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Meat consumption and risk of breast cancer in the UK Women's Cohort Study

Running Title: Meat consumption and risk of breast cancer

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Abstract

We performed a survival analysis to assess the effect of meat consumption and meat type on the risk of breast cancer in the UK Women's Cohort Study. Between 1995 and 1998 a cohort of 35 372 women was recruited, aged between 35 and 69 years with a wide range of dietary intakes, assessed by a 217-item food frequency questionnaire. Hazard ratios (HRs) were estimated using Cox regression adjusted for known confounders. High consumption of total meat compared with none was associated with premenopausal breast cancer, HR=1.20 (95% CI: 0.86–1.68), and high non-processed meat intake compared with none, HR=1.20 (95% CI: 0.85–1.70). Larger effect sizes were found in postmenopausal women for all meat types, with significant associations with total, processed and red meat consumption. Processed meat showed the strongest HR=1.64 (95% CI: 1.14–2.37) for high consumption compared with none. Women, both pre- and postmenopausal, who consumed the most meat had the highest risk of breast cancer.

Keywords: prospective studies, breast neoplasms, meat, risk factors

Introduction

While evidence that links meat consumption with cancers of the stomach, colorectum and pancreas is increasing [Gonzalez et al., 2006;Larsson et al., 2006a;Larsson et al., 2006b;Lewin et al., 2006;Sandhu et al., 2001], studies of meat consumption and breast cancer have produced more conflicting results. A meta-analysis of 31 case-control and cohort studies published before 2003 found a 17% increase in risk associated with the highest category of meat intakes [Boyd et al., 2003]. However, a pooled analysis of the raw data from eight prospective cohort studies from North America, Canada and Western Europe was unable to demonstrate such an association [Missmer et al., 2002].

Further evidence suggests a possible interaction between cooking methods and diet in the pathogenesis of breast cancer. Studies, however, are few and inconsistent. A case-control study of Chinese women in Shanghai found that the positive association of breast cancer risk with red meat intake was primarily restricted to those who used deep-frying cooking methods, particularly among those who deep-fried foods to well-done [Dai et al., 2002] suggesting an effect of heterocyclic amines or other carcinogens formed at high temperatures. However, the Nurses' Health nested case-control study found no increase in the risk of breast cancer with cooking method or meat intake even for consumption of charred meat more than once a week in rapid acetylators [Gertig et al., 1999].

Some of the inconsistency in the literature may be due to differences between studies in the definitions of total meat, red, and processed meats and the derivation of the meat content of meat dishes. Further inconsistencies may arise owing to a variety of biases, errors and the homogeneity of diet within individual population groups [Kaaks and Riboli, 1997a;Hankin, 1993]. The UK Women's Cohort Study (UKWCS) was established in 1993 to investigate relationships between diet and cancer incidence and mortality (from selected causes). The cohort is highly suited for exploration of meat consumption and breast cancer risk. The survival analysis discussed in this paper assesses the effect of meat consumption on the risk of breast cancer incidence in the UKWCS.

Materials and Methods

Study population

The formation of the UKWCS has been explained in detail previously [Cade et al., 2004;Cade et al., 2007]. In brief, the UKWCS cohort was formed from 500,000 responders to a direct mail survey of the World Cancer Research Fund (WCRF). One hundred and seventy-four local research ethics committees were contacted and permission to carry out the baseline study was obtained [Woodhouse et al., 1997]. 75% of the responders agreed to take part in a more detailed survey; those eligible for inclusion were women, aged between 35 and 69 years at the completion date of the original mail survey. The 35,372 women who returned completed questionnaires formed the UK Women's Cohort. The cohort was specifically designed to have a wide range of dietary intakes and patterns therefore increasing the potential power to detect statistically significant associations between specific diets and disease; 28% are self reported vegetarians.

Baseline data were gathered between 1995 and 1998 using a 217-item postal food frequency questionnaire (FFQ), developed from that of the European Prospective Investigation into Cancer and Nutrition (EPIC) study [Linseisen et al., 2002]. This was validated in terms of nutrients, against a semi-weighed 4-day food diary. Further information on the validation carried out has been provided previously [Spence et al., 2002].

Details of women fulfilling the eligibility criteria were submitted to the UK Office of National Statistics and subsequently flagged on the NHS central register. Incident cancers and cause of death were coded according to the International Classification of Diseases 9 and 10. The investigation censor date was 31st October 2004, with median follow-up of 8 years. In the specified analysis period, there have been a total of 1,750 incident malignant cancer cases. Of these were 283 pre-menopausal breast cancers and 395 post-menopausal breast cancers. Menopausal status was based upon answers to the baseline questionnaire regarding menstrual and obstetric history and the age of the cohort women at baseline. Power calculations suggested 283 pre-menopausal breast cancer cases would give approximately 80% power to detect a relative risk of 1.4 comparing two levels of a binary exposure with equal numbers in each group ($p<0.05$), or more than 90% power for a relative risk of 1.5. In terms of post-menopausal breast cancer, 395 cases would give approximately 90% power to detect a relative risk of 1.4 ($p<0.05$). Analysing the exposure as a continuous variable would provide even more power.

Meat consumption

For the purpose of the study, meat types and meat dishes were grouped into the following categories: red meat, poultry, offal and processed meat. Total meat was the sum of these four categories. Non-processed was the sum of red meat, poultry and offal. Red meat consisted of beef, pork, lamb and other red meats included in mixed dishes, for example, meat lasagne, moussaka, ravioli and filled pasta with sauce; poultry included roast chicken, chicken slices, bread crumbed chicken, chicken or turkey in a creamy sauce and chicken curry; meats considered as processed were bacon, ham, corned beef, spam, luncheon meats, sausages, pies, pasties, sausage rolls, liver pate, salami and meat pizza; offal (organ meats) existed as a single item on the FFQ.

Daily intakes of each of the four main meat types (red, poultry, offal and processed) were calculated by summing the daily intakes of the individual food items within each meat type as described above. Intakes of each item were determined by using the frequency categories to estimate the number of daily portions. These were then converted into weights by referring to standard portion sizes for each food item [Food Standards Agency, 2002]. Intakes of each meat type were grouped into consumption categories of 'none', 'low', 'medium' and 'high' by classing zero intakes as 'non-consumers' and dividing non-zero intakes into tertiles. Consumption of offal tended to be more limited and naturally fell into the 3 categories 'none', 'low' and 'high' consumption only, where low consumption was defined as 2g per day and high as 7g to 80g per day.

Statistical Analysis

Exposures of interest were total meat consumption, non-processed versus processed meat consumption and consumption of different meat types. Total meat was formed from red meat, poultry, offal and processed meat. The three meat types investigated were red meat, poultry and offal; these were also considered together as non-processed meat. Processed meat formed a separate category to be compared against non-processed meat. Survival analyses were conducted in Stata version 9 using Cox regression weighted by the inverse of the probability of being sampled to take into account the large proportion of vegetarians in the cohort. The time variable used in the survival analysis was time in the study (person years), calculated as the time from the date the questionnaire was filled in until either a report of incident breast cancer, death or the censor date of the analysis, whichever came first. Women with extremely high or low total energy intake (more than 6000 kcal and less than 500 kcal) were excluded, as were women with prevalent breast cancer.

Two models were developed. Model 1 adjusted only for age (continuous) and energy intake by the residuals method (split into quartiles) [Willett and Stampfer, 1986;Margetts B.M. and Nelson M., 2000]. Model 2 adjusted for age, energy intake, body mass index (BMI) (continuous), physical activity (continuous), parity (no children, 1-2 children, 3-4 children and 5+ children) and combined fruit and vegetable consumption (split into quartiles). Smoking status, hormone replacement therapy use (HRT) and) and oral contraceptive pill use (OCP) of women were also included and all classed as present, past or never. The inclusion of additional confounders such as socio-economic class (professional & managerial, intermediate and routine & manual), level of educational qualifications gained (none beyond age 14, O level, A level and degree level). Fractional polynomials were used to fit a smooth curve to the relationship between breast cancer and total meat intake using Model 2.

Based on the possibility that breast cancer may present as different diseases in the two menopause status groups, an initial analysis combining both pre- and post-menopausal women and incorporating menopausal status as a confounder in the model was carried out. Furthermore, a test for interaction between meat consumption and menopausal status confirmed a potential modifying effect of menopausal status hence our analyses have treated cancer in pre- and post-menopausal women independently. The proportional hazards assumption was checked using graphical methods of log-log curves and Schoenfeld goodness of fit tests [Schoenfeld, 1982] which confirmed the hazards were proportional. Due to the likelihood of differences in lifestyle characteristics between vegetarians and meat-eaters in addition to the absence of the meat component within their diet, sensitivity analyses were undertaken with the exclusion of vegetarians. The sensitivity of results to excluding women with any cancer incident within one year of entry to the study, and to the model building strategy was assessed. Further analysis regarding the sensitivity of results to categorisation of menopausal status was carried out by excluding women aged between 48 and 55 whose menopausal status may have been ambiguous. HRT users (past and present) were also excluded from an analysis to investigate sensitivity of the results.

Results

Basic characteristics and meat consumption in the cohort

Characteristics of the 33,725 women in the study are shown in Table 1. At baseline the mean age of the women was 52 years and the average BMI was 24.5kgm^{-2}. Cohort participants were relatively health conscious, with low rates of smoking (11%) and alcohol consumption more than once per week (52%). Most did not use full-fat milk (28,383, 88%), and a large proportion reported taking dietary supplements (18,561, 58%). Meat-eaters account for a higher percentage of present HRT users than vegetarians although it must be taken into consideration that vegetarians will tend to be younger on average and therefore less likely to be using HRT. In general, the cohort is well educated and middle class: 8,784 (27%) had been educated to degree level and 20,879 (63%) worked in professional or managerial positions. More detail regarding the cohort women has been provided previously [Cade et al., 2004].

Table 1 shows that non-meat consumers were younger, undertook more physical activity, and had a lower mean BMI than consumers. High meat consumers were more likely to be smokers, had the highest total energy intake, highest mean BMI, highest proportion with no education beyond age 14, and lowest proportion employed in professional or managerial occupations. Medium meat-consumers were most likely to be low fruit and vegetable consumers (less than 400 grams daily). The lowest energy intake was seen in the group with low meat consumption.

Meat consumption and breast cancer

The associations between meat consumption and pre-menopausal breast cancer are presented in Table 3 for both model 1 and model 2. Use of the complex model showed risk of breast cancer in pre-menopausal women to increase with consumption of total meat, HR=1.20 (95% CI: 0.86 to 1.68) for high consumers versus non-consumers. The estimated relative risks of pre-menopausal breast cancer for an increase in total meat consumption of 50 grams/day (approximately half a portion), were 1.12 (95% CI: 1.02 to 1.23, P_{trend}=0.02). Non-processed meat consumption was positively associated with risk of pre-menopausal breast cancer, HR=1.20 (95% CI: 0.86 to 1.68) for high consumers versus non-consumers with a relative risk per 50g/day of 1.13 (95% CI: 1.01 to 1.26, P_{trend}=0.03). The association with processed meat was not statistically significant although the risk of breast cancer in high consumers was similar to that observed for non-processed meat consumption. The borderline non-significant association with red meat consumption tended to show the largest effect sizes of all meat types, HR=1.32 (95% CI: 0.93 to 1.88) for high consumption versus the reference category with relative risk per 50g/day of 1.13 (95% CI: 0.99 to 1.29, P_{trend}=0.08).

In post-menopausal women, slight positive trends were observed across the low, medium and high meat categories. There was a more prominent difference between women that do not consume meat and those that do. However further investigation splitting the meat-eating categories into more groups by dividing the low consumers into low and very low consumers, showed hazard ratios that strengthened the dose response relationship of meat consumption and breast cancer. There was a tendency for the point estimates of the association between meat and breast cancer to be somewhat larger in post-menopausal women than for pre-menopausal women (using model 2), as shown in Table 4. Total meat intake was positively associated with post-menopausal breast cancer, HR=1.63 (95% CI: 1.10 to 2.30) for high consumption versus the reference category, and when treated as a continuous variable, resulted in a significant linear trend and relative risk per 50g/day of 1.10 (95% CI: 1.01 to 1.20, P_{trend} =0.02). Relationships between both processed meat and red meat and post-menopausal breast cancer were also significant. Risks for the three meat types were similar when considering hazard ratios of the categorical analysis, however, fitting meat in the model as a continuous predictor resulted in a much stronger relationship between processed meat and post-menopausal breast cancer, giving a relative risk per 50g/day of 1.64 (95% CI: 1.09 to 2.27, P_{trend} =0.003).

HRs in the highest meat consumption category for model 1 in pre-menopausal women, were slightly lower than for model 2 for all meat types with the exception of offal (total meat: model 1 HR=1.16, model 2 HR=1.20). Tests for trend were more significant in model 2. The opposite is true for breast cancer risk in post-menopausal women where HRs are lowered in the refined model and p-values become less significant with adjustment for more potential confounders. Figure 1 presents the fitted curve from fractional polynomials for total meat intake showing similar increasing risk with increasing total meat intake for both pre- and post-menopausal women, apart from pre-menopausal vegetarians who appear at increased risk.

The initial analysis combining both pre- and post-menopausal women to test for effect modification by menopausal status, (results shown in Table 2), showed several significant interactions. Indeed when independent analyses were conducted for each menopausal status, trends were considerably different. When the sensitivity of the results to the exclusion of vegetarians was assessed, estimates were broadly the same and conclusions remained unchanged, emphasising a dose response across the consumption categories of meat in both pre- and post-menopausal women. Sensitivity analyses investigating possible ambiguous menopausal statuses and women diagnosed with any cancer incident within one year of entry to the study did not substantially alter hazard ratios or overall trends. The links between meat consumption, cooking methods (grilling, frying and casseroling of meat) and the risk of incident breast cancer were investigated by considering interactions within model 2; there was no evidence to suggest changes in risk of breast cancer. Excluding HRT users from the analysis of post-menopausal women appeared to strengthen the relationship with breast cancer.

Discussion

The UKWCS is one of the largest cohorts investigating diet and cancer in women in the UK. It was designed to include participants with a wide range of dietary exposures to optimise comparisons between different levels of meat intake, as proposed by previous cohorts [Kaaks and Riboli, 1997b;Schatzkin et al., 2001]. In our analysis, significant increased risks of incident pre-menopausal breast cancer in relation to increased consumption of total meat and non-processed meat were observed. Borderline non-significant associations with red meat were also seen. We found positive associations between post-menopausal breast cancer and total meat, processed meat and red meat consumption.

Relationships between both pre- and post-menopausal breast cancer and total and red meat consumption confirm findings of a case control study among Chinese women in Shanghai where positive associations were observed in a combined analysis of pre- and post-menopausal breast cancer [Dai et al., 2002]. This study also considered pre- and post-menopausal women separately although the full data is not shown. Positive associations among both pre- and post-menopausal women who usually deep-fried red meat until well done, were found, although this was only statistically significant in pre-menopausal women.

The association with red meat intake and both pre- and post-menopausal breast cancer may be due to a combination of nutritionally related factors, such as content of fat, protein, and iron, and/or meat preparation (e.g. cooking or preserving methods) [Sinha, 2002]. A comparison of high consumer hazard ratios for all meat types investigated showed that high consumers of red meat are most at risk of pre-menopausal breast cancer when compared to the reference category of non-consumers (HR=1.32, 95% CI: 0.93-1.88). The association found between non-processed meat (red meat, poultry and offal) and pre-menopausal breast cancer could also be caused by the red meat component within the non-processed meat category.

Results of a large case-control study (10,149 cases, 7,990 controls) in northern Italy between 1983 and 1996 also found statistically significant positive associations of breast cancer (combined analysis of pre- and post-menopausal women) with red meat consumption [Tavani et al., 2000]. A pooled analysis of eight previous cohort studies has shown no significant association between consumption of total meat, red meat or white meat and risk of breast cancer [Missmer et al., 2002] in both combined and separate analyses of pre- and post-menopausal women. However, an earlier meta-analysis of 12 case-control and 5 cohort studies published between 1966 and 1993 found increased risks of breast cancer (combined pre- and post-menopausal) in high consumers, the association with red meat (RR = 1.54, 95% CI:1.31 to 1.82) being stronger than that observed for total meat [Boyd et al., 2003]. The pooled analysis was not able to correct for measurement error and there were considerable differences in questionnaire design between the studies limiting the power of specific food analyses. Also, meat cooking practices could not be taken into account.

Previous studies have tended to find inverse relationships with consumption of poultry [Ronco et al., 2003;Delfino et al., 2000] and generally these have been statistically non-significant. Our findings do not provide strong evidence of an association with poultry intake and breast cancer in both pre- and post-menopausal women. However, a study by Ambrosone et al. showed statistically significant inverse trends between consumption of poultry and post-menopausal breast cancer [Ambrosone et al., 1998]. One study investigated differences in risk associated with consumption of poultry eaten with and without skin [Ronco et al., 2003]. It was found that risks were increased when chicken was consumed with skin suggesting that fat rather than muscle meat may be the cause. Other studies have suggested a link between fat and breast cancer incidence [Boyd et al., 2003;Cho et al., 2003;Hunter et al., 1996;Smith-Warner et al., 2001;Howe et al., 1991;Willett et al., 1992].

Although hazard ratios for pre-menopausal breast cancer indicate a positive association with meat intake, low consumers are at less risk than vegetarians. Low meat consumers also had the lowest energy and fat intakes but investigating the effect of including the percentage of energy from fat as a confounder, calculated using the residuals method [Willett and Stampfer, 1986], did not significantly modify the risk estimates. Vegetarians possess unique characteristics other than a zero consumption of meat and these may influence the association with risk of breast cancer in some way. Although we adjusted for characteristics known to be represented differently in meat-eaters and vegetarians [Cade et al., 2004;Davey et al., 2003] and performed various sensitivity analyses with the exclusion of the vegetarian group, it is still possible that some residual confounding remains.

Genetic causes of breast cancer only account for a small proportion of breast cancers (approximately 5-10%). It is expected that the UKWCS will have a higher proportion than this since the women sampled are supporters of the WCRF; it may be that a family history of breast cancer has encouraged them to become supporters. In addition, some of these women may have taken up a vegetarian diet in the belief that it is protective against breast cancer. However, if these women are also genetically pre-disposed to breast cancer, then the chances of developing breast cancer are increased. This is more likely amongst the pre-menopausal women because genetic causes tend to lead to early onset of breast cancer. This could explain why, in the pre-menopausal women, vegetarians have a higher risk than others.

Risks for pre- and post-menopausal women were examined separately in this study, based on variability in some risk factors and the possibility that breast cancer may present as different diseases depending on menopausal status [Ambrosone et al., 1998] In addition, a descriptive analysis of meat consumption showed that mean intakes of certain meats varied significantly between the two menopausal groups. After the menopause, adipose tissue is the major site for oestrogen synthesis, and oestrogen-related factors may create an elevated level of endogenous oestrogens [Siiteri, 1987]. The association between intake of carcinogens from foods cooked at high temperature and breast cancer risk may be modified by oestrogens and oestrogen-related factors. Other analysis has shown that there is a difference in impact of dietary fibre on risk of breast cancer between pre and post- menopausal women [Cade et al., 2007].

There are a number of mechanisms whereby meat intake could potentially contribute to increased risk of breast cancer. Meat and in particular processed meats can be a rich source of saturated fat. Whilst dietary fat intake has been shown to have an effect on mammary carcinogenesis in animals, the relevance of these data to the human application is controversial [Ip, 1993]. A review of prospective epidemiological studies has shown that dietary fat reduction can lower serum oestradiol levels [Wu et al., 1999]. Many established risk factors are linked to oestrogens such as early menarche, late menopause and obesity in postmenopausal women [Key and Verkasalo, 1999]. Other mechanisms related to meat concern the formation of heterocyclic amines during cooking or nitroso compounds found in processed meat [Willett, 2005]. This relationship may be altered by inherited polymorphisms such as the rapid variant of N-acetyltransferase 2 [Williamson et al., 2005]. Red meat also contains high biological value protein and important micronutrients, all of which are essential for good health throughout life.

In post-menopausal women, the largest effect sizes were seen in the relationship between processed meat and breast cancer and this was statistically significant, HR=1.64 (95% CI: 1.14 to 2.37) for high consumers versus non-consumers with relative risk per 50g/day of 1.64 (95% CI: 1.19 to 2.27, P_{trend}=0.003). Risks were increased by almost 50% for even low consumers of processed meat. Results from a case-control study undertaken in a sub-cohort of the Nurses' Health Study (466 cases) supports this. In this study breast cancer (combined pre- and post-menopausal) was 40% more likely in women consuming more than 0.07 portions of bacon daily in comparison to non-consumers [Gertig et al., 1999]. Although trends were statistically non-significant, non-processed meat and poultry were both positively associated with post-menopausal breast cancer. Differences in outcome trends for pre- and post-menopausal women may possibly be explained by the fact that oestrogen metabolism pathways differ according to menopausal status [Muti et al., 2000]. If meat influences breast cancer development by affecting oestrogen metabolism, it is possible that the effect may be relatively more important among women with lower levels of circulating oestrogens.

The strength of this study was the wide range of meat intake within the cohort which reduces the impact of measurement error [Kaaks and Riboli, 1997b;Schatzkin et al., 2001;White et al., 1994]. Previous studies have been limited in terms of the FFQs used which may not have been designed to capture specific food groups in sufficient detail [Missmer et al., 2002]. An analysis of EPIC-Norfolk data concluded that dietary measurement error through the use of their food frequency questionnaire may be the explanation for the absence of a significant association between dietary fat and breast cancer risk and this may also be an explanation for some of the inconsistencies in the epidemiological literature on meat [Bingham et al., 2003].

In conclusion, women generally consuming most total meat, red and processed meat, were at the highest increased risk compared to non-meat consumers, though red and processed meat were only statistically significant post-menopausally. Effect sizes were smaller in non-processed meat and only statistically significant in pre-menopausal women. There were no statistically significant linear associations with consumption of poultry or offal in either pre- or post-menopausal women. This study indicates relationships with certain meats and breast cancer in both pre- and post-menopausal women and merits further investigation with more cases or in a larger cohort.

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References

Ambrosone CB, Freudenheim JL, Sinha R, Graham S, Marshall JR, Vena JE, Laughlin R, Nemoto T, Shields PG (1998) Breast cancer risk, meat consumption and N-acetyltransferase (NAT2) genetic polymorphisms. International Journal of Cancer 75: 825-830

Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day N (2003) Are imprecise methods obscuring a relation between fat and breast cancer? Lancet 362: 212-214

Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ, Minkin S (2003) Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. British Journal of Cancer 89: 1672-1685

Cade JE, Burley VJ, Greenwood DC (2004) The UK Women's Cohort Study: comparison of vegetarians, fish-eaters and meat-eaters. Public Health Nutrition 7: 871-878

Cade JE, Burley VJ, Greenwood DC, UK Women's Cohort Study Steering Group (2007) Dietary fibre and risk of breast cancer in the UK Women's Cohort Study. International Journal of Epidemiology - Advance Publication

Cho EY, Spiegelinan D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA, Willett WC (2003) Premenopausal fat intake and risk of breast cancer. Journal of the National Cancer Institute 95: 1079-1085

Dai Q, Shu XO, Jin F, Gao YT, Ruan ZX, Zheng W (2002) Consumption of animal foods, cooking methods, and risk of breast cancer. Cancer Epidemiology Biomarkers & Prevention 11: 801-808

Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ (2003) EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. Public Health Nutr 6: 259-269

Delfino RJ, Sinha R, Smith C, West J, White E, Lin HJ, Liao SY, Gim JSY, Ma HL, Butler J, Anton-Culver H (2000) Breast cancer, heterocyclic aromatic amines from meat and N-acetyltransferase 2 genotype. Carcinogenesis 21: 607-615

Food Standards Agency (2002) Food Portion Sizes. London: The Stationary Office:

Gertig DM, Hankinson SE, Hough H, Spiegelman D, Colditz GA, Willett WC, Kelsey KT, Hunter DJ (1999) N-acetyl transferase 2 genotypes, meat intake and breast cancer. International Journal of Cancer 80: 13-17

Gonzalez CA, Jakszyn P, Pera G, Agudo A, Bingham S, Palli D, Ferrari P, Boeing H, del Giudice G, Plebani M, Carneiro F, Nesi G, Berrino F, Sacerdote C, Tumino R, Panico S, Berglund G, Siman H, Nyren O, Hallmans G, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Allen N, Key TJ, Day NE, Linseisen J, Nagel G, Bergmann MM, Overvad K, Jensen MK, Tjonneland A, Olsen A, Bueno-De-Mesquita HB, Ocke M, Peeters PHM, Numans ME, Clavel-Chapelon F, Boutron-Ruault MC, Trichopoulou A, Psaltopoulou T, Roukos D, Lund E, Hemon B, Kaaks R, Norat T, Riboli E (2006) Meat intake and risk of stomach and Esophageal adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC). Journal of the National Cancer Institute 98: 345-354

Hankin JH (1993) Role of Nutrition in Womens Health - Diet and Breast-Cancer. Journal of the American Dietetic Association 93: 994-999

Howe GR, Friedenreich CM, Jain M, Miller AB (1991) A Cohort Study of Fat Intake and Risk of Breast-Cancer. Journal of the National Cancer Institute 83: 336-340

Hunter DJ, Spiegelman D, Adami HO, Beeson L, vandenBrandt PA, Folsom AR, Fraser GE, Goldbohm RA, Graham S, Howe GR, Kushi LH, Marshall JR, McDermott A, Miller AB, Speizer FE, Wolk A, Yaun SS, Willett W (1996) Cohort studies of fat intake and the risk of breast cancer - A pooled analysis. New England Journal of Medicine 334: 356-361

Ip C (1993) Controversial issues of dietary fat and experimental mammary carcinogenesis. Prev Med 22: 728-737

Kaaks R, Riboli E (1997a) The role of multi-centre cohort studies in studying the relation between diet and cancer. Cancer Letters 114: 263-270

Kaaks R, Riboli E (1997b) Validation and calibration of dietary intake measurements in the EPIC project: Methodological considerations. International Journal of Epidemiology 26: S15-S25

Key TJ, Verkasalo PK (1999) Endogenous hormones and the aetiology of breast cancer. Breast Cancer Res 1: 18-21

Larsson SC, Hakanson N, Permert J, Wolk A (2006a) Meat, fish, poultry and egg consumption in relation to risk of pancreatic cancer: A prospective study. International Journal of Cancer 118: 2866-2870

Larsson SC, Orsini N, Wolk A (2006b) Processed meat consumption and stomach cancer risk: A meta-analysis. Journal of the National Cancer Institute 98: 1078-1087

Lewin MH, Bailey N, Bandaletova T, Bowman R, Cross AJ, Pollock J, Shuker DEG, Bingham SA (2006) Red meat enhances the colonic formation of the DNA adduct O-6-carboxymethyl guanine: Implications for colorectal cancer. Cancer Research 66: 1859-1865

Linseisen J, Kesse E, Slimani N, Bueno-De-Mesquita HB, Ocke MC, Skeie G, Kumle M, Iraeta MD, Gomez PM, Janzon L, Stattin P, Welch AA, Spencer EA, Overvad K, Tjonneland A, Clavel-Chapelon F, Miller AB, Klipstein-Grobusch K, Lagiou P, Kalapothaki V, Masala G, Giurdanella MC, Norat T, Riboli E (2002) Meat consumption in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts: results 24-hour dietary recalls. Public Health Nutrition 5: 1243-1258

Margetts B.M., Nelson M. (2000) Design Concepts in Nutritional Epidemiology. Oxford University Press:

Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ (2002) Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. International Journal of Epidemiology 31: 78-85

Muti P, Bradlow HL, Micheli A, Krogh V, Freudenheim JL, Schunemann HJ, Stanulla M, Yang J, Sepkovic DW, Trevisan M, Berrino F (2000) Estrogen metabolism and risk of breast cancer: A prospective study of the 2 : 16 alpha-hydroxyestrone ratio in premenopausal and postmenopausal women. Epidemiology 11: 635-640

Ronco AL, De Stefani E, Fabra A (2003) White meat intake and the risk of breast cancer: a case-control study in Montevideo, Uruguay. Nutrition Research 23: 151-162

Sandhu MS, White IR, McPherson K (2001) Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: A meta-analytical approach. Cancer Epidemiology Biomarkers & Prevention 10: 439-446

Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, Hurwitz PE, Coyle L, Schussler N, Michaud DS, Freedman LS, Brown CC, Midthune D, Kipnis V (2001) Design and serendipity in establishing a large cohort with wide dietary intake distributions - The National Institutes of

Health-American Association of Retired Persons Diet and Health Study. American Journal of Epidemiology 154: 1119-1125

Schoenfeld D (1982) Partial Residuals for the Proportional Hazards Regression-Model. Biometrika 69: 239-241

Siiteri PK (1987) Adipose-Tissue As A Source of Hormones. American Journal of Clinical Nutrition 45: 277-282

Sinha R (2002) An epidemiologic approach to studying heterocyclic amines. Mutat Res 506-507: 197-204

Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ (2001) Types of dietary fat and breast cancer: A pooled analysis of cohort studies. International Journal of Cancer 92: 767-774

Spence M, Cade JE, Burley VJ, Greenwood DC (2002) Ability of the UK Women's Cohort food frequency questionnaire to rank dietary intakes: a preliminary validation study. Proceedings of the Nutrition Society 61: 117A

Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F, Negri E (2000) Red meat intake and cancer risk: A study in Italy. International Journal of Cancer 86: 425-428

White E, Kushi LH, Pepe MS (1994) The Effect of Exposure Variance and Exposure Measurement Error on Study Sample-Size - Implications for the Design of Epidemiologic Studies. Journal of Clinical Epidemiology 47: 873-880

Willett W, Stampfer MJ (1986) Total Energy-Intake - Implications for Epidemiologic Analyses. American Journal of Epidemiology 124: 17-27

Willett WC (2005) Diet and cancer: an evolving picture. JAMA 293: 233-234

Willett WC, Hunter DJ, Stampfer MJ, Colditz G, Manson JE, Spiegelman D, Rosner B, Hennekens CH, Speizer FE (1992) Dietary-Fat and Fiber in Relation to Risk of Breast-Cancer - An 8-Year Follow-Up. Jama-Journal of the American Medical Association 268: 2037-2044

Williamson CS, Foster RK, Stanner SA, Buttriss JL (2005) Red meat in the diet. Nutrition Bulletin 30: 323-355

Woodhouse A, Calvert C, Cade J (1997) The UK Women's Cohort Study: background and obtaining local ethical approval. Proceedings of the Nutrition Society 24: 267

Wu AH, Pike MC, Stram DO (1999) Meta-analysis: Dietary fat intake, serum estrogen levels, and the risk of breast cancer. Journal of the National Cancer Institute 91: 529-534

Table 1 Baseline characteristics by category of meat consumption

	Total Meat Consumption				
	None (0 g) n=8,881	Low (< 62g) n=8,281	Medium (62g - 103g) n=8,282	High (> 103g) n=8,281	Total n=33,725
Age (years), mean (SD)	49(8)	53(9)	54(9)	53(9)	52(9)
BMI (kgm^{-2}), mean (SD)	23.3(3.8)	24.0(4.1)	24.9(4.3)	25.7(5.9)	24.5(4.4)
Energy intake (MJ), mean (SD)	9.8(3.0)	8.9(2.8)	9.4(2.5)	11.2(3.1)	9.9(3.4)
Physical activity (minutes), mean (SD)	17(29)	14(28)	13(26)	14(31)	14(28)
Current smoker (%)	10	11	10	13	11
Current HRT use (%)	14	20	22	23	20
Current OCP use (%)	5	4	3	4	4
No children (%)	27	23	17	14	20
Professional and managerial (%)	70	66	60	57	63
Low intake of fruit and vegetables (%)	18	27	31	25	25
Total meat (grams), mean (SD)	0	34(19)	82(12)	148(48)	65(62)

Table 2 Combined pre- and post-menopausal breast cancer

	Consumption (g/day)	Person years (mean)	Cases/Non-Cases	Model 1[a]		Model 2[b]	
				HR	95% CI	HR	95% CI
Total meat							
Categorical							
None (ref)	0	8.30	149/8881	1.00	-	1.00	-
Low	< 62	8.05	162/8281	1.10	(0.88 , 1.39)	1.04	(0.82 , 1.33)
Medium	62-103	7.59	182/8282	1.30	(1.04 , 1.63)	1.25	(0.98 , 1.60)
High	> 103	7.43	185/8281	1.40	(1.12 , 1.75)	1.34	(1.05 , 1.71)
Continuous			Risk per 50g/day	1.11	(1.05 , 1.17)	1.11	(1.04 , 1.18)
				p (trend) < 0.001		p (trend) = 0.001	
Test for effect modification by menopausal status				0.0269		0.0492	
Fresh meat (including red meat, poultry and offal)							
Categorical							
None (ref)	0	8.31	151/9135	1.00	-	1.00	-
Low	< 50	8.02	163/8196	1.12	(0.89 , 1.41)	1.07	(0.84 , 1.36)
Medium	50-84	7.59	185/8198	1.34	(1.07 , 1.68)	1.34	(1.05 , 1.70)
High	> 84	7.43	179/8196	1.37	(1.09 , 1.72)	1.33	(1.04 , 1.69)
Continuous			Risk per 50g/day	1.11	(1.04 , 1.18)	1.10	(1.03 , 1.19)
				p (trend) = 0.003		p (trend) = 0.007	
Test for effect modification by menopausal status				0.0454		0.0452	
Processed meat							
Categorical							
None (ref)	0	8.31	175/10306	1.00	-	1.00	-
Low	< 10	7.88	160/7824	1.17	(0.93 , 1.47)	1.19	(0.94 , 1.53)
Medium	10-20	8.57	172/7814	1.31	(1.04 , 1.64)	1.30	(1.02 , 1.66)
High	> 20	7.49	171/7781	1.35	(1.08 , 1.70)	1.39	(1.09 , 1.78)
Continuous			Risk per 50g/day	1.40	(1.18 , 1.67)	1.59	(1.22 , 2.06)
				p (trend) < 0.001		p (trend) < 0.001	
Test for effect modification by menopausal status				0.1365		0.4523	
Red meat							
Categorical							
None (ref)	0	8.32	186/11199	1.00	-	1.00	-
Low	< 32	7.95	162/7512	1.28	(1.02 , 1.61)	1.21	(0.95 , 1.54)
Medium	32-57	7.52	163/7560	1.36	(1.08 , 1.71)	1.40	(1.10 , 1.78)
High	> 57	7.37	167/7454	1.47	(1.17 , 1.84)	1.41	(1.11 , 1.81)
Continuous			Risk per 50g/day	1.12	(1.03 , 1.21)	1.12	(1.03 , 1.22)
				p (trend) = 0.005		p (trend) = 0.007	
Test for effect modification by menopausal status				0.0325		0.0577	
Poultry							
Categorical							
None (ref)	0	8.28	160/9607	1.00	-	1.00	-
Low	< 14	7.76	160/7401	1.24	(0.97 , 1.57)	1.19	(0.92 , 1.54)
Medium	14-23	7.61	191/8678	1.30	(1.03 , 1.63)	1.25	(0.98 , 1.59)
High	> 23	7.68	167/8039	1.25	(0.99 , 1.58)	1.22	(0.95 , 1.56)
Continuous			Risk per 50g/day	1.14	(0.95 , 1.35)	1.11	(0.92 , 1.34)
				p (trend) = 0.154		p (trend) = 0.285	
Test for effect modification by menopausal status				0.7242		0.8897	
Offal							
Categorical							
None (ref)	0	8.03	366/20499	1.00	-	1.00	-
Low	2	7.59	190/7833	1.34	(1.11 , 1.61)	1.35	(1.11 , 1.64)
-	-			-	-	-	-
High	7 +	7.53	122/5393	1.22	(0.99 , 1.52)	1.17	(0.93 , 1.48)
Continuous			Risk per 50g/day	1.92	(0.81 , 4.53)	1.75	(0.68 , 4.50)
				p (trend) = 0.136		p (trend) = 0.248	
Test for effect modification by menopausal status				0.6334		0.6039	

[a] adjusting for age, energy intake and menopausal status

[b] adjusting for age, energy intake, menopausal status, BMI, physical activity, smoking status, HRT use, OCP use, parity, total fruit and vegetable intake

Table 3 Pre-menopausal Breast Cancer

	Consumption (g/day)	Person years (mean)	Cases/Non-Cases	Model 1[a]		Model 2[b]	
				HR	95% CI	HR	95% CI
Total meat							
Categorical							
None (ref)	0	8.30	98/5435	1.00	-	1.00	-
Low	< 62	8.15	52/3586	0.72	(0.51 , 1.03)	0.68	(0.47 , 0.99)
Medium	62-103	7.76	63/3309	1.00	(0.72 , 1.39)	1.08	(0.76 , 1.53)
High	> 103	7.63	70/3334	1.16	(0.85 , 1.58)	1.20	(0.86 , 1.68)
Continuous			Risk per 50g/day	1.10	(1.00 , 1.20)	1.12	(1.02 , 1.23)
				p (trend) = 0.046		p (trend) = 0.02	
Fresh meat (including red meat, poultry and offal)							
Categorical							
None (ref)	0	8.30	98/5556	1.00	-	1.00	-
Low	< 50	8.12	51/3539	0.73	(0.51 , 1.04)	0.69	(0.47 , 1.01)
Medium	50-84	7.77	66/3271	1.09	(0.79 , 1.51)	1.18	(0.83 , 1.66)
High	> 84	7.63	68/3298	1.17	(0.86 , 1.6)	1.20	(0.86 , 1.68)
Continuous			Risk per 50g/day	1.10	(0.99 , 1.22)	1.13	(1.01, 1.26)
				p (trend) = 0.069		p (trend) = 0.03	
Processed meat							
Categorical							
None (ref)	0	8.31	109/6069	1.00	-	1.00	-
Low	< 10	8.02	55/3196	0.88	(0.62 , 1.24)	0.94	(0.65 , 1.36)
Medium	10-20	7.75	56/3223	0.94	(0.67 , 1.32)	1.04	(0.72 , 1.51)
High	> 20	7.69	63/3176	1.13	(0.82 , 1.56)	1.20	(0.85 , 1.70)
Continuous			Risk per 50g/day	1.44	(0.96 , 2.18)	1.45	(0.95 , 2.23)
				p (trend) = 0.079		p (trend) = 0.09	
Red meat							
Categorical							
None (ref)	0	8.32	113/6463	1.00	-	1.00	-
Low	< 32	8.04	50/3328	0.83	(0.58 , 1.18)	0.80	(0.55 , 1.17)
Medium	32-57	7.71	59/3050	1.11	(0.79 , 1.55)	1.19	(0.83 , 1.7)
High	> 57	7.58	61/2823	1.28	(0.93 , 1.77)	1.32	(0.93 , 1.88)
Continuous			Risk per 50g/day	1.10	(0.97 , 1.25)	1.13	(0.99 , 1.29)
				p (trend) = 0.143		p (trend) = 0.08	
Poultry							
Categorical							
None (ref)	0	8.30	99/5700	1.00	-	1.00	-
Low	< 14	7.97	53/2854	1.05	(0.74 , 1.48)	1.07	(0.74 , 1.54)
Medium	14-23	7.79	64/3486	1.06	(0.77 , 1.47)	1.05	(0.75 , 1.49)
High	> 23	7.80	67/3624	1.10	(0.81 , 1.51)	1.15	(0.82 , 1.61)
Continuous			Risk per 50g/day	1.23	(0.91 , 1.65)	1.28	(0.93, 1.75)
				p (trend) = 0.172		p (trend) = 0.13	
Offal							
Categorical							
None (ref)	0	8.12	183/10616	1.00	-	1.00	-
Low	2	7.77	69/3252	1.24	(0.93 , 1.66)	1.32	(0.98 , 1.78)
-	-			-	-	-	-
High	7 +	7.76	31/1796	0.99	(0.67 , 1.47)	0.96	(0.63 , 1.45)
Continuous			Risk per 50g/day	1.53	(0.22 , 10.36)	1.63	(0.22 , 11.9)
				p (trend) = 0.665		p (trend) = 0.63	

[a] adjusting for age and energy intake

[b] adjusting for age, energy intake, BMI, physical activity, smoking status, HRT use, OCP use, parity, total fruit and vegetable intake

Table 4 Post-menopausal Breast Cancer

	Person Years (Mean)	Cases/Non-cases	Consumption (g per day)	Model 1[a]		Model 2[b]	
				HR	95% CI	HR	95% CI
Total meat							
Categorical							
None (ref)	8.31	51/3297	0	1.00		1.00	-
Low	7.98	110/4533	< 62	1.68	(1.19 , 2.36)	1.52	(1.06 , 2.18)
Medium	7.46	119/4791	62-103	1.81	(1.29 , 2.56)	1.58	(1.09 , 2.27)
High	7.28	115/4762	> 103	1.87	(1.33 , 2.63)	1.63	(1.13 , 2.35)
Continuous			Risk per 50g/day	1.11	(1.03 , 1.19)	1.10	(1.01 , 1.20)
				p (trend) = 0.004		p (trend) = 0.021	
Fresh meat (including red meat, poultry and offal)							
Categorical							
None (ref)	8.31	53/3428	0	1.00		1.00	-
Low	7.94	112/4494	< 50	1.62	(1.14 , 2.31)	1.53	(1.06 , 2.21)
Medium	7.47	119/4742	50-84	1.74	(1.22 , 2.46)	1.63	(1.13 , 2.36)
High	7.29	111/4719	> 84	1.72	(1.21 , 2.44)	1.59	(1.1 , 2.3)
Continuous			Risk per 50g/day	1.11	(1.01 , 1.21)	1.09	(0.99 , 1.20)
				p (trend) = 0.023		p (trend) = 0.088	
Processed meat							
Categorical							
None (ref)	8.31	66/4062	0	1.00		1.00	-
Low	7.79	105/4468	< 10	1.53	(1.09 , 2.15)	1.48	(1.04 , 2.12)
Medium	7.44	116/4419	10-20	1.76	(1.26 , 2.47)	1.60	(1.12 , 2.29)
High	7.34	108/4434	> 20	1.70	(1.21 , 2.39)	1.64	(1.14 , 2.37)
Continuous			Risk per 50g/day	1.40	(1.16 , 1.70)	1.64	(1.19 , 2.27)
				p (trend) = 0.001		p (trend) = 0.003	
Red meat							
Categorical							
None (ref)	8.32	73/4550	0	1.00		1.00	-
Low	7.88	112/4022	< 32	1.78	(1.28 , 2.47)	1.63	(1.15 , 2.31)
Medium	7.39	104/4347	32-57	1.67	(1.19 , 2.33)	1.64	(1.15 , 2.34)
High	7.24	106/4464	> 57	1.73	(1.24 , 2.41)	1.56	(1.09 , 2.23)
Continuous			Risk per 50g/day	1.13	(1.02 , 1.25)	1.12	(1.01 , 1.26)
				p (trend) = 0.019		p (trend) = 0.040	
Poultry							
Categorical							
None (ref)	8.25	61/3747	0	1.00		1.00	-
Low	7.62	107/4387	< 14	1.43	(1 , 2.05)	1.32	(0.9 , 1.93)
Medium	7.50	127/5001	14-23	1.51	(1.07 , 2.14)	1.39	(0.96 , 2.02)
High	7.58	100/4248	> 23	1.41	(0.99 , 2.01)	1.30	(0.89 , 1.89)
Continuous			Risk per 50g/day	1.06	(0.85 , 1.33)	1.00	(0.78 , 1.28)
				p (trend) = 0.585		p (trend) = 0.985	
Offal							
Categorical							
None (ref)	7.93	183/9517	0	1.00		1.00	-
Low	7.47	121/4391	2	1.39	(1.09 , 1.76)	1.37	(1.05 , 1.77)
-			-			-	-
High	7.41	91/3475	7 +	1.34	(1.03 , 1.73)	1.26	(0.95 , 1.67)
Continuous			Risk per 50g/day	2.01	(0.79 , 5.13)	1.62	(0.57 , 4.59)
				p (trend) = 0.142		p (trend) = 0.363	

[a] adjusting for age and energy intake

[b] adjusting for age, energy intake, BMI, physical activity, smoking status, HRT use, OCP use, parity, total fruit and vegetable intake

Figure 1 Association between total meat intake and breast cancer for pre- and postmenopausal women.