European Journal of Cancer 90 (2018) 73–82

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Red and processed meat consumption and breast cancer: UK Biobank cohort study and meta-analysis

Jana J. Anderson [a], Narisa D.M. Darwis [a], Daniel F. Mackay [a], Carlos A. Celis-Morales [b], Donald M. Lyall [a], Naveed Sattar [b], Jason M.R. Gill [b], Jill P. Pell [a,*]

[a] *Institute of Health and Wellbeing, University of Glasgow, 1 Lilybank Gardens, Glasgow, UK*
[b] *Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK*

Received 22 August 2017; received in revised form 25 October 2017; accepted 22 November 2017

KEYWORDS
Breast cancer;
Pre-menopausal;
Post-menopausal;
Diet;
Red meat;
Processed meat;
UK Biobank

Abstract ***Aim:*** Red and processed meat may be risk factors for breast cancer due to their iron content, administration of oestrogens to cattle or mutagens created during cooking. We studied the associations in UK Biobank and then included the results in a meta-analysis of published cohort studies.

Methods: UK Biobank, a general population cohort study, recruited participants aged 40–69 years. Incident breast cancer was ascertained via linkage to routine hospital admission, cancer registry and death certificate data. Univariate and multivariable Cox proportional hazard models were used to explore the associations between red and processed meat consumption and breast cancer. Previously published cohort studies were identified from a systematic review using PubMed and Ovid and a meta-analysis conducted using a random effects model.

Results: Over a median of 7 years follow-up, 4819 of the 262,195 women developed breast cancer. The risk was increased in the highest tertile (>9 g/day) of processed meat consumption (adjusted hazard ratio [HR] 1.21, 95% confidence interval [CI] 1.08–1.35, p = 0.001). Collation with 10 previous cohort studies provided data on 40,257 incident breast cancers in 1.65 million women. On meta-analysis, processed meat consumption was associated with overall (relative risk [RR] 1.06, 95% CI 1.01–1.11) and post-menopausal (RR 1.09, 95% CI 1.03–1.15), but not pre-menopausal (RR 0.99, 95% CI 0.88–1.10), breast cancer. In UK Biobank and the meta-analysis, red meat consumption was not associated with breast cancer (adjusted HR 0.99 95% CI 0.88–1.12 and RR 1.03, 95% CI 0.99–1.08, respectively).

* *Corresponding author*: Institute of Health and Wellbeing, University of Glasgow, 1 Lilybank Gardens, Glasgow, G12 8RZ, UK. Fax: +44 (0) 141 330 1874.
E-mail address: jill.pell@glasgow.ac.uk (J.P. Pell).

https://doi.org/10.1016/j.ejca.2017.11.022

Conclusions: Consumption of processed meat, but not red meat, may increase the risk of breast cancer.

1. Introduction

In the United Kingdom, 1 in 8 women will develop breast cancer [1], but more than one-quarter of cases could be prevented by reduced exposure to exogenous oestrogens, reduced obesity, increased physical activity and breastfeeding [1]. There is a lack of consensus on whether red and processed meat consumption is a risk factor for breast cancer [2]. Four meta-analyses have produced conflicting results [3–6] due to wide inclusion criteria, resulting in the inclusion of very heterogeneous studies. We studied whether red and processed meat consumption were associated with the risk of breast cancer in UK Biobank; then included the results in a meta-analysis of prospective cohort studies using rigorous inclusion criteria.

2. Materials and methods

2.1. UK Biobank

UK Biobank recruited 273,466 women aged 40–69 years from the general population between 2007 and 2010. Baseline socioeconomic and lifestyle information were collected via a self-completed, touch-screen questionnaire and anthropometric measurements taken by trained staff. Self-reported moderate and vigorous physical activity were converted to $\text{METs}\cdot\text{min}\cdot\text{week}^{-1}$, and dichotomised to inactive ($<600\ \text{METs}\cdot\text{min}\cdot\text{week}^{-1}$) and active ($\geq600\ \text{METs}\cdot\text{min}\cdot\text{week}^{-1}$). Dietary information was collected using a self-completed food frequency questionnaire. Frequency of beef, pork and lamb intake (excluding processed meat) and frequency of processed meat intake were recorded. These were converted into probabilities of daily consumption, multiplied by normal portion sizes [7] and then weighted by size of portion: small 0.5, medium 1.0 or large 1.5. We then derived four categories of red/processed meat intake: zero intake and tertiles of consumption for those consuming some. Follow-up information (min 5.33 years and max 9.89 years) on the date of first diagnosis of cancer was obtained via linkage to three routine administrative databases: cancer registrations, death certificates and hospital admissions. Date and cause of death were obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Date and cause of hospital admissions were obtained from the Health Episode Statistics (HES) for England and Wales and the Scottish Morbidity Record 01 (SMR01) for Scotland. At the time of analysis, mortality data were available up to 31 January 2016 and hospital admission and cancer registry data until 31 March 2015. Therefore, follow-up was censored at 31 January 2016 or date of death if this occurred earlier. There were 54 participants who withdrew consent from UK Biobank at the time of analysis. All databases used the International Classification of Diseases and we defined breast cancer as ICD10 code C50.

We excluded women with a record of breast cancer at baseline. Cox proportional hazard models were used to examine the associations between red/processed meat consumption and breast cancer using zero consumption as the referent category. We ran four incremental models for each: univariate, multivariable adjusted for sociodemographic factors (age, sex, ethnic group and deprivation index); multivariable also adjusted for lifestyle factors (smoking status, frequency of alcohol consumption, body mass index and physical activity) and multivariable also adjusted for potential dietary confounders (cooked vegetables, raw vegetables and type of bread). We tested for statistical interactions and, where significant, subgroup analyses were undertaken. All analyses were repeated after stratifying women into pre- and postmenopausal subgroups. In the latter, we included the use of hormone replacement therapy as a covariate in the fully adjusted model. We also conducted landmark analyses, excluding the first 2 years of follow-up. This study was performed under generic ethical approval obtained by UK Biobank from the NHS National Research Ethics Service (ref 11/NW/0382, 17 June 2011). All analyses were undertaken using Stata, version 14.

2.2. Meta-analysis

Two authors (JJA and NDMD) searched PubMed and Ovid using the search term breast cancer combined with meat, red meat, processed meat, preserved meat, pork, beef, veal, mutton, lamb, ham, sausage or bacon; consistent with the most recently published meta-analysis [6]. However, inclusion was restricted to prospective, general population cohort studies. We excluded case-control studies and studies that measured only beef intake. Where more than one study was conducted on the same cohort, only the most recent was included. The last search was conducted on 15 January 2017. Meta-analysis was undertaken using a random effects model; stratified by type of meat (red and processed) and outcome (pre-,

Table 1
Demographic, lifestyle and dietary characteristics of female UK Biobank participants according to whether or not they developed breast cancer.

Characteristics	No breast cancer	Breast cancer	P value*
	N = 257,376	N = 4819	
	N (%)	N (%)	
Ethnic group			
White	242,024 (94.5)	4621 (96.3)	<0.001
Asian	4414 (1.7)	58 (1.2)	
Black	4519 (1.8)	42 (0.9)	
Other	5206 (2.0)	76 (1.6)	
Missing	1213	22	
Smoking status			
Never	153,066 (59.8)	2774 (54.8)	0.002
Former	79,787 (31.2)	1609 (33.6)	
Current	23,090 (9.0)	413 (8.6)	
Missing	1433	23	
Physical activity			
Inactive	124,496 (48.4)	2440 (50.6)	0.002
Active	132,880 (51.6)	2379 (49.4)	
Missing	0	0	
Alcohol frequency			
Never	41,104 (16.0)	905 (16.7)	0.017
Special occasions	52,595 (20.5)	1069 (22.2)	
1–2/month	66,088 (25.8)	1209 (25.2)	
1–2/week	33,561 (13.1)	608 (12.7)	
3–4/week	38,734 (15.1)	686 (14.3)	
Daily	24,586 (9.6)	431 (9.0)	
Missing	708	11	
Cooked vegetables (spoons/day)			
0	6444 (2.5)	117 (3.0)	0.528
1	35,749 (14.1)	663 (13.9)	
2	87,239 (34.3)	1645 (34.5)	
3	72,735 (28.6)	1361 (28.5)	
4	28,167 (11.1)	563 (11.8)	
≥5	24,133 (9.5)	425 (8.9)	
Missing	2909	45	
Raw vegetables (spoons/day)			
0	18,097 (7.1)	385 (8.1)	0.048
1	80,302 (31.6)	1545 (32.3)	
2	64,216 (25.3)	1187 (24.9)	
3	40,895 (16.1)	766 (16.0)	
4	21,855 (8.6)	398 (8.3)	
≥5	28,839 (11.3)	496 (10.4)	
Missing	3172	42	
Bread			
Brown/wholemeal	178,913 (73.8)	3374 (73.9)	0.828
White/other	63,570 (26.2)	1190 (26.1)	
Missing	14,893	255	
Red meat (g/day)			
0	22,059 (8.7)	376 (7.9)	<0.001
1–19	116,675 (45.9)	2069 (43.6)	
19–25	42,869 (16.7)	858 (18.1)	
>25	72,539 (28.5)	1477 (30.5)	
Missing	3234	69	
Processed meat (g/day)			
0	32,456 (12.7)	521 (10.9)	0.023
1–4	99,269 (38.7)	1875 (39.1)	
5–9	70,313 (27.4)	1393 (29.0)	
>9	54,268 (21.2)	1011 (21.1)	
Missing	1070	19	
	Mean (SD)	Mean (SD)	
Age	56.2 (8.0)	57.6 (7.6)	
Missing	0	0	
Deprivation index	−1.3 (3.1)	−1.5 (3.0)	<0.001
Missing	313	3	
Body mass index (kg/m^2)	27.1 (5.2)	27.6 (5.1)	<0.001
Missing	4818	87	

*t-test for age, BMI and fibre intake; Mann–Whitney U test for deprivation index; chi-squared test for sex, ethnic group and type of bread; chi-squared test for trend for smoking and intake of alcohol, meat and vegetables.
N, number; BMI, body mass index; SD, standard deviation.

post-menopausal and overall breast cancer). We performed Egger's and Begg's tests and used funnel plots to assess potential bias. Heterogeneity between the studies was tested using the I-squared statistic. All analyses were undertaken using Stata, version 14.

3. Results

3.1. UK Biobank

Of the 273,466 female participants, 262,195 had no record of breast cancer at baseline and, therefore, were eligible for inclusion. Of these, 4819 (1.8%) developed incident breast cancer over a median follow-up period of 7 years (interquartile range, IQR 6.3–7.7). The participants who developed breast cancer were older, more affluent, less physically active, more likely to be white and former smokers, had higher body mass indices and reported lower alcohol and raw vegetable intake, but higher intake of red and processed meat (Table 1).

Overall, 3303 (1.3%) of the 262,195 women had missing data on consumption of red meat; of the remainder, 22,435 (8.6%) consumed no red meat, 118,744 (45.3%) consumed <19 g/day, 43,727 (16.7%) 19–25 g/day and 73,986 (28.2%) >25 g/day. In relation to processed meat consumption, 1089 (0.4%) had missing data and, of the remainder, 32,977 (12.6%) consumed none, 101,144 (38.6%) <4 g/day, 71,706 (27.4%) 4–9 g/day and 55,279 (21.1%) >9 g/day.

In the univariate Cox proportional hazards model, there was a significant overall association between red meat consumption and risk of incident breast cancer (Table 2). Adjustment for potential sociodemographic confounders attenuated the overall association and, following further adjustment for potential lifestyle and dietary confounders, it was no longer statistically significant. There were no significant interactions with any of the covariates or menopausal status. On subgroup analyses, the associations between red meat consumption and breast cancer were not significant in either pre- or post-menopausal women. Landmark analyses, excluding the first 2 years of follow-up, did not alter the results. Supplementary Table 1 contains the results rerun using the lowest tertile of red meat intake as the referent category.

Table 2
Cox proportional hazard models of the risk of breast cancer associated with red and processed meat consumption.

Intake	Univariate			Multivariable*			Multivariable**			Multivariable***		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Red meat (g/day)												
		N = 258,892	0.008		N = 257,876	0.177		N = 252,309	0.622		N = 235,233	0.431
0	1			1			1			1		
<19	1.04	0.93–1.16	0.511	0.99	0.89–1.11	0.885	0.96	0.86–1.08	0.528	0.96	0.85–1.08	0.469
19–25	1.12	1.00–1.27	0.064	1.06	0.93–1.12	0.395	1.02	0.90–1.16	0.747	1.02	0.90–1.16	0.738
>25	1.12	1.00–1.25	0.058	1.04	0.93–1.16	0.537	0.99	0.88–1.11	0.828	0.99	0.88–1.12	0.914
Processed meat (g/day)												
		N = 261,106	0.001		N = 260,064	<0.001		N = 254,356	0.002		N = 236,876	0.005
0	1			1			1			1		
<4	1.17	1.07–1.30	0.001	1.15	1.05–1.28	0.003	1.15	1.04–1.27	0.006	1.15	1.04–1.28	0.007
4–9	1.22	1.11–1.35	<0.001	1.21	1.09–1.33	<0.001	1.19	1.07–1.32	0.001	1.19	1.07–1.33	0.002
>9	1.22	1.10–1.36	<0.001	1.23	1.10–1.36	<0.001	1.21	1.09–1.35	0.001	1.21	1.08–1.35	0.001

*Adjusted for age, deprivation and ethnic group, **also adjusted for smoking, alcohol, body mass index and physical activity, ***also adjusted for consumption of cooked and raw vegetables and type of bread; HR, hazard ratio; CI, confidence interval; N, number.

In the univariate analysis, there was a statistically significant dose–response relationship between processed meat consumption and breast cancer (Table 2). Adjustment for potential sociodemographic, lifestyle and dietary confounders did not attenuate the results. There was a significant dose–response relationship across the tertiles of processed meat consumption; whereby, participants in the low, medium and highest tertiles of consumption remained significantly more likely to develop breast cancer than those with zero intake. In the fully adjusted model the results were as follows: <4 g/day hazard ratio (HR) 1.15, 95% confidence interval (CI) 1.04–1.28, p = 0.007; 4–9 g/day HR 1.19, 95% CI 1.07–1.33, p = 0.002; >9 g/day HR 1.21, 95% CI 1.08–1.35, p = 0.001 (overall p_{trend} = 0.005). There was a statistically significant interaction with the intake of cooked vegetables (p = 0.009). There was a weaker association between processed meat intake and breast cancer among participants with the lowest intake of cooked vegetable. This was due to the absolute risk already being higher in this subgroup; among participants who ate no processed meat, the incidence of breast cancer was 2.46 per 1000 population per annum among those with low intake of cooked vegetables compared with only 2.01 per 1000 per annum among those with high vegetable intake. Among participants who had the highest intake of processed meat, the incidence of breast cancer was 2.55 per 1000 population per annum among those with low cooked vegetable intake and 2.35 per 1000 per annum among those with high intake. There was no significant interaction with menopausal status. However, in the subgroup of pre-menopausal women, the increased risk of breast cancer only reached statistical significance in the highest tertile of processed meat intake (fully adjusted model: <4 g/day HR 1.24, 95% CI 0.98–1.57, p = 0.069; 4–9 g/day HR 1.21, 95% CI 0.95–1.54, p = 0.131; >9 g/day HR 1.32, 95% CI 1.03–1.69, p = 0.032). Among post-menopausal women, the risk of breast cancer was significantly higher among all groups that consumed processed meat (fully adjusted model: <4 g/day HR 1.16, 95% CI 1.03–1.31, p = 0.016; 4–9 g/day HR 1.20, 95% CI 1.05–1.36, p = 0.006; >9 g/day HR 1.20, 95% CI 1.05–1.37, p = 0.008). In the landmark analyses, excluding the first 2 years of follow-up, the effect estimates remained unaffected (fully adjusted model: <4 g/day HR 1.15, 95% CI 1.02–1.29, p = 0.022; 4–9 g/day HR 1.19, 95% CI 1.05–1.34, p = 0.006; >9 g/day HR 1.23, 95% CI 1.08–1.39, p = 0.002). Supplementary Table 1 shows the results re-run using the first tertile of processed meat consumption as the reference category.

3.2. Meta-analysis

A total of 124 and 84 publications were identified by searching the PubMed and Ovid databases, respectively, of which 78 were excluded as duplicates. The remaining 130 articles were screened, together with nine additional publications identified from reference lists. Of these, 122 were excluded because they did not satisfy the inclusion criteria. A further five studies were excluded due to repeat analyses conducted on the same cohort and two due to inadequate exposure information; resulting in 10 eligible cohort studies in addition to UK Biobank (Fig. 1). The 10 previous studies comprised a total of 35,438 incident cancers occurring in 1,386,799 women [8–17]. Combined with UK Biobank, this produced a total of 11 studies with data on 40,257 incident cancers in 1,648,994 women (Table 3).

Of the 11 cohort studies, 10 reported the association between red meat consumption and overall risk of breast cancer; of these, six also reported results separately for pre- and post-menopausal breast cancer. The 11th study only examined the association with post-menopausal breast cancer (Table 3). The 10 studies produced a pooled relative risk (RR) for breast cancer, overall, of 1.03 (95% CI 0.99–1.08) (Fig. 2). The funnel plot was reasonably symmetrical with one small study outlier (Supplementary Fig. 1a), and both Begg's

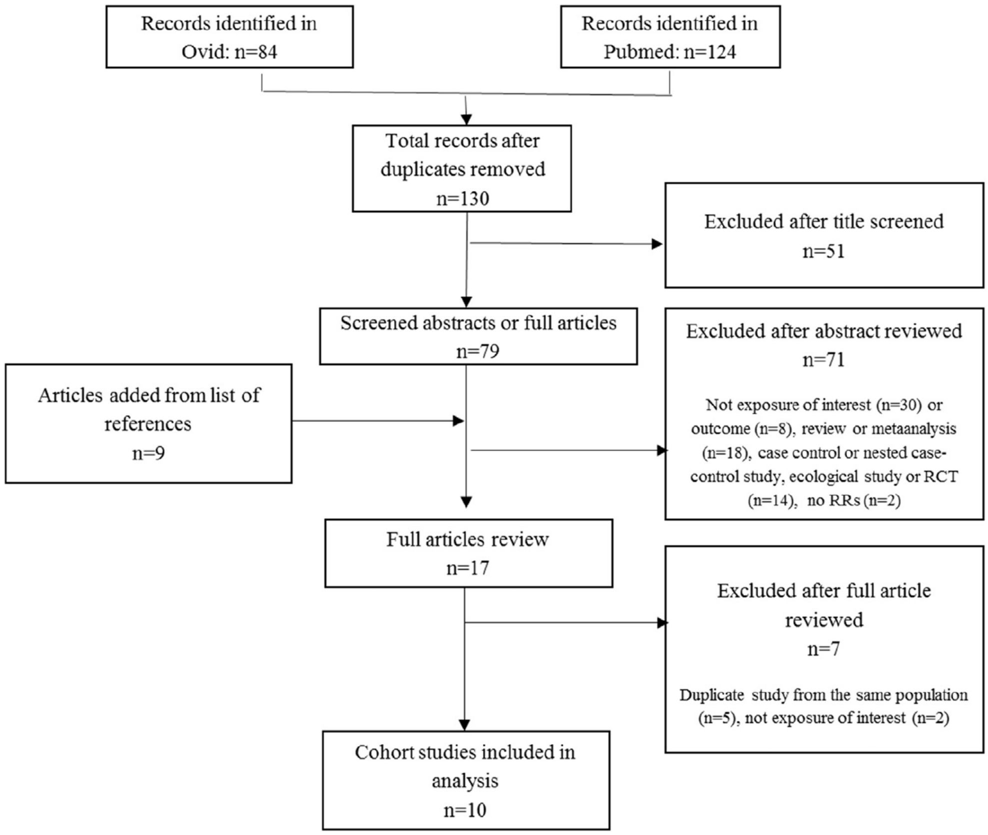

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study selection process (Presented according to PRISMA guidelines).

($p = 0.210$) and Egger's ($p = 0.317$) tests were non-significant. Overall there was a medium-level heterogeneity (I^2 44.0%) that was not statistically significant ($p = 0.065$).

The six studies on pre-menopausal breast cancer produced a pooled RR for high consumption of red meat of 1.02 (95% CI 0.92–1.11) (Fig. 2). Both Begg's ($p = 0.573$) and Egger's ($p = 0.272$) tests were non-significant indicating no significant publication bias, and the funnel plot was symmetrical with no study outliers (Supplementary Fig. 1b). The level of heterogeneity was low (I^2 0.0%) and not statistically significant ($p = 0.530$). The pooled RR for post-menopausal breast cancer, from the six relevant studies, was 1.03 (95% CI 0.97–1.08) (Fig. 2). Both Begg's ($p = 0.764$) and Egger's ($p = 0.483$) tests were non-significant, and the funnel plot was symmetrical with one small study outlier (Supplementary Fig. 1c). Overall there was low heterogeneity (I^2 34.6%) that was not statistically significant ($p = 0.177$).

Of the nine cohort studies on processed meat consumption, eight examined the association with overall risk of breast cancer (Fig. 3); five of these also studied both pre- and post-menopausal breast cancer. The ninth study reported results for post-menopausal breast cancer only. For overall risk of breast cancer, the pooled RR from the eight studies was 1.06 (95% CI 1.01–1.11) (Fig. 3). The funnel plot was reasonably symmetrical with one small study outlier (Supplementary Fig. 2a). Both Egger's ($p = 0.141$) and Begg's ($p = 0.108$) tests were non-significant indicating no significant publication bias. Overall there was a medium-level heterogeneity (I^2 61.5%) that was statistically significant ($p = 0.011$).

The pooled RR for pre-menopausal breast cancer, from the five relevant studies, was 0.99 (95% CI 0.88–1.10) (Fig. 3). Both Begg's ($p = 1.000$) and Egger's ($p = 0.662$) tests were non-significant, and the funnel plot was symmetrical with one small study outlier (Supplementary Fig. 2b). The level of heterogeneity was medium (I^2 39.5%) and not statistically significant ($p = 0.158$). The six relevant studies produced a pooled RR for post-menopausal breast cancer of 1.09 (95% CI 1.03–1.15) (Fig. 3). Both Begg's ($p = 0.348$) and Egger's ($p = 0.570$) tests were non-significant, and the funnel plot was symmetrical with one small study outlier (Supplementary Fig. 2c). Overall there was medium heterogeneity (I^2 40.2%) that was not statistically significant ($p = 0.137$).

4. Discussion

Among the 262,195 women in UK Biobank, those who consumed processed meat were at a higher risk of breast cancer; independent of sociodemographic, lifestyle, obesity and dietary factors included in this study. Our

Table 3
Characteristics of the cohort studies included in the meta-analysis.

Reference	Country	Cohort	Participants		Exposure details	Intake	Follow-up (years)	Breast cancer		Result		
			Age (years)	N				N	Type	RR	Lower CI	Upper CI
Holmes *et al.* (2003)												
	USA	NHS	30–55	88,647	Red meat	≥1.32 serving/day	18	4107	Overall	0.94	0.84	1.05
		NHS			Processed meat	≥0.46 serving/day			Overall	0.94	0.85	1.05
		NHS			Red meat				Post-menopausal	0.99	0.86	1.13
		NHS			Processed meat				Post-menopausal	1	0.88	1.13
		NHS			Red meat				Pre-menopausal	0.94	0.72	1.22
		NHS			Processed meat				Pre-menopausal	0.86	0.67	1.09
Cross *et al.* (2007)												
	USA	NIH AARP	50–71	494,036	Red meat	62.7 g/1,000 kcal	8.2	5872	Overall	1.02	0.93	1.12
		NIH AARP			Processed meat	22.6 g/1,000 kcal			Overall	1.03	0.94	1.12
Taylor *et al.* (2007)												
	UK	UK WCS	35–69	33,725	Red meat	>57 g/day	8	678	Overall	1.41	1.11	1.81
		UK WCS			Processed meat	>20 g/day			Overall	1.39	1.09	1.78
		UK WCS			Red meat				Post-menopausal	1.56	1.09	2.23
		UK WCS			Processed meat				Post-menopausal	1.64	1.14	2.37
		UK WCS			Red meat				Pre-menopausal	1.32	0.93	1.88
		UK WCS			Processed meat				Pre-menopausal	1.2	0.85	1.7
Ferucci *et al.* (2009)												
	USA	PLCOCST	55–74	52,158	Red meat	52.8 g/1,000 kcal	5.5	1205	Overall	1.23	1	1.51
		PLCOCST			Processed meat	16.9 g/1,000 kcal			Overall	1.12	0.92	1.36
Larsson *et al.* (2009)												
	Swedish	Swedish MC	40–71	61,433	Red meat	≥98 g/day	17.4	2952	Overall	0.98	0.86	1.12
Pala *et al.* (2009)												
	Europe	EPIC	25–75	319,826	Red meat	84.6 g/day	8.8	7119	Overall	1.06	0.98	1.14
					Processed meat	56.5 g/day			Overall	1.1	1	1.2
		EPIC			Red meat				Post-menopausal	1.05	0.94	1.18
					Processed meat				Post-menopausal	1.13	1	1.28
		EPIC			Red meat				Pre-menopausal	0.94	0.8	1.1
					Processed meat				Pre-menopausal	0.99	0.82	1.19
Genkinger *et al.* (2013)												
	USA	BWHS	21–69	52,062	Red meat	≥400 g/week	12	1268	Overall	1.02	0.83	1.24
					Processed meat	≥200 g/week			Overall	0.99	0.82	1.2
		BWHS			Red meat				Post-menopausal	0.86	0.62	1.2
					Processed meat				Post-menopausal	0.93	0.69	1.27
		BWHS			Red meat				Pre-menopausal	1.01	0.78	1.3
					Processed meat				Pre-menopausal	0.92	0.72	1.18
Farvid *et al.* (2014)												
	USA	NHSII	33–52	88,803	Red meat	1.50 serving/day	20	2830	Overall	1.22	1.06	1.4
		NHSII			Red meat				Post-menopausal	1.23	0.96	1.57
		NHSII			Red meat				Pre-menopausal	1.12	0.93	1.35
Pouchieu *et al.* (2014)												
	France	SUVIMAX		2367	Red meat	>63.7 g/day	11.3	102	Overall	1.01	0.58	1.74
		SUVIMAX			Processed meat	>43.5 g/day			Overall	2.46	1.28	4.72

Inoue-choi *et al.* (2016)											
USA	NIH AARP	62 (5.3)	193,742	Red meat	43.4 g/1,000 kcal	9.4	9305	Post-menopausal	1.03	0.96	1.11
	NIH AARP			Processed meat	14.5 g/1,000 kcal			Post-menopausal	1.09	1.01	1.17
Anderson *et al.* (2017)											
UK	UK Biobank	40–69	262,195	Red meat	37.8 g/day	7	4819	Overall	0.99	0.88	1.12
								Post-menopausal	0.95	0.82	1.1
								Pre-menopausal	1.09	0.85	1.4
				Processed meat	20.2 g/day			Overall	1.21	1.08	1.35
								Post-menopausal	1.2	1.05	1.37
								Pre-menopausal	1.32	1.03	1.69

N, number; RR, relative risk; CI, confidence interval; USA, United States of America; NHS, Nurses Health Study; NIH, National Institutes of Health; AARP, American Association for Retired Persons; UK, United Kingdom; WCS, Women's Cohort Study; PLCOCST, Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial; SU.VI.MAX, Supplementation en Vitamines et Mineraux Antioxydants; BWHS, Black Women's Health Study; EPIC, European Prospective Investigation into Cancer and Nutrition; Swedish MC, The Swedish Mammography Cohort. Referent category: Taylor *et al.* (2007) and Anderson *et al.* (2017) zero intake; otherwise zero/lowest intake (i.e. lowest intake category including zero intake).

results and the meta-analysis suggested the overall association is largely driven by the risk of post-menopausal breast cancer. Red meat consumption was not a risk factor for breast cancer in UK Biobank, after adjusting for confounding; nor in the meta-analysis.

A number of possible underlying mechanisms have been mooted [18]. Processed meat contains high levels of amines, and nitrate and nitrite are commonly added to enhance colour and flavour. All are precursors of N-nitroso compounds which are carcinogenic. The added nitrate together with the heme iron present in red meat enhances endogenous N-nitroso compound formation [17], whereas antioxidants inhibit it [19]. In a randomised controlled trial, consumption of processed meat (HR 2.46; 95% CI 1.28–4.72) and dietary heme (HR 2.80, 95% CI 1.42, 5.54) were both associated with breast cancer in the control arm, but not in the intervention arm which was given low-dose antioxidants [16,19]. A recent study has implicated the high content of N-glycolylneuraminic acid, an animal sugar, as a possible cause of chronic inflammation and tumour formation [20].

The mechanism most extensively studied has been the possible role of cooking. Cooking red meat can produce carcinogenic compounds such as heterocyclic amines and polycyclic aromatic hydrocarbons [21,22]. The likelihood of carcinogens being formed varies according to the method, temperature and duration of cooking. In a case-control study of 2386 women with breast cancer and 1703 healthy controls, there was an overall association between red meat consumption and breast cancer. However, on subgroup analysis the association was significant in women using high temperature cooking methods (odds ratio [OR] 1.5, 95% CI 1.3–1.9, $p < 0.001$) but not those using other cooking methods (OR 1.1, 95% CI 0.9–1.3, $p = 0.429$) [21]. A recent study found that high intake of smoked meats, that are high in polycyclic aromatic hydrocarbons, was associated with mortality from breast cancer [23].

Because the UK Biobank participants are not representative of the general population, summary statistics such as disease frequency cannot be generalised; however, estimates of effect size can [24]. Repeated 24-h dietary recall questionnaires are generally more accurate than food frequency questionnaires, but take longer to complete, and were only available on a minority of UK Biobank participants. Therefore, our study used data from the self-completed food frequency questionnaire; the usual methodology adopted in large-scale studies. To date, there has been no internal validation of the food frequency data within the UK Biobank population. Participants who completed the Oxford WebQ were more likely to be female, white, older, more affluent and better educated compared with the rest of the UK Biobank participants, which may have introduced response bias. Breast cancer was ascertained through a combination of hospital admission, cancer registry and death certificate data; therefore, it should be reasonably complete and

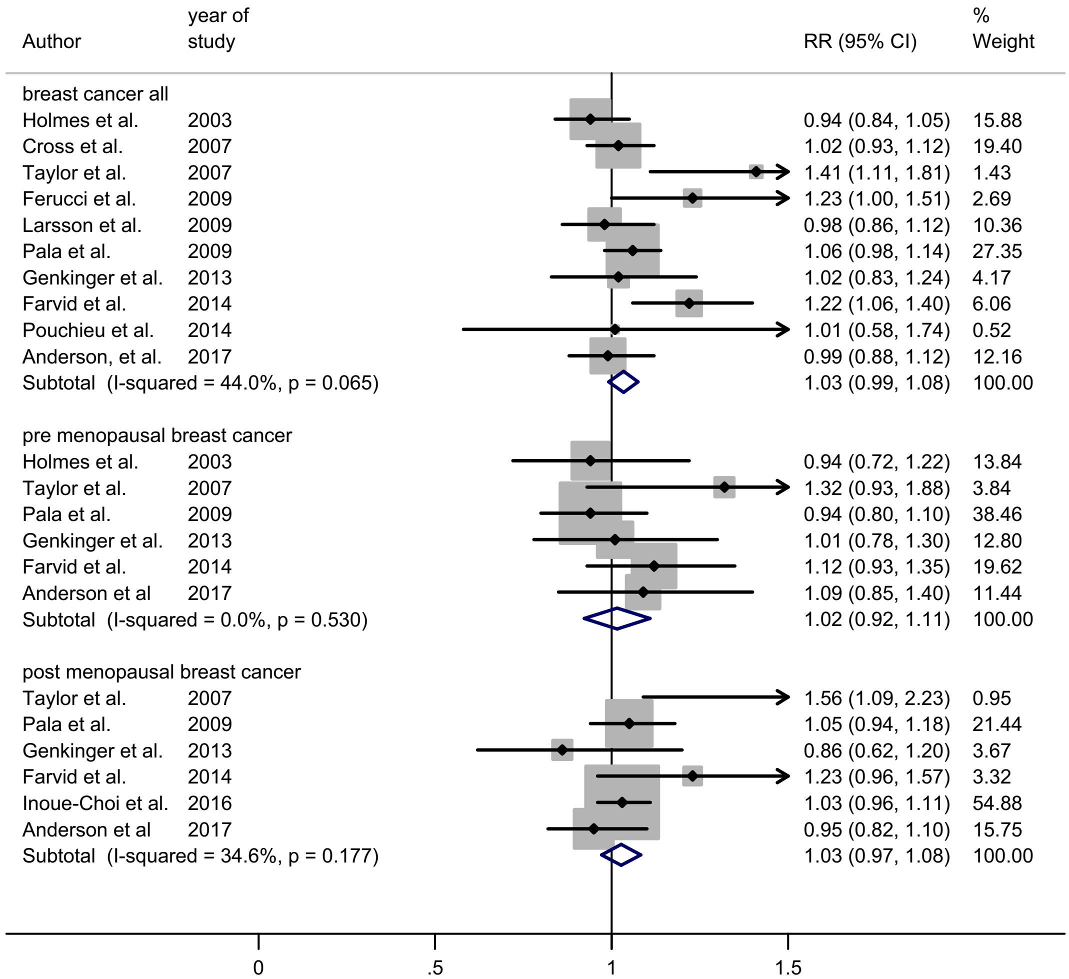

Fig. 2. Forest plot of cohort studies examining the association between red meat intake and breast cancer. RR, relative risk; CI, confidence interval.

selection bias unlikely. We were able to adjust for a wide range of confounders including sociodemographic, lifestyle and dietary factors; however, residual confounding is possible in any observational study. Although there was some evidence of a possible dose relationship, the largest increase in risk of breast cancer was between zero and low intake (4 g/day) of processed meat. Women who ate no processed meat may differ in other, unmeasured, ways or may have changed their diet as a result of ill-health. To check for potential reverse causation, we repeated the analyses using landmark analyses, and the results were similar. A limitation of our study was the inability to determine whether the associations varied according to the hormonal receptor status of tumours, due to lack of these data in UK Biobank. Our meta-analysis was the largest to date, including data on 40,257 incident cancers in over 1.6 million women from 11 independent cohorts. A limitation of our meta-analysis was the inconsistent approaches adopted by the individual studies in the number and range of confounders they included; therefore, we used a random effects approach to allow for differences in effect size between different study populations.

We obtained a similar pooled estimate as Guo *et al.* [6] for processed meat consumption but a non-significant pooled estimate for red meat consumption. The latter is due to our meta-analysis employing stricter inclusion criteria and methodology. We included only cohort studies, did not include duplicate information from repeat studies on the same cohort, included only estimates based on comparisons of the highest and lowest intake categories, excluded estimates based on increments in intake, included only evaluations of red meat and processed meat intake and excluded studies that analysed total meat consumption or only selected types of red meat, such as beef. In comparison, the most recently published meta-analysis, by Guo *et al.*, included three nested case-control studies [25–27] as well as cohort studies, and treated ORs as equivalent to RRs [26,27]. One of the nested case-control studies produced atypically high estimates of the associations, but these were derived from a study population with much higher levels of meat consumption in the highest category than our UK Biobank study. Guo *et al.* also included two studies that were undertaken on the same cohort as two

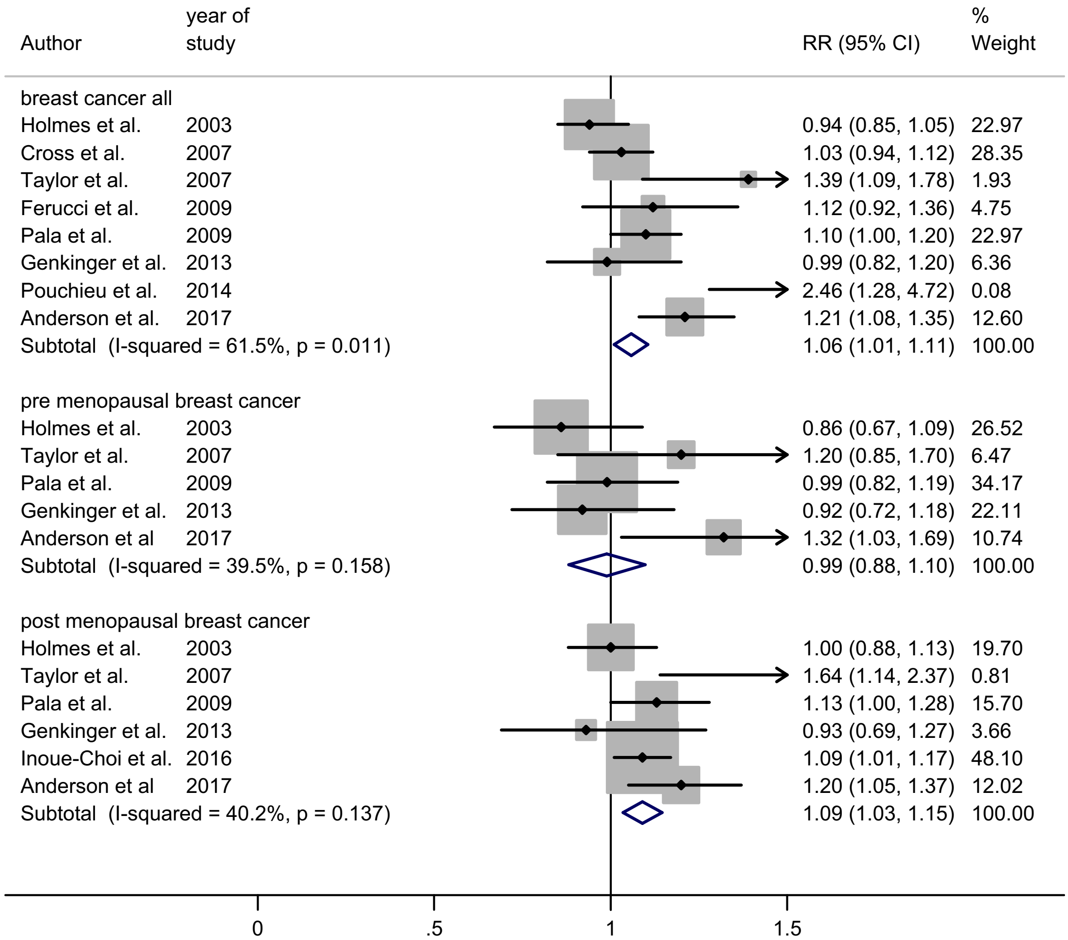

Fig. 3. Forest plot of cohort studies examining the association between processed meat intake and breast cancer. RR, relative risk; CI, confidence interval.

other included studies [15,28]. Furthermore, they included a study on 6156 women who participated in the National Health Epidemiologic Follow-up Study, which compared women according to beef, rather than total red meat, intake [29]. Therefore, the groups reporting no and low beef intake will have included women who consumed other forms of red meat; such as pork, lamb and game. Because of our tighter inclusion criteria, the heterogeneity of the studies included in our meta-analysis was lower than those included in the meta-analysis conducted by Guo *et al.*: I-square for red meat 44.0% versus 62.2%.

A previous meta-analysis based on estimates of incremental intake of red and processed meat conducted by the World Cancer Research fund reported similar findings to this study [30]. They found that there was no association between red meat intake and breast cancer, whereas the pooled RR for 50 g/day intake of processed meat and post-menopausal breast cancer was 1.13, 95% CI 0.99–1.29.

In conclusion, high consumption of processed meat was associated with higher overall risk of breast cancer; but this association was driven by post-menopausal breast cancer. After taking account of confounding, red meat consumption was not associated with an overall risk of breast cancer either in UK Biobank or the meta-analysis.

Conflict of interest statement

JPP and NS are members of the UK Biobank steering committee. These facts had no bearing on the study. Otherwise the authors have declared that no competing interests, including financial interests, exist.

Acknowledgements

The authors are grateful to the UK Biobank participants. This research has been conducted using the UK Biobank Resource under Application Number 7155. This work was supported by the Glasgow University Paterson Endowment Fund. The funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2017.11.022.

References

[1] Cancer Research UK. Cancer statistics reports-breast cancer. 2014. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero;2014. [Accessed 15 August 2017].
[2] Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, et al. Carcinogenicity of consumption of red and processed meat. Lancet Oncol 2015;16:1599–600.
[3] Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, et al. Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. Int J Epidemiol 2002;31:78–85.
[4] Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ, Minkin S. Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. Br J Cancer 2003;89:1672–85.
[5] Alexander DD, Morimoto LM, Mink PJ, Cushing CA. A review and meta-analysis of red and processed meat consumption and breast cancer. Nutr Res Rev 2010;23:349–65.
[6] Guo J, Wei W, Zhan L. Red and processed meat intake and risk of breast cancer: a meta-analysis of prospective studies. Breast cancer Res Treat 2015;151:191–8.
[7] Food Standards Agency. Food portion sizes. 3rd ed. Mills Alison; 1994.
[8] Genkinger JM, Makambi KH, Palmer JR, Rosenberg L, Adams-Campbell LL. Consumption of dairy and meat in relation to breast cancer risk in the Black Women's Health Study. Cancer Causes Control CCC 2013;24:675–84.
[9] Pala V, Krogh V, Berrino F, Sieri S, Grioni S, Tjonneland A, et al. Meat, eggs, dairy products, and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Am J Clin Nutr 2009;90:602–12.
[10] Larsson SC, Bergkvist L, Wolk A. Long-term meat intake and risk of breast cancer by oestrogen and progesterone receptor status in a cohort of Swedish women. Eur J Cancer (Oxford, England 1990) 2009;45:3042–6.
[11] Ferrucci LM, Cross AJ, Graubard BI, Brinton LA, McCarty CA, Ziegler RG, et al. Intake of meat, meat mutagens, and iron and the risk of breast cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Br J Cancer 2009;101:178–84.
[12] Taylor EF, Burley VJ, Greenwood DC, Cade JE. Meat consumption and risk of breast cancer in the UK Women's Cohort Study. Br J Cancer 2007;96:1139–46.
[13] Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R. A prospective study of red and processed meat intake in relation to cancer risk. PLoS Med 2007;4, e325.
[14] Holmes MD, Colditz GA, Hunter DJ, Hankinson SE, Rosner B, Speizer FE, et al. Meat, fish and egg intake and risk of breast cancer. Int J Cancer 2003;104:221–7.
[15] Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC. Dietary protein sources in early adulthood and breast cancer incidence: prospective cohort study. BMJ (Clinical research ed) 2014;348: g3437.
[16] Pouchieu C, Deschasaux M, Hercberg S, Druesne-Pecollo N, Latino-Martel P, Touvier M. Prospective association between red and processed meat intakes and breast cancer risk: modulation by an antioxidant supplementation in the SU.VI.MAX randomized controlled trial. Int J Epidemiol 2014;43:1583–92.
[17] Inoue-Choi M, Sinha R, Gierach GL, Ward MH. Red and processed meat, nitrite, and heme iron intakes and postmenopausal breast cancer risk in the NIH-AARP Diet and Health Study. Int J Cancer 2016;138:1609–18.
[18] Wolk A. Potential health hazards of eating red meat. J Intern Med 2016;281:106–22.
[19] Diallo A, Deschasaux M, Partula V, Latino-Martel P, Srour B, Hercberg S, et al. Dietary iron intake and breast cancer risk: modulation by an antioxidant supplementation. Oncotarget 2016; 7:79008–16.
[20] Samraj AN, Pearce OMT, Läubli H, Crittenden AN, Bergfeld AK, Banda K, et al. A red meat-derived glycan promotes inflammation and cancer progression. Proc Natl Acad Sci U S A 2015;112:542–7.
[21] Knize MG, Salmon CP, Pais P, Felton JS. Food heating and the formation of heterocyclic aromatic amine and polycyclic aromatic hydrocarbon mutagens/carcinogens. Adv Exp Med Biol 1999;459: 179–93.
[22] Fu Z, Deming SL, Fair AM, Shrubsole MJ, Wujcik DM, Shu XO, et al. Well-done meat intake and meat-derived mutagen exposures in relation to breast cancer risk: the Nashville Breast Health Study. Breast Cancer Res Treat 2011;129:919–28.
[23] Parada Jr H, Steck SE, Bradshaw PT, Engel LS, Conway K, Teitelbaum SL, et al. Grilled, barbecued, and smoked meat intake and survival following breast cancer. J Natl Cancer Inst 2017;109.
[24] Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with the general population. Am J Epidemiol 2017;186(9):1026–34.
[25] Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I, et al. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. Eur J Cancer Prev 2008;17:39–47.
[26] Shannon J, Ray R, Wu C, Nelson Z, Gao DL, Li W, et al. Food and botanical groupings and risk of breast cancer: a case-control study in Shanghai, China. Cancer Epidemiol Biomarkers Prev 2005;14:81–90.
[27] van der Hel OL, Peeters PH, Hein DW, Doll MA, Grobbee DE, Ocke M, et al. GSTM1 null genotype, red meat consumption and breast cancer risk (The Netherlands). Cancer Causes Control CCC 2004;15:295–303.
[28] Cho E, Chen WY, Hunter DJ, Stampfer MJ, Colditz GA, Hankinson SE, et al. Red meat intake and risk of breast cancer among premenopausal women. Arch Intern Med 2006;166: 2253–9.
[29] Byrne C, Ursin G, Ziegler RG. A comparison of food habit and food frequency data as predictors of breast cancer in the NHANES I/NHEFS cohort. J Nutr 1996;126:2757–64.
[30] World Cancer Research Fund International Continuous Update Project (CUP). The associations between food, nutrition and physical activity and the risk of breast cancer. Syst Lit Rev 2015. Available at: http://www.wcrf.org/sites/default/files/CUP_breast_cancer_SLR_2015_version5.pdf. [Accessed 18 October 2017].