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Trans-fatty acids and cancer: the evidence reviewed

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The present review comes from the authors of the recent Scientific Advisory Committee on Nutrition (SACN) review *Update on Trans Fatty Acids and Health*, and focuses on assessing the strength of the evidence for a link between *trans*-fatty acid (*trans*-FA) intake and cancer. It evaluates a range of human ecological, case–control and prospective studies with *trans*-FA exposure assessed using either dietary assessment methods or *trans*-FA levels in tissues. Relevant animal studies are also presented in order to elucidate potential mechanisms. It concludes that there is weak and inconsistent evidence for a relationship between *trans*-FA and breast or colorectal cancer. Evidence for an association between *trans*-FA and prostate cancer is limited, but a recent large case–control study has shown a strong interaction between risk and *trans*-FA intake for the *RNASEL* QQ/RQ genotype that is present in about 35 % of the population. This potential association requires further investigation. The single study on non-Hodgkin's lymphoma reported a strong positive association, but only used a single assessment of dietary *trans*-FA made at the start of the study in 1980, and the significant changes in *trans*-FA intakes between then and the end of follow-up in 1994 limit the reliability of this observation. There is insufficient evidence to allow any differentiation between the effects of *trans*-FA from animal or vegetable origin on cancer risk.

***Trans*-fatty acids: Cancer: Breast cancer: Colorectal cancer**

Introduction

The impact of *trans*-fatty acids (*trans*-FA) on blood lipids and the subsequent increase in risk of CHD has been extensively described. However, their impact on cancer risk has received less attention. The McGovern report in 1977[1] concluded that there was a 'strong correlation' between dietary fatty acids and breast or colon cancer, with a possible mechanism being changes in membrane permeability to carcinogens. SFA were initially targeted as the primary culprit, but Eniq *et al.*[2] pointed towards a statistical association between vegetable fat intake but not animal fat intake, and suggested that the increase in *trans*-FA through the consumption of hydrogenated vegetable fats may be responsible for the observed link between dietary fat and cancer. Since then, there have been a number of studies based on the premise that increased *trans*-FA consumption may affect risk of cancer, with a focus on cancers of the breast, colon and prostate, with the possibility of *trans*-FA having potentially adverse hormone-like activity. The current authors wrote the recently published Scientific Advisory Committee on Nutrition (SACN) report *Update on* Trans *Fatty Acids and Health*[3], and the present review reports the main findings regarding the evidence for a link between *trans*-FA consumption and cancer. The report did not include any detailed consideration of the effects of conjugated linoleic acid (CLA), for which there is evidence for beneficial effects in mammary tumours (animal studies) and breast cancer cell lines, possibility due to the anti-oestrogen-like properties of CLA.

Background

Trans-*fatty acids in the diet*

Trans-FA are unsaturated fatty acids with one or more of their double bonds in the 'trans' rather than the common 'cis' configuration. They occur naturally at low levels in dairy products and meats from ruminant animals, but are also produced during the industrial hydrogenation of vegetable oils. The latter process is responsible for many of the semi-solid and solid fats that are widely available as spreads (for example, margarines) and used as a more solid fat source in commercial baked goods (biscuits, pastries) and catering outlets. The predominant *trans*-FA isomers are vaccenic acid (*trans*-18 : 1*n*-7) and elaidic acid

Abbreviations: CLA, conjugated linoleic acid; EPIC, European Prospective Investigation into Cancer and Nutrition; NHL, non-Hodgkin's lymphoma; RR, relative risk; *trans*-FA, *trans*-fatty acid.

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(*trans*-18 : 1*n*-9), although other MUFA (14 : 1, 16 : 1, 18 : 1) and PUFA (18 : 2 and 18 : 3) isomers may also be present at detectable levels in both food products and tissue samples.

The average adult (19–64 years) intake of *trans*-FA in the UK was reported to be 1·2 % energy in 2000–1[4]. Recent re-estimation of intake, using dietary data from the National Diet and Nutrition Survey (2000–1) and updated *trans*-FA composition data, has given an estimated average value of 1·0 % energy for current *trans*-FA intake in the UK adult population[3]. This is significantly lower than in the USA, where the average *trans*-FA intake was 2·6 % energy in 2003[5]. In Europe, intakes in 1995 ranged from 0·5 to 2·1 %, with the lowest intake levels in the Mediterranean countries and the highest intakes in Iceland[6].

Assessment of trans*-fatty acid intake*

The most common methods of estimating *trans*-FA intake are through FFQ or measuring the levels of *trans*-FA in tissues. A number of fatty acids are primarily sourced from the diet and cannot be synthesised *de novo* in the body, including the essential fatty acids linoleic acid (18 : 2*n*-6) and linolenic acid (18 : 3*n*-3), the long-chain *n*-3 PUFA (only limited synthetic capacity) and *trans*-FA. Levels of these fatty acids in tissue lipid pools are considered to be a more reliable assessment of dietary exposure than dietary questionnaires. This may be particularly important for the relative quantification of *trans*-FA exposure, as the inability of food composition databases to keep pace with rapidly changing compositions of foods, which include partially hydrogenated vegetable oil sources, may result in significant inaccuracies in estimations of dietary *trans*-FA intake levels. *Trans*-FA levels in plasma lipid pools such as cholesteryl esters and phospholipids, in platelets and erythrocytes, and in adipose tissue, may be used as indices of integrated exposure over the previous few days, few months and 1–2 years respectively. However, some disease states result in changes in fatty acid metabolism that are reflected in altered tissue compositions, which could confound retrospective case–control comparisons. In addition, because fatty acid compositional data are expressed as percentage of total fatty acids, any increase or decrease in one fatty acid will result in reciprocal changes in one or more of the other fatty acids present. A further limitation is the inability to directly quantify intake from tissue fatty acid composition. Therefore tissue fatty acid composition data cannot be directly translated into public health recommendations for dietary intake levels associated with reduced risk of disease.

Some prospective studies reported in the present review have undertaken only a single measure of diet at baseline, which may lead to misclassification of habitual *trans*-FA intake in long-term follow-up, due to changes in subjects' habitual diets over time, as well as changes in food formulations. Given the significant recent changes in fat formulation because of the efforts made by food manufacturers to replace *trans*-FA in oils and spreads, reliance on historical estimates of intake may lead to large inaccuracies in estimating *trans*-FA-disease associations.

Presentation of statistical data

Throughout the present review, the OR and relative risk (RR) stated are those that have been fully adjusted for potential confounding factors. The *P* for trend values refer to the level of difference between the highest and lowest tertile, quartile or quintile of intake.

When a significant difference in an associated risk was reported, the specific factors that were adjusted for in the model have been shown within the tables. Standard confounding factors for which data have normally been adjusted for include age, BMI and family history. In the case of breast cancer, adjustment for a large number of site-specific risk factors relating to lifetime hormonal exposure (for example, age at menses, menopause, hormone replacement therapy use, parity, age at first pregnancy, breast-feeding), adiposity, height and alcohol intake are also normally applied.

Dietary *trans*-FA intakes positively correlate with dietary SFA and total fat intakes. Since total and SFA intakes have been associated with risk of cancers at some sites, it would be expected that epidemiological studies designed to assess the association between dietary *trans*-FA intake and cancer risk fully adjust for potential confounding by these dietary variables[7,8]. Details of adjustments made by each study are given in the tables. The tables show the adjusted RR or OR; however, where adjustment for another dietary variable significantly alters the adjusted RR or OR, this is noted within the text.

Evidence for an association between *trans*-fatty acids and breast cancer

Animal studies

Selenskas *et al.* [9] investigated the effect of a high-*trans*-FA diet on a dimethylbenz[a]anthracene-induced rat mammary tumour model. The diets contained 20 % fat by weight, which was either a partially hydrogenated mixture of 50 % soyabean oil and 50 % cottonseed oil (57·5 % 18 : 1; 22·5 % *cis*-monoene and 35 % *trans*-monoene) or a mixture of 58 % olive oil, 40 % cocoa butter and 2 % coconut oil (54·7 % 18 : 1; all in *cis* configuration). Apart from differences in *trans*-FA, the diets contained similar levels of other fatty acids. Tumour incidences for the *trans*- and *cis*-fatty acid diets were 32 and 40 %, respectively, with no statistical difference between groups.

Using the same blend of *trans*- and *cis*-fatty acids, Erickson *et al.* [10] examined effects of the diets on the growth and metastasis of implanted mammary tumour cells. The study also considered varying amounts of fat, with diets containing either 5 or 20 % fat by weight. Cells were injected into female BALB/c mice either subcutaneously or intravenously. Mice with subcutaneous implants showed no differences in latency period, tumour growth rate or final tumour size, regardless of fat type or amount. However, in mice receiving the intravenous implants, the liver and spleen from those fed the *cis*-fatty acid diets contained significantly more viable tumour cells than did those from mice fed the *trans*-FA diets.

The desaturation of *trans*-18 : 1*n*-7 to form CLA has been observed in rodents, ruminants and human subjects[11], with

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reported conversion rates in rodents of 5–12 %[12] and 19 % in humans[13]. Lock *et al.* [11] observed that when *trans*-18 : 1*n*-7 is converted to CLA it exerts an anticarcinogenic effect against rat mammary tumour initiation and growth. However, the presence of *trans*-18 : 1*n*-7 does not affect cancer development when this conversion is blocked.

Ecological studies

The methodology and findings for the human studies examining the association between *trans*-FA and breast cancer are summarised in Table 1.

Bakker *et al.* [14] investigated the association of breast cancer incidence and *trans*-FA status across eleven populations. A statistically significant correlation was found between *trans*-FA and the incidence of breast cancer, with a Pearson correlation coefficient (*r*) of 0·89. An increase of 1 g *trans*-FA per 100 g fatty acids in adipose tissue corresponded to a rise in incidence of 19·3 cases of breast cancer per 100 000 person-years.

Case–control studies

London *et al.* [15] analysed the gluteal adipose tissue of 380 US women with newly diagnosed stage I or II breast cancer and 176 with proliferative benign breast disease. Although *trans*-FA levels in adipose tissue showed no statistically significant association with the risk of breast cancer, this study used controls subjects who may have had breast abnormalities, which may have biased the findings. Petrek *et al.* [16] also compared the breast and abdomen tissue fatty acid profiles of women with invasive breast cancer with those of women with a negative diagnosis for breast cancer. No differences in *trans*-FA concentration were found between the case and control groups for either tissue type.

The European Community Multicentre Study on Antioxidants, Myocardial Infarction, and Breast Cancer (EURAMIC) study[17] compared gluteal adipose tissue *trans*-FA levels in 698 cases of postmenopausal primary breast cancer and matched controls. There was a strong positive correlation between the adipose tissue level of *trans*-FA and breast cancer (OR 1·40). The relationship between *trans* intake and breast cancer appeared to be modified by PUFA intake. OR after stratification by PUFA tertiles were 3·65 and 0·97 for the lowest and highest PUFA tertile, respectively.

Aro *et al.* [18] reported serum fatty acid levels in 195 cases of breast cancer and 208 population-based controls identified from pre- and postmenopausal Finnish women. The authors reported an inverse association between *trans*-18 : 1*n*-7 and risk of breast cancer with an OR for the lowest v. the highest quintiles of 0·2, but the authors failed to report the statistical significance of this trend. Other *trans* isomers showed no differences between the case and control populations.

Prospective studies

Holmes *et al.* [19] assessed the links between diet and breast cancer in 88 795 pre- and postmenopausal women over 14 years in the Nurses' Health Study. There was a small inverse association between *trans*-FA intake and risk of breast cancer, although this was not statistically significant. Additional analysis of the data, including postmenopausal women who had not reported a diagnosis of benign breast disease, also found no association between *trans*-FA and breast cancer[20]. Similar analysis using 90 655 premenopausal women enrolled in the second phase of the Nurses' Health Study again showed no relationship between the disease and dietary *trans*-FA intake[21]. The most recent report on the original cohort brings total follow-up to 20 years, and again reports no association between *trans*-FA and breast cancer[22].

Pala *et al.* [23] conducted a prospective study of erythrocyte fatty acids and pre-diagnostic breast cancer (the Hormone and Diet Etiology of Breast Cancer (ORDET) study) in northern Italy. The 4052 postmenopausal participants were followed for an average of 5·5 years, with each case of breast cancer matched with two randomly selected controls. Oleic acid and MUFA were positively associated with the risk of breast cancer, but *trans*-18 : 1*n*-9 (the only *trans*-FA reported) was not associated with breast cancer risk.

Serum fatty acid concentrations from 197 pre- and postmenopausal cases of breast cancer and matched population-based controls in the New York Women's Health Study were assessed by Saadatian-Elahi *et al.* [24]. The authors found no association between risk of developing breast cancer and serum levels of *trans*-18 : 1*n*-9. No other *trans*-FA were evaluated in the study.

Voorrips *et al.* [25] analysed the data from dietary questionnaires of 941 cases of breast cancer and 1598 subcohort controls in the Netherlands Cohort Study. There was a significant positive association between increasing *trans*-FA intake and risk of breast cancer (*P* for trend = 0·01), although the 95 % CI for the lowest *v.* the highest quintile of dietary intake of *trans*-FA encompassed 1·0 (RR 1·30; 95 % CI 0·93, 1·80). Further analysis to consider the effect of *trans*-18 : 1*n*-7 showed similar results, with a highly significant trend across the quintiles of intake (*P* for trend = 0·006). However, the 95 % CI for individual quintiles were consistently non-significant (RR 1·34; 95 % CI 0·98, 1·82 for the lowest *v.* the highest quintile).

Rissanen *et al.* [26] studied the relationship between serum *trans*-FA and risk of breast cancer in 127 incident breast cancer cases and 242 matched population-based controls from a prospective study of 8196 women in Finland. Higher serum *trans*-18 : 1*n*-7 levels were associated with an increased risk of breast cancer (OR 3·69), increasing after further adjustment for BMI, serum cholesterol, alcohol intake, education, exercise and parity (OR 4·23). The relationship appeared to be stronger in postmenopausal than in premenopausal women, but the trend failed to reach statistical significance in either group. There was no significant correlation with total MUFA *trans*-FA.

A subset of women was randomly selected from a large trial (266 064 women) of breast self-examination in Shanghai by Shannon *et al.* [27]. Erythrocyte fatty acids were analysed in 322 cases of breast cancer and 367 controls, matched for age and menstrual status. A strong positive association was found between the concentration of *trans*-18 : 1*n*-7 in the erythrocytes and breast cancer (OR 2·21). No other *trans*-FA were included in the study.

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Table 1. Human studies investigating the association of *trans*-fatty acids (*trans*-FA) with breast cancer

Reference	Subject population	Measure of exposure	*Trans*-FA intake or level (median of group unless otherwise specified)	Adjusted RR or OR with 95 % CI	*P* for trend	Factors adjusted for in analysis
Population study						
Bakker *et al.* [14] Europe and Israel (ten countries)	Cancer data 1982–1987 FA sample 1991–2	% *trans*-FA of total FA in adipose tissue	Lowest centre (Granada) 0·13 g/100 g total FA Highest centre (Zeist) 1·98 g/100 g total FA	Pearson correlation coefficient *r* 0·89 (0·62, 0·97)	N/A	Age, sex, study centre and laboratory methods
Case–control studies						
London *et al.* [15], USA	556 cases/397 hospital-based controls	% *trans*-FA of total FA in gluteal adipose tissue	Total *trans*-FA: Q1 = 2·74, Q5 = 5·42	1·2 (0·7, 1·9)	0·94	Risk factors for breast cancer*, menopause, weight 5 years before study, alcohol intake and prior history of benign breast disease
Petrek *et al.* [16], USA	154 cases/125 hospital-based controls	% *trans*-FA of total FA in breast and abdomen tissue	Whole population: Cases: mean 3·80 (SD 1·13) % Controls: mean 4·07 (SD 1·14) %	0·528 (0·257, 1·08)	0·13	Menopausal status and BMI
Kohlmeier *et al.* [17], EURAMIC, Europe (five countries)	698 cases/698 postmenopausal population-based controls	% *trans*-FA of total FA in gluteal adipose tissue	Whole population: 25th percentile 0·68 % 75th percentile 1·60 % % PUFA in tissue: T1 < 12·14 T3 > 15·09	Whole population: 1·40 (1·02, 1·93), stratified by % PUFA: 3·65 (2·17, 6·14) 0·97 (0·67, 1·40)	0·035 0·001 0·85	Standard confounding factors†, smoking, age, socio-economic status, study centre, HRT and adipose PUFA levels
Aro *et al.* [18] Finland	195 cases/208 population-based controls	% *trans*-FA of total FA in serum	18 : 1*n*-7 : Q1 = 0·17, Q5 = 0·40	0·2 (0·1, 0·6)	NR	Age (at time of study, menarche, first full-term pregnancy), area (rural/urban), oral contraceptive use, HRT, family history of breast cancer, history of benign breast disease, education, alcohol intake, smoking, physical activity, waist:hip ratio and BMI
Prospective studies						
Holmes *et al.* [19], Prospective cohort (NHS), USA	88 795 pre- and postmenopausal women, 2956 events 1980–94	% energy from *trans*-FA as assessed by FFQ	Intake of *trans*-FA for cohort not given RR for increase of 1 % of energy from total *trans*-FA: All women 0·92 (0·86, 0·98) Premenopausal 1·00 (0·88, 1·11) Postmenopausal 0·91 (0·84, 0·99)		NR	Standard confounding factors†, risk factors for breast cancer*, age at menopause, vitamin A intake, time period, weight change since age 18 years, BMI at age 18 years, menopausal status, HRT, history of benign breast disease
Pala *et al.* [23], Prospective nested case–control (ORDET), Italy	71 cases/142 postmenopausal population-based controls 1987–95	% 18 : 1*n*-9 *trans*-FA of total FA in erythrocytes	T1 < 0·25 %, T3 ≥ 0·36 %	0·7 (0·30, 1·64)	0·42	Age (at time of study, at menarche, menopause, first birth), BMI, waist:hip ratio, months of lactation, parity, and educational level were considered but none exerted a major confounding effect for *trans*-FA level. Therefore, the authors chose to only present only unadjusted OR

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Table 1. *Continued*

Reference	Subject population	Measure of exposure	*Trans*-FA intake or level (median of group unless otherwise specified)	Adjusted RR or OR with 95 % CI	*P* for trend	Factors adjusted for in analysis
Bryne *et al.*[20], Prospective cohort (NHS), USA	31 673 women, postmenopausal, 1071 events, 1980–94	% energy from *trans*-FA as assessed by FFQ	Total *trans*-FA level of quintiles not given Total *trans*-FA for cohort: mean 1·4 (SD 0·5) %	0·91 (0·73, 1·13)	0·33	Standard confounding factors†, risk factors for breast cancer*, use of postmenopausal hormones, BMI at age 18 years, weight change since age 18 years, vitamin A intake, and other fat subtypes
Saadatian-Elahi *et al.*[24], Prospective nested case–control (New York Women's Health Study), USA	197 cases/197 population-based controls, 1985–91	%18 : 1*n*-9 *trans*-FA of total FA in serum	Levels of total *trans*-FA (quartiles not given) Premenopausal: Cases: mean 0·4 (SD 0·2) %; Controls: mean 0·5 (SD 0·8) % Postmenopausal: Cases: mean 0·4 (SD 0·8) %; Controls: mean 0·3 (SD 0·1) %	All women, 0·66 (0·33, 1·31) Premenopausal: 1·02 (0·36, 2·88) Postmenopausal: 0·36 (0·13, 1·03)	0·25 0·80 0·33	Age at first full-term birth, family history of breast cancer, history of benign breast disease and total cholesterol
Voorrips *et al.*[25], Prospective nested case–control (Netherlands Cohort Study), The Netherlands	941 cases/1598 population-based controls, 1986–92	Intake (g/d) of *trans*-FA as assessed by FFQ and diet record	Q1 = 1·5, Q5 = 3·6 *Trans*-18 : 1*n*-7: Q1 = 0·3, Q5 = 1·2 Other 18 : 1 *trans* isomers: Q1 = 0·4, Q5 = 2·3	1·30 (0·93, 1·80) 1·34 (0·98, 1·82) 0·89 (0·65, 1·21)	0·01 0·006 0·91	Standard confounding factors†, risk factors for breast cancer*, age at menopause, history of benign breast disease, oral contraceptive use, BMI, education, smoking and energy-adjusted fat intake
Cho *et al.*[21] Prospective cohort (NHS II), USA	90 655 women, premenopausal 714 events 1991–9	% of energy from *trans*-FA as assessed by FFQ	Q1 = 0·9, Q5 = 2·3	0·96 (0·70, 1·31)	0·38	Standard confounding factors†, risk factors for breast cancer*, history of benign breast disease, smoking, oral contraceptives, menopausal status, energy, protein intake, other types of fat and cholesterol
Rissanen *et al.*[26], Prospective nested case–control (Mobile Clinic Health Examination Survey), Finland	127 cases/242 population-based controls, 1973–91	% *trans*-FA of total FA in serum	Whole population: *Trans*-18 : 1: T1 < 0·85, T3 < 1·15 *Trans*-18 : 1*n*-7: T1 < 0·32, T3 > 0·41 Postmenopausal: *Trans*-18 : 1: T1 < 0·32, T3 > 0·41 *Trans*-18 : 1*n*-7: T1 < 0·32, T3 > 0·41	1·47 (0·65, 3·32) 3·69 (1·35, 10·06) 7·90 (1·46, 42·69) 2·05 (0·54, 7·77)	0·18 0·17 0·49 0·22	Adjusted for standard confounding factors†, smoking, serum cholesterol, number of pregnancies, parity, leisure-time exercise and education; if no significant difference between adjusted and unadjusted results the latter were reported. The results presented here were unadjusted
Kim *et al.*[22], Prospective cohort (NHS), USA	80 375 women, postmenopausal, 3537 events, 1980–2000	Dietary *trans*-FA assessed by FFQ	Intake of *trans*-FA for cohort not given; RR for increase of 1 % energy from total *trans*-FA: All women 0·99 (0·91, 1·08); Stratified by retrospective premenopausal intake 1·08 (1·01, 1·15)		NR	Standard confounding factors†, risk factors for breast cancer*, time period, weight change since age 18 years, BMI at age 18 years, age at menopause, HRT and benign breast disease

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Table 1. *Continued*

Reference	Subject population	Measure of exposure	*Trans*-FA intake or level (median of group unless otherwise specified)	Adjusted RR or OR with 95 % CI	*P* for trend	Factors adjusted for in analysis
Shannon *et al.* [27], Prospective nested case–control, China	322 cases/367 population-based controls, 1995–2000	% *trans*-FA of total FA in erythrocytes	*Trans* 18 : 1*n*-7: Q1 ≤ 0·85, Q4 ≥ 1·01	2·21 (1· 25, 3·88)	0·002	Year of interview, age (at time of study and at first birth), duration of breast-feeding, time since last induced abortion and duration of intra-uterine device use
Chajès *et al.* [28], Prospective nested case–control (E3N-EPIC), France	363 cases/702 population-based controls, 1995–2002	% *trans*-FA of total FA in serum	*Trans*-16 : 1*n*-7: Cases: mean 0·50 (SD 0·16) Controls: mean 0·50 (SD 0·16)	2·24 (1·30, 3·36)	0·02	BMI, alcohol consumption, height, HRT, education level, parity, family history of breast cancer, family history of benign breast disease
			Trans-16 : 1*n*-7 + 18 : 1*n*-9: Cases: mean 0·37 (SD 0·17) Controls: mean 0·39 (SD 0·17)	1·75 (1·08, 2·83)	0·018	

RR, relative risk; FA, fatty acid; N/A, not applicable; Q1, quartile 1 or quintile 1; Q5, quintile 5; EURAMIC, European Community Multicentre Study on Antioxidants, Myocardial Infarction, and Breast Cancer; T1, tertile 1; T3, tertile 3; NR, not reported; HRT, hormone replacement therapy; NHS, Nurses' Health Study; ORDET, Hormone and Diet Etiology of Breast Cancer; NHS II, Nurses' Health Study second phase; EPIC, European Prospective Investigation into Cancer and Nutrition; Q4, quartile 4.

* Risk factors for breast cancer: age at time of study, age at menarche, age at first birth, height, family history of breast cancer and parity.

† Standard confounding factors: energy intake and alcohol consumption.

The association between serum phospholipid *trans*-FA and breast cancer risk during 7 years of follow-up was assessed in the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC) study[28] (19 934 women). The 363 cases of incident invasive breast cancer were matched to two controls by age, menopausal status at blood collection, whether the subjects were fasting before blood collection, date and collection centre. Increasing levels of serum phospholipid *trans*-16 : 1*n*-7, and combined *trans*-16 : 1*n*-7 and *trans*-18 : 1*n*-9 were correlated with risk of breast cancer (OR 2·24 and 1·70, respectively). The levels of *cis* isomers were unrelated to breast cancer risk.

Summary of evidence for an association between trans*-fatty acids and breast cancer*

Prospective cohort, case–control and ecological studies reported between 1994 and 2006 were reviewed. Most of the prospective studies assessed *trans*-FA exposure by dietary questionnaire; one nested case–control study was based on analysis of erythrocyte fatty acids while another two analysed serum. The five case–control studies used either serum or adipose tissue fatty acids as the measure of exposure. Data from the prospective studies that evaluated dietary *trans*-FA intake are summarised in Fig. 1.

One of four case–control studies showed a strong positive association between *trans* levels in tissues and risk of breast cancer. One study reported a negative association between serum vaccenic acid and breast cancer but failed to report values for statistical significance. Three of the ten prospective studies have shown a positive association, with two of these based on measurement of serum or erythrocyte *trans*-FA levels and one based on dietary *trans*-FA assessment. For the latter study, the OR was 1·3 for a highest v. lowest quintile range of 1·5–3·6 g/d, which is similar to the current range of intakes in the UK[3]. However, there was no significant association found in the three large studies (the Nurses' Health Study, the Hormone and Diet Etiology of Breast Cancer (ORDET) study and the New York Women's Health Study), which have had up to 20 years of follow-up. Overall, the evidence for an association between *trans*-FA intake and breast cancer is weak. There are limited data from animal studies, and the findings do not provide any evidence to support an effect of *trans*-FA consumption on mammary tumorigenesis.

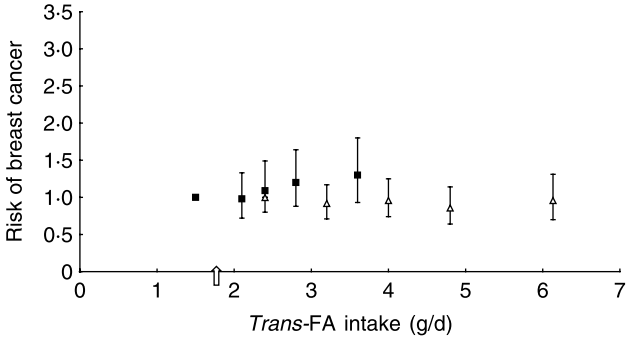

Fig. 1. Risk of breast cancer from prospective epidemiological studies that evaluated dietary intake of *trans*-fatty acids (*trans*-FA): Voorips *et al.*[25] (■) and Cho *et al.*[21] (Δ). The current mean *trans*-FA intake for women in the UK has recently been estimated to be 1·0 % of total energy or 1·7 g/d[3] (⇧). Risk of breast cancer is plotted as the relative risk (RR), with vertical bars representing the 95 % CI for intake ranges above reference (RR = 1) in each study. Data from Cho *et al.*[21] were converted from percentage of total energy to g/d based on an energy intake of 1700 kcal/d (7113 kJ/d).

Evidence for an association between *trans*-fatty acids and colorectal cancer

The methodology and findings for the human studies examining the association between *trans*-FA and colorectal cancer are summarised in Table 2.

Animal studies

Watanabe *et al.*[29] used the dimethyihydrazine model to examine the effect of *trans*-FA on colon cancer in Fischer rats. A partially hydrogenated maize oil and olive oil were used at 10 % by weight in the diet, and fed for 15 months. The partially hydrogenated maize oil contained 42 % *trans*-18 : 1 and 27·2 % *cis*-18 : 1 fatty acids, whereas the olive oil contained 74·1 % *cis*-18 : 1. No statistically significant difference in colon tumour incidence was observed, with incidence rates of 35·3 and 31·3 % in animals receiving partially hydrogenated maize oil and olive oil, respectively.

A similar study with a strain of animals especially susceptible to colon cancer (Wistar–Furth–Osaka) was carried out by Sugano *et al.*[30]. High-*trans*-FA partially hydrogenated maize oil was compared with high-18 : 1 safflower-seed oil at 5 % of energy. The incidence of dimethylbenz[a]anthracene-induced tumours in the small and large intestines were 63 and 75 %, respectively in the animals fed partially hydrogenated maize oil and 65 and 71 %, respectively, in the group fed high-18 : 1 safflower-seed oil.

Hogan & Shamsuddin[31] fed inbred female F344 rats a diet containing 25 % *trans*-18 : 1 fat or 25 % *cis*-18 : 1 fat, and injected the animals weekly with azoxymethane to induce large-intestinal carcinomas. Although more animals receiving the diet containing *trans*-fat developed tumours than those receiving the *cis*-fat diet, this difference was not statistically significant. Identical numbers of animals from each group developed extracolonic neoplasms.

Reddy *et al.*[32] studied the effect of increasing dietary levels of *trans*-fat on azoxymethane-induced colon carcinogenesis in rats. Three diets were prepared, each containing 23·5 % fat by weight, but with varying amounts of the *trans*-fat mix and oleic acid-rich safflower-seed oil (Oleinate), the latter used to balance the amount of 18 : 1 across the diets. The three diets were referred to as low-*trans*-fat (5·9 % *trans*-fat + 11·7 % Oleinate + 5·9 % maize oil), intermediate-*trans*-fat (11·7 % *trans*-fat + 5·9 % Oleinate + 5·9 % maize oil) and high-*trans*-fat (17·6 % *trans*-fat + 5·9 % maize oil). For the low-, intermediate- and high-*trans*-fat diets, there was no significant differences between diets, with incidences of colon tumours of 63, 67 and 57 %, respectively, while incidences of small-intestinal tumours were 40, 43 and 37 %, respectively.

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Table 2. Human studies investigating the association of *trans*-fatty acids (*trans*-FA) with colorectal cancer

Reference Population study	Subject population	Measure of exposure	*Trans*-FA intake or level	Adjusted RR or OR with 95 % CI	*P* for trend	Factors adjusted for in analysis
Bakker *et al.*[14], Ecological, Europe and Israel (ten countries)	Male and female, Cancer data 1982–1987, FA sampling 1991–2	% *trans*-FA of total FA in adipose tissue	Lowest centre (Granada) 0·13 g/100 g total FA Highest centre (Zeist) 1·98 g/100 g total FA	Pearson correlation coefficient *r* 0·93 (0·74, 0·98)	N/A	Age, sex, study centre and laboratory methods
Case–control studies						
McKelvey *et al.*[33], USA	516 cases/551 controls, male and female	g/d *trans*-FA intake as assessed by FFQ	Group 1 < 2, group 4 > 6	1·6 (0·82, 3·2)	Not reported	Additional confounding factors*, age, sex, BMI, red meat consumption, vegetable consumption and use of NSAID
Slattery *et al.*[34], case–control, USA	1993 cases/2410 controls, male and female	*Trans*-FA g/1000 kcal energy intake as assessed by FFQ	Men: Q1≤ 1·69, Q5>3·34 Women: Q1≤ 1·53, Q5>2·99 Women and HRT: Q1 + HRT Q5 + HRT Q1 no HRT Q5 no HRT	 1·2 (0·9, 1·7) 1·5 (1·1, 2·0) 1·00 0·9 (0·6, 1·5) 0·8 (0·6, 1·3) 1·6 (1·1, 2·5)	 0·34 0·04 *P* for interaction 0·06	Age at diagnosis, body size, physical activity, aspirin and/or NSAID use, energy intake, and dietary Ca
Nkondjock *et al.*[35], Canada	402 cases/668 population-based controls, male and female	% of energy from *trans*-FA as assessed by FFQ	Q1 < 0·32, Q4 > 1·60	0·83 (0·58, 1·19)	0·309	Standard confounding factors†, marital status and physical activity. Total energy, HRT, fibre, vitamin C and E intakes were not significantly different between cases and controls, and were not included
Theodoratou *et al.*[36], Scotland (UK)	1455 cases/1455 population-based controls, male and female	g/d *trans*-FA intake as assessed by FFQ	Q1 < 2·88 Q4 > 4·24	1·15 (0·85, 1·55)	0·548	Standard confounding factors†, additional confounding factors*, use of NSAID, fibre intake and total FA.
			Trans-MUFA: Q1 < 2·21, Q4 > 3·24	 1·30 (0·97, 1·75)	 0·251	Fully adjusted for all factors
Prospective study						
Lin *et al.*[37], Prospective cohort (Women's Health Study) USA	37 547 women, 202 events, 1993–2003	% of energy from *trans*-FA as assessed by FFQ	Q1 = 0·6, Q5 = 1·9	1·30 (0·89, 2·05)	0·18	Standard confounding factors†, additional confounding factors*, random treatment assignment, history of colorectal polyps and HRT
				1·59 (0·94, 2·70)	0·06	Additional adjustment for other types of fat and cholesterol
			Trans-18 : 1, *n*-9: Q1 = 0·5, Q5 = 1·7 *Trans*-18 : 2: Q1 = 0·03, Q5 = 0·09	1·94 (0·92, 2·58) 1·58 (0·94, 2·67)	0·08 0·09	Isomer analysis included adjustment for types of fat and cholesterol

RR, relative risk; FA, fatty acid; NSAID, non-steroidal anti-inflammatory drugs; Q1, quartile 1 or quintile 1; Q5, quintile 5; Q4, quartile 4; HRT, hormone replacement therapy.
* Additional confounding factors: smoking, physical activity, energy intake and alcohol intake.
† Standard confounding factors: age, BMI and family history of colorectal cancer.

Ecological studies

An ecological investigation of the association between colon cancer and *trans*-FA status found a statistically significant correlation between colon cancer and the level of *trans*-FA in adipose tissue (r 0·93)[14].

Case–control studies

The association between colorectal adenomatous polyps and the consumption of foods containing partially hydrogenated oils was examined by McKelvey *et al.* [33]. Dietary intake was obtained from a self-administered FFQ. While there was evidence of a positive association between total dietary *trans*-FA and adenomas, this did not reach statistical significance.

Slattery *et al.* [34] studied 1993 cases with colon cancer and 2410 population-based controls matched for age and sex. Dietary information was assessed from a detailed diet history questionnaire. A significant positive association was found between *trans*-FA consumption and colon cancer risk in women (OR 1·5), with a positive but not statistically significant association in men. Postmenopausal women who were not taking hormone replacement therapy had a twofold increase in risk from high levels of *trans*-FA in the diet, while the risk of developing colon cancer was unaffected by dietary *trans*-fat in women on hormone replacement therapy.

Nkondjock *et al.* [35] compared the data from the dietary questionnaires of 402 cases of colorectal cancer with 668 population-based controls in Montreal, but found no effect of *trans*-FA in either men or women. A similar study involving 1455 cases and matched population-based controls in Scotland (UK)[36] also observed no association between total *trans*-FA consumption and colorectal cancer after adjustment for intake of energy and total fatty acids.

Prospective studies

Lin *et al.* [37] used dietary and health questionnaires from 37 547 women in the Women's Health Survey to examine associations between diet and colorectal cancer. The authors found no statistically significant link between the consumption of *trans*-FA and colorectal cancer through their standard multivariate risk analysis, although the RR for *trans*-FA intake became stronger when adjusted for the consumption of other types of fat and cholesterol. There was a strong positive association between the intake of fried foods away from home and colorectal cancer risk (RR 1·86 (95 % CI 1·09, 3·16); P for trend = 0·01).

Summary of evidence for an association between trans*-fatty acids and colorectal cancer*

One prospective cohort, one ecological and four case–control studies reported between 1997 and 2007 were reviewed. Apart from the ecological study, all studies used dietary assessment as the measure of exposure to *trans*-FA. Data from these case–control and prospective cohort studies are summarised in Fig. 2.

There are limited data available to assess evidence for an association between *trans*-FA intakes and incidence of colon cancer. Only one case–control study has shown a positive association, and this was significant only in women[34]. In this study, the RR was 1·5 for a highest *v.* lowest quintile range of $< 2{\cdot}6$ to $> 5{\cdot}1$ g *trans*-FA per d (based on an energy intake of 1700 kcal/d (7112 kJ/d)), which is notably higher than the recent estimate of mean intake in the UK for women of 1·7 g/d[3].

Overall the epidemiological data are limited, with weak evidence to support an adverse effect of *trans*-FA intakes on colon cancer. The animal studies, which included very high

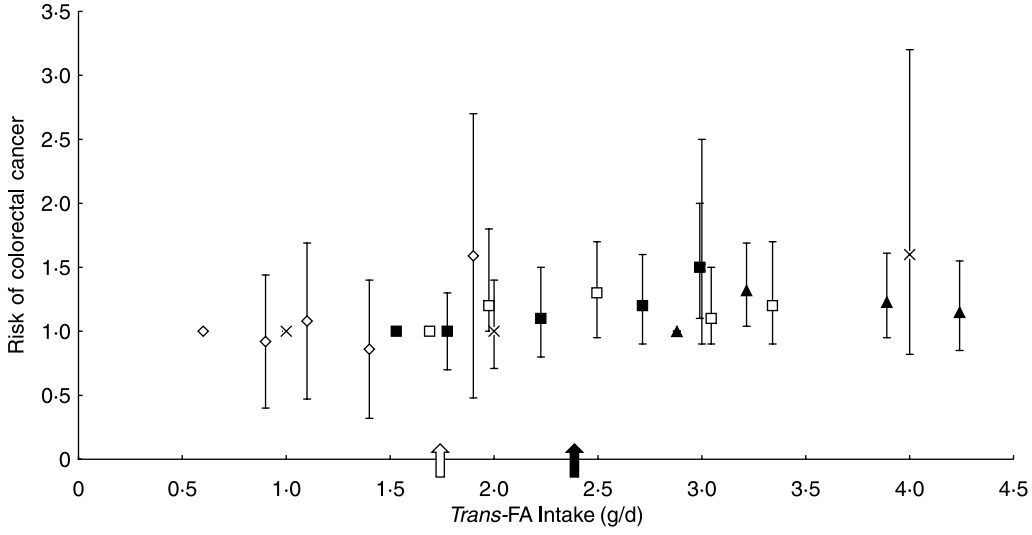

Fig. 2. Risk of colorectal cancer from case–control and prospective epidemiological studies that evaluated dietary intake of *trans*-fatty acids (*trans*-FA): McKelvey *et al.* [33] (×), Slattery *et al.* [34] (men □; women ■), Lin *et al.* [37] (◇) and Theodoratou *et al.* [36] (▲). The current mean *trans*-FA intake in the UK has recently been estimated to be 1·0 % of total energy or 1·7 g/d for women (⇧) and 1·0 % of total energy or 2·4 g/d for men (↑)[3]. Risk of colorectal cancer is plotted as the relative risk (RR), with vertical bars representing the 95 % CI for intake ranges above reference (RR = 1) in each study. Data from Lin *et al.* [37] were converted from percentage of total energy to g/d based on an energy intake of 1700 kcal/d (7113 kJ/d) (study only included women).

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exposures to *trans*-FA, provided no evidence that *trans*-FA can enhance the development of colon tumours.

Evidence for an association between *trans*-fatty acids and prostate cancer

The methodology and findings for the studies examining the association between *trans*-FA and prostate cancer are summarised in Table 3.

Ecological studies

The ecological study by Bakker *et al.* [14] examined the association between prostate cancer and *trans*-FA status measured in adipose tissue, but found no statistically significant correlation.

Case–control studies

Liu *et al.* [38] assessed the potential modification of prostate cancer risk by a functional polymorphism in the RNASEL gene (R462Q). The study involved 1012 cases of prostate cancer and matched controls. Among Caucasians (*n* 834), a statistically significant positive association between prostate cancer and the intake of *trans*-FA (OR 2·77) was evident. The association remained strongly significant for all groups of *trans* isomers (16 : 1, 18 : 1 and 18 : 2; all $P < 0{\cdot}005$). There was no significant association in African American individuals. When the data for Caucasians were stratified by genotype, the association between total and isomer *trans*-FA intake and prostate cancer was strongest among men with the QQ/RQ genotype (OR 4·80). For men with the RR genotype, neither total *trans*-FA intake nor intake of any group of *trans* isomers was associated with prostate cancer.

Prospective studies

The Netherlands Cohort Study recruited 58 279 men between 55 and 69 years of age, with an average follow-up of 6·3 years[39]. No association was found between total *trans*-FA consumption estimated through dietary questionnaires and development of prostate cancer.

Serum phospholipid *trans*-FA levels were compared in subjects that had been recruited for the β-Carotene and Retinol Efficacy Trial (CARET), a randomised trial of supplemental β-carotene and retinol for the prevention of lung cancer among 18 314 heavy smokers and asbestos-exposed workers[40]. A sample of 272 men that developed prostate cancer and 426 matched controls showed increasing prostate cancer risk with higher levels of serum *trans*-18 : 1*n*-7 (OR 1·69). Other *trans*-C18 fatty acids had positive trends with *P* values of between 0·07 and 0·12, but none of the *trans*-C16 fatty acids were close to statistical significance.

Chavarro *et al.* [41] analysed the *trans*-FA levels in whole blood from 476 men diagnosed with prostate cancer and controls matched according to age and smoking status at recruitment. The subjects were part of the Physicians' Health Study, a randomised trial of aspirin and β-carotene in which subjects received either the test compound or a placebo. There was no association between *trans*-FA levels and total prostate cancer risk, but stratification according to type of tumour showed significant correlations between total and isomer levels of *trans*-FA and non-aggressive tumours (OR 2·21). This association was stronger in overweight and obese men than in men with a normal BMI at baseline, and in men receiving placebo compared with men receiving aspirin. However, these interactions did not reach statistical significance. There was no association between *trans*-FA and aggressive prostate cancer for any *trans*-FA isomer or for any stratification of the cohort.

Summary of evidence for an association between trans*-fatty acids and prostate cancer*

One ecological, one case–control and three prospective studies were reviewed. Two of the prospective studies used serum phospholipids or whole-blood levels as the measure of exposure to *trans*-FA; the others used dietary assessment. Data from these case–control and prospective cohort studies that evaluated dietary *trans*-FA intake are summarised in Fig. 3.

There are very limited data available on which to base conclusions concerning possible adverse effects of *trans*-FA on prostate cancer. Two nested case–control studies have demonstrated a positive association between *trans*-FA intake and prostate cancer[40,41], although in the most recent study this correlation was only for non-aggressive tumours. A large case–control study has observed a moderate increase in risk for the Caucasian population, but a very marked increase in risk for the RNASEL QQ/RQ genotype (about 35 % of the population)[38]. The RNASEL gene is involved in protein coding and is a mediator of interferon action. Mutations in this gene have been associated with predisposition to prostate cancer, and the gene has been identified as a candidate for the hereditary prostate cancer 1 (HPC1) allele. The finding of an association between this gene, *trans*-FA and prostate cancer warrants further study.

Evidence for an association between *trans*-fatty acids and other cancer types

The methodology and findings for the studies examining the association between *trans*-FA and other types of cancer are summarised in Table 4.

Non-Hodgkin's lymphoma

It has been suggested that a higher intake of dietary fats could decrease immune response, leading to increased risk of developing non-Hodgkin's lymphoma (NHL). In the Nurses' Health Study, Zhang *et al.* [42] examined the links between NHL and amount and composition of dietary fat. After 14 years of follow-up, a strong positive relationship was found between total *trans*-FA intake and an increased risk of NHL (RR 2·4). The statistically significant association between *trans*-FA consumption and development of NHL remained after further adjustments for other types of fat, protein, alcohol, and fruit and vegetable intake. The lowest to highest quintiles of *trans*-FA intake

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Table 3. Human studies investigating the association of *trans*-fatty acids (*trans*-FA) with prostate cancer

Reference	Subject population	Measure of exposure	*Trans*-FA intake or level	Adjusted RR or OR with 95 % CI	*P* for trend	Factors adjusted for in analysis
Population study						
Bakker *et al.* [14], Ecological, Europe and Israel (ten countries)	Cancer data 1982–7, FA sampling 1991–2	% *trans*-FA of total FA in adipose tissue	Lowest centre (Granada) 0·13 g/100 g total FA Highest centre (Zeist) 1·98 g/100 g total FA	Pearson correlation coefficient *r* 0·50 (−0·15, 0·85)	N/A	Age, study centre and laboratory methods
Case–control study						
Liu *et al.* [38], USA	1012 case/1012 population-based controls	g/d *trans*-FA intake as assessed by FFQ	African-Americans: Group 1 < 2·83, group 4 ≥ 7·59	0·43 (0·10, 1·78)	0·21	Age, race, medical institution and total energy intake. Some analyses were also adjusted for genotype
			Caucasians: Group 1 < 2·52, group 4 ≥ 5·76	2·77 (1·60, 4·79)	0·0003	
			QQ or RQ genotype: Group 1 < 2·52, group 4 ≥ 5·76	4·80 (2·29, 10·08)	0·0001	
			RR genotype: Group 1 < 2·52, group 4 ≥ 5·76	1·27 (0·54, 2·98)	0·58	
Prospective studies						
Schuurman *et al.* [39], Prospective cohort (Netherlands Cohort Study), The Netherlands	58 279 men, 642 events, 1986–92	% of energy from *trans*-FA as assessed by FFQ	Q1 < 1·9, Q5 > 4·7	0·99 (0·70, 1·40)	0·72	Age, family history of prostate carcinoma, socio-economic status, total energy intake, and total energy-adjusted fat intake
King *et al.* [40], Prospective nested case–control (CARET), USA	272 cases/426 population-based controls	% *trans*-FA of total FA in serum	*Trans*-18 : 1*n*-7: Q1 > 0·31, Q4 > 0·55	1·69 (1·03, 2·77)	0·04	Asbestos exposure, period of enrolment, enrolment centre, enrolment age group, year of randomisation, ethnicity, baseline smoking status, age during study, BMI, alcohol use
			Trans-18 : 1*n*-9: Q1 > 0·21, Q4 > 0·38	1·39 (0·87, 2·28)	0·10	
			No significant effect for any other *trans* isomer (16 : 1 t9, 16 : 1 t7, 18 : 1 t8, 18 : 1 t10, 18 : 1 t12)			
Chavarro *et al.* [41], Prospective nested case–control, (Physicians' Health Study), USA	476 cases/476 controls	% *trans*-FA of total FA in whole blood	Total *trans*: Q1 = 1·27 %, Q4 = 2·62 %	All prostate cancers: 1·53 (1·01, 2·32)	0·23	Age, smoking status at baseline, length of follow-up
				Non-aggressive tumours: 2·21 (1·14, 4·29)	0·06	
				Aggressive tumours: 1·15 (0·64, 2·08)	0·93	
			Total *trans* 18 : 2	Non-aggressive tumours: 1·97 (1·03, 3·75)	0·01	
			Trans 18 : 1*n*-9	Non-aggressive tumours: 2·16 (1·12, 4·17)	0·11	

RR, relative risk; FA, fatty acid; CARET, β-Carotene and Retinol Efficacy Trial; Q1, quartile 1 or quintile 1; Q4, quartile 4; Q5, quintile 5.

were 1·3–3·2 g/d, which are similar or slightly higher than the range of UK intakes[3]. The authors also considered the importance of the source of the *trans*-FA, and found that the link between NHL and *trans*-FA consumption was stronger for vegetable fat sources (RR 1·9) than animal fat sources (RR 1·4). However, it must be noted that this study based *trans*-FA intake on the dietary questionnaire completed in 1980, which is likely to introduce significant error due to the changes in food manufacturing and personal food choices over the course of the study.

Ovarian cancer

Data from the Nurses' Health Study were also used to assess the possible link between diet and risk of ovarian cancer[43]. In the 80 258 pre- and postmenopausal women included in the analysis, 301 cases of ovarian cancer were diagnosed. There was no association between consumption of *trans*-FA and development of the disease.

Pancreatic cancer

Michaud *et al.* [44] used the dietary and health data from the Nurses' Health Study to determine whether there was an association between diet and the risk of developing pancreatic cancer, but found no significant relationship.

Summary of evidence for an association between trans*-fatty acids and other forms of cancer*

There are limited data available to assess evidence for an association between *trans*-FA intakes and other forms of cancer. Data from the Nurses' Health Study provide preliminary evidence of a potential association between *trans*-fat consumption and NHL. However, further studies are required to enable the findings to be verified.

Discussion

Overall, there are few studies that have assessed the relationship between *trans*-FA intakes and cancer at specific sites. Many of the studies have been based in populations with intakes of *trans*-FA higher than those currently estimated for the UK. However, despite the higher intakes, the literature provides only limited evidence for a positive relationship between *trans*-FA consumption and cancer risk.

The cancer site for which most evidence is available on which to base a risk assessment is breast cancer, for which there are four case–control and ten prospective studies reported in the literature. Of the prospective studies, three are outputs from the original Nurses' Health Study, which has now reported follow-up of breast cancer over a period of 20 years with no evidence of an association with *trans*-FA intakes[19,20,22]. Three other prospective studies have reported a positive association[25,26,28]. Animal studies provide no evidence for an effect of *trans*-FA on mammary tumorigenesis. A plausible biological mechanism to explain any adverse effect of *trans*-FA on breast cancer is lacking.

Evidence for an association between *trans*-FA and cancers at other sites is sparse or limited and does not enable any meaningful risk assessment to be undertaken. However, the evidence for an association with particular types of prostate cancer[41] or in individuals with specific genotypes[38] warrants further investigation. The strong association between NHL and *trans*-FA intakes reported from the Nurses' Health Study[43] will require further verification by means of intake data based on more recent estimates of *trans*-FA in this study population.

A statistically significant association was reported for vegetable oil *trans*-FA but not animal *trans*-FA and NHL[43]. One prospective study on breast cancer[26] and a prospective study on prostate cancer[40] reported a positive association that was strongest for *trans*-18 : 1*n*-7. However, the presence

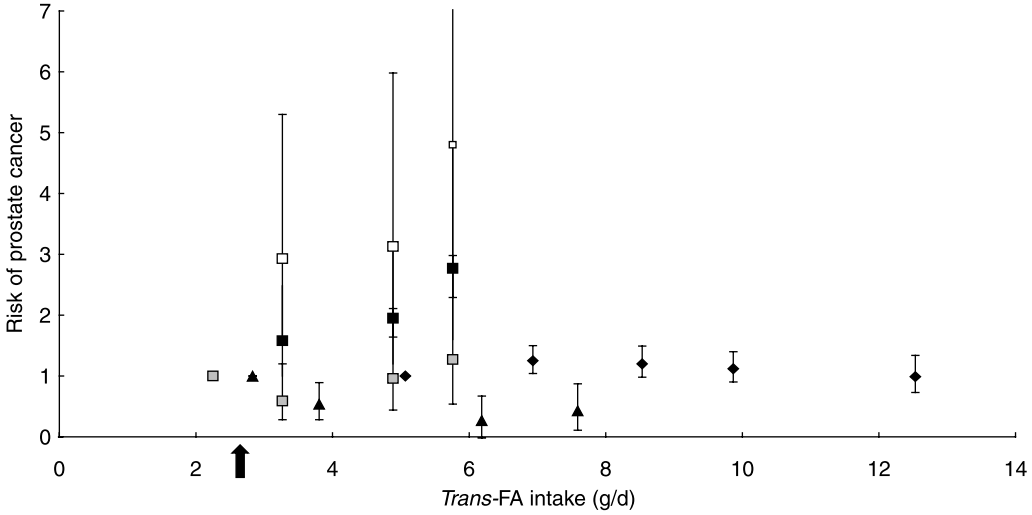

Fig. 3. Risk of prostate cancer from case–control and prospective epidemiological studies that evaluated dietary intake of *trans*-fatty acids (*trans*-FA): Schuurman *et al.* [39] (all men ◆) and Liu *et al.* [38] (African-American ▲; Caucasian ■; Caucasian Q allele □; Caucasian no Q allele ■). The current mean *trans*-FA intake in the UK for men has recently been estimated to be 1·0 % of total energy or 2.4 g/d (↑)[3]. Risk of prostate cancer is plotted as the relative risk (RR), with vertical bars representing the 95 % CI for intake ranges above reference (RR 1) in each study. Data from Schuurman *et al.* [39] were converted from percentage of total energy to g/d based on an energy intake of 2400 kcal/d (10 042 kJ/d). Reference points for Caucasians and genotypes from Liu *et al.* [38] are all at 2·25 g/d.

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Table 4. Human studies investigating the association of *trans*-fatty acids (*trans*-FA) with other types of cancer

Reference	Subject population	Measure of exposure	*Trans*-FA intake/level	Adjusted RR or OR with 95 % CI	*P* for trend	Factors adjusted for in analysis
Non-Hodgkin's lymphoma						
Zhang *et al.*[42] Prospective cohort (NHS) USA	88 410 women, 199 events, 1980–94	% of energy from *trans*-FA as assessed by FFQ	Q1 = 1·3, Q5 = 3·2 Vegetable *trans*-FA: Q1 = 0·5, Q5 = 2·3 Animal *trans*-FA: Q1 = 0·5, Q5 = 1·3	2·4 (1·3, 4·6) 1·9 (1·2, 3·1) 1·4 (0·8, 2·2)	0·01 0·03 0·15	Age, total energy, length of follow-up, geographic region, smoking, height, intake of other fat types, dietary protein, alcohol intake, fruit and vegetable intake
Ovarian cancer						
Bertone *et al.*[43] Prospective cohort (NHS) USA	80 258 women, 449 events, 1980–96	Dietary *trans*-FA assessed by FFQ	No values for *trans*-FA intake given	1·03 (0·72, 1·47)	0·87	Age (at time of study and at menarche), parity, oral contraceptive use and duration, menopausal status, HRT, tubal ligation and smoking
Pancreatic cancer						
Michaud *et al.*[44] Prospective cohort (NHS) USA	88 802 women, 178 events, 1980–98	g/d *trans*-FA intake as assessed by FFQ	Q1 = 2·5, Q5 = 5·7	0·91 (0·58, 1·43)	0·44	Age, smoking, BMI, history of diabetes mellitus, energy intake, height, physical activity, menopausal status and glycaemic load intake

RR, relative risk; NHS, Nurses' Health Study; Q1, quintile 1; Q5, quintile 5; HRT, hormone replacement therapy.

of *trans*-18 : 1*n*-7 in both vegetable oil and animal products prevents these data from providing clear conclusions on the effects of the different sources.

Future work

There is a lack of consistent evidence for an association between *trans*-FA intake and either breast or colon cancers from human studies, and published outcomes from animal studies have yet to provide a plausible mechanism for such a relationship. Consideration should be given to the possibility that, if the impact of *trans*-FA intake on risk is small or moderate, then measurement error[7,8], in dietary assessment and/or biomarker fatty acid analyses, may have reduced the possibility of obtaining positive findings. Measurement error in dietary assessment can be reduced though use of multiple methods of assessment (diet records, food frequency, questionnaires, 24 h recalls) and through repeat measurement during the period of follow-up. Repeat measurement is of particular importance in the case of *trans*-FA, because intakes may have changed considerably over time due to changes in food manufacturing processes. These ideal conditions apply to only a few studies included within the present review. Further prospective studies are needed in which repeat measurements, using more than one assessment method, are made throughout the period of follow-up. Data from the EPIC study, which has applied these criteria in the dietary assessment protocols and which includes populations with a wide range of *trans*-FA intakes, would be of particular value.

Despite the small number of studies, the data reviewed here suggest that the evidence for a link between *trans*-FA and prostate cancer appears to be growing. However, it is critical that assumptions regarding this potential association are not made without sufficient basis. The current information appears sufficient to justify initiating prospective studies that are well designed and to consider the possibility of a genotype interaction. Additional investigation into possible mechanisms would also be worthwhile; although there is little basis for such studies at present, possible hormonal effects of *trans*-FA should be considered given the existing evidence for a possible protective anti-oestrogen-like action for CLA.

The single study looking at *trans*-FA and NHL raises the possibility of an association, but this is an inadequate basis upon which to advise further new investigations. Existing cohorts that have information on *trans*-FA intake or tissue levels and the potential to access information on NHL cases are encouraged to conduct the appropriate statistical analysis and publish their findings in order to help clarify whether this is a real association.

Further animal studies would appear to be of limited value, since outcomes from the very large number of studies conducted to assess relationship between fat or specific fatty acid intakes and cancer appear to have little relevance to human diet exposures and risk of cancer.

Conclusion

There is weak and inconsistent evidence for a relationship between *trans*-FA and breast or colorectal cancer. Evidence

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for an association between *trans*-FA and prostate cancer is limited, but there are two prospective studies that report positive correlations, and a recent large case–control study has shown a strong interaction between risk and *trans*-FA intake for a particular genotype that makes up about 35 % of the population. This potential association requires further investigation. Use of an existing cohort that includes rigorous dietary assessment and tissue sampling for biomarker fatty acid measurement (such as EPIC) would appear to be strongly justified. The strong association between NHL and *trans*-FA intakes reported in a single study require further verification by means of intake data based on more recent estimates of *trans*-FA intake. There is inadequate information in order to distinguish between the effects of *trans*-FA of animal or vegetable origin on the risk of cancer.

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References

1. McGovern G (1977) *Dietary Goals for the United States; Report of the Select Committee on Nutrition and Human Needs, US Senate*. Cambridge, MA: MIT Press.
2. Eniq M, Munn R & Keeney M (1978) Dietary fat and cancer trends – a critique. *Fed Proc* **37**, 2215–2220.
3. Williams C, Thompson A, Shaw D, *et al* (2007) *Update on* Trans-*Fatty Acids and Health. Position Statement by the Scientific Advisory Committee on Nutrition*. London: The Stationery Office.
4. Henderson L, Gregory J, Irving K, *et al* (2003) *The National Diet and Nutrition Survey: Adults Aged 19–64 Years*, vol. 2. London: HM Stationery Office.
5. Food and Drug Administration & HHS (2003) Food labeling: *trans* fatty acids in nutrition labeling, nutrient content claims, and health claims. Final rule. *Fed Reg* **68**, 41433–41506.
6. Hulshof K, van Erp-Baart M, Anttolainen M, *et al*. (1999) Intake of fatty acids in Western Europe with emphasis on *trans* fatty acids: the TRANSFAIR study. *Eur J Clin Nutr* **53**, 143–157.
7. Margetts BM & Nelson M (1997) *Design Concepts in Nutritional Epidemiology*, 2nd ed. Oxford: Oxford University Press.
8. Department of Health (1998) *Nutritional Aspects of the Development of Cancer*. London: The Stationery Office.
9. Selenskas SL, Ip MM & Ip C (1984) Similarity between *trans* fat and saturated fat in the modification of rat mammary carcinogenesis. *Cancer Res* **44**, 1321–1326.
10. Erickson KL, Schlanger DS, Adams DA, *et al*. (1984) Influence of dietary fatty acid concentration and geometric configuration on murine mammary tumorigenesis and experimental metastasis. *J Nutr* **114**, 1834–1842.
11. Lock AL, Corl BA, Barbano DM, *et al*. (2004) The anticarcinogenic effect of *trans*-11 181 is dependent on its conversion to *cis*-9, *trans*-11 CLA by Δ9-desaturase in rats. *J Nutr* **134**, 2698–2704.
12. Santora JE, Palmquist DL & Roehrig KL (2000) *Trans*-vaccenic acid is desaturated to conjugated linoleic acid in mice. *J Nutr* **130**, 208–215.
13. Turpeinen AM, Mutanen M, Aro A, *et al*. (2002) Bioconversion of vaccenic acid to conjugated linoleic acid in humans. *Am J Clin Nutr* **76**, 504–510.
14. Bakker N, van't Veer P, Zock PL, *et al*. (1997) Adipose fatty acids and cancers of the breast, prostate and colon: an ecological study. *Int J Cancer* **72**, 387–391.
15. London SJ, Sacks FM, Stampfer MJ, *et al*. (1993) Fatty acid composition of the subcutaneous adipose tissue and risk of proliferative benign breast disease and breast cancer. *J Natl Cancer Inst* **85**, 785–793.
16. Petrek JA, Hudgins LC, Levine B, *et al*. (1994) Breast cancer risk and fatty acids in the breast and abdominal adipose tissues. *J Natl Cancer Inst* **86**, 53–56.
17. Kohlmeier L, Simonsen N, van 't Veer P, *et al*. (1997) Adipose tissue *trans* fatty acids and breast cancer in the European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer. *Cancer Epidemiol Biomarkers Prev* **6**, 705–710.
18. Aro A, Männistö S, Salminen I, *et al*. (2000) Inverse association between dietary and serum conjugated linoleic acid and risk of breast cancer in postmenopausal women. *Nutr Cancer* **38**, 151–157.
19. Holmes MD, Hunter DJ, Colditz GA, *et al*. (1999) Association of dietary intake of fat and fatty acids with risk of breast cancer. *JAMA* **281**, 914–920.
20. Byrne C, Rockett H & Holmes MD (2002) Dietary fat, fat subtypes, and breast cancer risk: lack of an association among postmenopausal women with no history of benign breast disease. *Cancer Epidemiol Biomarkers Prev* **11**, 261–265.
21. Cho E, Spiegelman D, Hunter DJ, *et al*. (2003) Premenopausal fat intake and risk of breast cancer. *J Natl Cancer Inst* **95**, 1079–1085.
22. Kim EHJ, Willett WC, Colditz GA, *et al*. (2006) Dietary fat and risk of postmenopausal breast cancer in a 20-year follow-up. *Am J Epidemiol* **164**, 990–997.
23. Pala V, Krogh V, Muti P, *et al*. (2001) Erythrocyte membrane fatty acids and subsequent breast cancer: a prospective Italian study. *J Natl Cancer Inst* **93**, 1088–1095.
24. Saadatian-Elahi M, Toniolo P, Ferrari P, *et al*. (2002) Serum fatty acids and risk of breast cancer in a nested case-control study of the New York University Women's Health Study. *Cancer Epidemiol Biomarkers Prev* **11**, 1353–1360.
25. Voorrips LE, Brants HAM, Kardinaal AFM, *et al*. (2002) Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: the Netherlands Cohort Study on Diet and Cancer. *Am J Clin Nutr* **76**, 873–882.
26. Rissanen H, Knekt P, Jarvinen R, *et al*. (2003) Serum fatty acids and breast cancer incidence. *Nutr Cancer* **45**, 168–175.
27. Shannon J, King IB, Moshofsky R, *et al*. (2007) Erythrocyte fatty acids and breast cancer risk: a case-control study in Shanghai. *China. Am J Clin Nutr* **85**, 1090–1097.
28. Chajes V, Thiebaut ACM, Rotival M, *et al*. (2008) Association between serum *trans*-monounsaturated fatty acids and breast cancer risk in the E3N-EPIC Study. *Am J Epidemiol* **167**, 1312–1320.
29. Watanabe M & Koga T (1985) Sugano M Influence of dietary *cis*- and *trans*-fat on 1,2-dimethylhydrazine-induced colon tumors and fecal steroid excretion in Fischer 344 rats. *Am J Clin Nutr* **42**, 475–484.
30. Sugano M, Watanabe M, Yoshida K, *et al*. (1989) Influence of dietary *cis* and *trans* fats on DMH-induced colon tumors, steroid excretion, and eicosanoid production in rats prone to colon cancer. *Nutr Cancer* **12**, 177–187.
31. Hogan ML & Shamsuddin AM (1984) Large intestinal carcinogenesis. I. Promotional effect of dietary fatty acid isomers in the rat model. *J Natl Cancer Inst* **73**, 1293–1296.
32. Reddy BS & Tanaka T (1985) Simi B Effect of different levels of dietary *trans* fat or corn oil on azoxymethane-induced

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colon carcinogenesis in F344 rats. *J Natl Cancer Inst* **75**, 791–798.
33. McKelvey W, Greenland S, Chen M-J, *et al*. (1999) A case-control study of colorectal adenomatous polyps and consumption of foods containing partially hydrogenated oils. *Cancer Epidemiol Biomarkers Prev* **8**, 519–524.
34. Slattery ML, Benson J, Ma K-N, *et al*. (2001) Trans-fatty acids and colon cancer. *Nutr Cancer* **39**, 170–175.
35. Nkondjock A, Shatenstein B, Maisonneuve P, *et al*. (2003) Assessment of risk associated with specific fatty acids and colorectal cancer among French-Canadians in Montreal: a case–control study. *Int J Epidemiol* **32**, 200–209.
36. Theodoratou E, McNeill G, Cetnarskyj R, *et al*. (2007) Dietary fatty acids and colorectal cancer: a case–control study. *Am J Epidemiol* **166**, 181–195.
37. Lin J, Zhang SM, Cook NR, *et al*. (2004) Dietary fat and fatty acids and risk of colorectal cancer in women. *Am J Clin Nutr* **160**, 1011–1022.
38. Liu X, Schumacher FR, Plummer SJ, *et al*. (2007) *Trans*-fatty acid intake and increased risk of advanced prostate cancer: modification by RNASEL R462Q variant. *Carcinogenesis* **28**, 1232–1236.
39. Schuurman AG, van den Brandt PA, Dorant E, *et al*. (1999) Association of energy and fat intake with prostate carcinoma risk: results from the Netherlands Cohort Study. *Cancer* **86**, 1019–1027.
40. King IB, Kristal AR, Schaffer S, *et al*. (2005) Serum *trans*-fatty acids are associated with risk of prostate cancer in beta-carotene and retinol efficacy trial. *Cancer Epidemiol Biomarkers Prev* **14**, 988–992.
41. Chavarro JE, Stampfer MJ, Campos H, *et al*. (2008) A prospective study of *trans*-fatty acid levels in blood and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* **17**, 95–101.
42. Zhang S, Hunter DJ, Rosner BA, *et al*. (1999) Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. *J Natl Cancer Inst* **91**, 1751–1758.
43. Bertone ER, Rosner BA, Hunter DJ, *et al*. (2002) Dietary fat intake and ovarian cancer in a cohort of US women. *Am J Epidemiol* **156**, 22–31.
44. Michaud DS, Giovannucci E, Willett WC, *et al*. (2003) Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. *Am J Epidemiol* **157**, 1115–1125.

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