in mainly postmenopausal women are consistent with those of the NIH-AARP Diet and Health Study.

This study has several strengths, including the prospective and population-based design, a large sample size, detailed information on diet and information about hormone receptor status of the tumours. The prospective design precluded recall bias and the almost complete follow-up of the study cohort by linkage with various Swedish population-based registers minimises the concern that our results were af-

affected by differential loss to follow-up. A limitation is that dietary intake was assessed with a self-administered food-frequency questionnaire, which will inevitably lead to some error in the measurement of meat intake and attenuated risk estimates. However, we have previously observed significant positive associations between meat intake and risk of cancer of the colorectum,²⁷ pancreas²⁸ and stomach,²⁹ suggesting that our assessment of meat is sufficiently accurate to detect a true association.

In conclusion, findings from this prospective cohort of Swedish women do not support the hypothesis that high intakes of red or processed meats increase the risk of breast cancer. We observed, however, a positive association between pan-fried meat intake and risk of ER+/PR- breast cancer. The association between fried meat intake and breast cancer subtypes warrants further study.

Conflict of interest statement

None declared.

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