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Review Article

Trans-fatty acids and cancer: a mini-review

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The association between *trans*-fatty acids (TFA) and cancer risk is poorly understood and remains controversial. It is recognised that unique biological effects are associated with specific isoforms within families of fatty acids such as those belonging to the *n*-3 fatty acids. Furthermore, the interactions between diet and genetic polymorphisms are increasingly recognised for their potential risk-modifying effects on human health and disease. Therefore, the aim of the present review is to evaluate whether specific TFA isomers and genetic polymorphisms differentially modify cancer risk in prostate, colon and breast cancers in animal and human models. Potential mechanisms of action by which TFA may affect cancer development are also reviewed. Overall, across a number of experimental models and human studies, there is insufficient and inconsistent evidence linking specific TFA isomers to cancers of the prostate, colon and breast. A number of methodological limitations and experimental considerations were identified which may explain the inconsistencies observed across these studies. Therefore, further research is warranted to accurately assess the relationship between TFA and cancer risk.

Cancer: *Trans*-fatty acids: Elaidic acid: Vaccenic acid

The potential harmful effects of *trans*-fatty acids (TFA) on blood lipids and CVD have been extensively researched; however, very little is known about the effects of TFA on cancer[1,2]. Cancer is a leading cause of death in North America[3,4]. Currently, the effect of TFA on cancer risk is not well understood, but recent studies suggest that specific TFA isomers may be associated with increased cancer risk[5,6].

Dietary TFA include isomers derived from natural and industrially produced sources. *Trans*-vaccenic acid (*trans*-11-18 : 1; VA), a MUFA, is the most prevalent *trans* isomer found naturally in foods such as dairy and ruminant-derived meat products[7,8]. In addition to VA, dairy foods and ruminant-derived meats also contain polyunsaturated TFA known as conjugated linoleic acid (CLA), but the primary focus of the present review will be on non-conjugated TFA. Industrially synthesised TFA are produced via partial hydrogenation of plant oils to produce a fat with a semi-solid texture, a higher melting point and a longer shelf life[9]. It has been reported that the major sources of dietary TFA are industrially produced and contribute 1 % of energy in the UK population and 2–3 % of energy in the USA[10,11]. Average TFA intake in Canada is estimated to be 3–9 g/d[12], and assuming an 8·4 MJ (2000 kcal) diet, this is about < 1–4 % of energy intake. It should also be noted that intake in some individuals may be upwards of + 10 % of energy.

It has been suggested that individual TFA isomers differ in their physiological and metabolic effects on various pathologies, including cancer[13]. The distribution of 18 : 1 TFA isomers differs markedly between natural and industrially produced food sources. Elaidic acid (*trans*-9-18 : 1; EA) is the major TFA found in partially hydrogenated oils[14,15]. Therefore, the source and type of TFA in the food supply may be important considerations as modifiers of health risk. Data on the potential adverse health effects associated with ruminant sources of TFA are limited and inconclusive[16–19]. In contrast, the adverse health effects of industrially synthesised TFA have been more consistently reported[13].

The present review will summarise animal and human evidence investigating the link between different TFA isomers and cancers of the prostate, colon and breast. In addition, potential mechanisms of action by which TFA contribute to cancer development will be discussed. A literature search of PubMed using the keywords '*trans* fatty acid' and 'cancer' were used to acquire the pertinent studies for the present review.

Abbreviations: CLA, conjugated linoleic acid; EA, elaidic acid; PL, phospholipids; TFA, *trans*-fatty acids; VA, vaccenic acid.

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Animal studies examining the effect of *trans*-fatty acids on cancer development

Animal model studies investigating the effect of TFA on prostate cancer have yet to be done but a limited number of studies involving models of breast and colon cancers have yielded conflicting results (Table 1). One of the earliest animal model studies in this field demonstrated that Ehrlich ascites tumour-bearing mice had 23 to 45 % reduced survival time when mice consumed a diet composed of 5 % EA compared with mice consuming a control diet of 5 % olive oil[20]. While EA was fed as a NEFA, the olive oil was comprised primarily of oleic (18 : 1*n*-9), linoleic (18 : 2*n*-6) and palmitic (16 : 0) acids in TAG form. Upon review, it may have been more appropriate to feed the EA in TAG form as non-esterified EA has a high melting point and is poorly digested[21]. This suggests that the nutritional status of the EA-fed mice may have been compromised, thereby contributing to the reduced survival time[21]. Another study in rats treated with azoxymethane and fed a diet high in EA (25 %, w/w) resulted in a non-significant but 2-fold higher incidence of cancer when compared with a 25 % oleic acid diet or a low-fat chow diet (4·5 % of energy from fat)[22]. EA and oleic acid were fed as a NEFA but oleic acid has a lower melting point suggesting that these two diets are not biologically comparable based on their differences in digestibility. Considering TFA are obtained in the diet as TAG, generating experimental diets whereby the fatty acids are supplied as TAG is more physiologically relevant. As such, a study in mice used a partially hydrogenated mixture of 50 % soyabean oil and 50 % cottonseed to produce a fat high in TFA as TAG[23]. A high-*cis*-fatty acid diet was generated using 58 % olive oil, 40 % cocoa butter and 2 % coconut oil. Maize oil was used as the control fat. All three diets were administered at two different levels of fat content, at 5 and 20 % (w/w of diet). These diets were then compared for their impact on 7, 12-dimethylbenz[a]anthracene-induced mammary tumorigenesis. Interestingly, both the 5 and 20 % (w/w) control maize oil diets, and not the TFA diets, significantly increased cancer incidence. In a subsequent study, a high-maize oil diet (23·5 %, w/w) was compared with three different diets containing varying amounts of TFA to examine the development of azoxymethane-induced colon tumours in rats[24]. Again, the high-maize oil diet resulted in higher tumour incidence when compared with all three diets. An explanation for these results may be that the TFA diets were low in essential fatty acids in contrast to the maize oil diet which is high in the *n*-6 essential fatty acid, linoleic acid, reinforcing observations suggesting a requirement of essential fatty acids for tumour growth[25].

Two other studies observed no difference in colon cancer tumorigenesis when comparing rats on partially hydrogenated maize oil diets (10 % (w/w) of fat) to rats on a high-oleic acid (10 % (w/w) of fat) control diet after treating with 1, 2-dimethylhydrazine to induce colon cancer[26,27]. Although the specific *trans* isomers were not independently analysed in either study, it is interesting to note that a decrease in α-tocopherol levels in the TFA diet was observed[27]. This implies that TFA may affect the oxidant:antioxidant balance, a factor that has been associated with cancer[28].

In a series of more recent animal studies, the anti-carcinogenic potential of VA was evaluated in rat mammary glands[29–31]. Methylnitrosourea-induced tumour growth in rat mammary glands was attenuated when rats were fed diets supplemented with 2 % (w/w) VA[29]. It was hypothesised that this effect was mediated through the conversion of VA to CLA via the Δ-9 desaturase enzyme. In a follow-up study, the cyclopropenoic fatty acid, sterculic oil, was used to effectively block the conversion of VA to CLA, resulting in an attenuated anti-carcinogenic effect of VA supplementation[31]. These data indicate that the observed reduction in tumour growth with VA supplementation is predominantly mediated through its conversion to CLA by Δ-9-desaturase.

In summary, there is some evidence of differential isomeric effects and that VA may have chemoprotective properties. However, results from animal studies employing partially hydrogenated vegetable oils or EA are equivocal. It appears that the selection of the type of oil used in the control diet is an important consideration and whether maize or olive oil may affect the interpretation of the study outcome. Given that maize oil contains a significant amount of linoleic acid, which is known to promote cancer in rodent models, it may not be suitable for use as a negative control and should be considered a positive control[32]. Considering that TFA are

Table 1. Animal model studies and *trans*-fatty acids (TFA)

Type of cancer	Model	Main finding	Contribution of TFA to diet (% energy)*	Reference
Mammary	Mice with Ehrlich ascites tumour	High-EA diet ↓ survival time	8	Awad (1981)[20]
Mammary	Rats injected with dimethylbenz[a]anthracene	No effect of TFA	1 and 13	Selenskas *et al.* (1984)[23]
Mammary	Rats injected with methylnitrosourea	VA ↓ premalignant lesions	2, 5 and 7	Banni *et al.* (2001)[29]
Mammary	Rats injected with methylnitrosourea	VA ↓ premalignant lesions	0·4–4	Corl *et al.* (2003)[30]
Mammary	Rats injected with methylnitrosourea	VA ↓ premalignant lesions by ↑ CLA	1 % and 4	Lock *et al.* (2004)[31]
Colon	Rats injected with azoxymethane	No effect of TFA	4, 8 and 12	Reddy *et al.* (1985)[24]
Colon	Rats injected with azoxymethane	High-EA diet non-significantly ↑ tumour development	25 % (w/w)	Hogan & Shamsuddin (1984)[22]
Colon	Rats injected with 1,2-dimethylhydrazine	No effect of TFA	22	Sugano *et al.* (1989)[26]
Colon	Rats injected with 1,2-dimethylhydrazine	α-Tocopherol levels were ↓ in TFA diet	0·8	Watanabe *et al.* (1985)[27]

EA, elaidic acid; ↓, decrease; VA, vaccenic acid; CLA, conjugated linoleic acid; ↑, increase.
* Unless otherwise stated, values are expressed as % energy and calculated from available information provided in the reference cited.

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Table 2. Human prostate cancer studies and *trans*-fatty acids (TFA)

Type of study	Subjects (*n*)	Subject characteristics	Method of assessment	Main finding	Reference
Ecological	690	From eleven different centres across Europe and Israel	Adipose tissue	TFA, ↑ risk	Bakker *et al.* (1997)[34]
Prospective	58 279 subjects, 642 cases, 1525 subcohort	Aged 55–69 years	FFQ	No relationship	Schuurman *et al.* (1999)[35]
Population based case–control	858 cases, 905 controls	High-grade tumours, aged < 70 years	FFQ	No relationship	Hodge *et al.* (2004)[36]
Case–control	272 cases, 426 controls	60 % aged > 60 years, 79 % overweight Caucasians	Serum phospholipids	VA and 9-*cis*, 12-*trans*-18 : 2 TFA, ↑ risk	King *et al.* (2005)[37]
Nested case–control	476 cases, 476 controls	Aged 40–84 years	Whole blood	EA, *trans*, *trans*-18 : 2*n*-6, *cis*, *trans*-18 : 2*n*-6, *trans*, *cis*-18 : 2*n*-6 TFA, ↑ risk in non-aggressive tumours	Chavarro *et al.* (2008)[5]
Case–control	506 cases, 506 control	82 % Caucasian cases had at least one of Gleason score > 7, tumour stage ≥ T2c or PSA > 10 ng/ml. Cases aged 65·7 (SD 8·2) years	FFQ	*Trans*-16 : 1, *trans*-18 : 1, *trans*-18 : 2 and total TFA, ↑ risk of advanced prostate cancer Risk is modulated by specific *RNASEL* single nucleotide polymorphisms	Liu *et al.* (2007)[6]

↑, Increase; VA, vaccenic acid; EA, elaidic acid; PSA, prostate-specific antigen.

more similar in structure to SFA, a saturated fat diet may be a more appropriate control diet for cancer studies. Also, many of the animal studies described have used TFA levels above usual human consumption between 2 and 3 % of energy[20,22–24,26,27,33]. Therefore, further studies are needed to reflect the need for the use of appropriate control diets, type of TFA isomer, and level in the diet.

Effect of *trans*-fatty acids in human cancer studies

The earliest studies investigating the effect of TFA on human cancer risk were reported in the early to mid 1990s. These studies primarily investigated the link between TFA and cancers of the prostate, colon and breast. The following section reviews the evidence in human studies examining the relationship between TFA intake and risk of these common cancers.

Effect of trans*-fatty acids in human prostate cancer studies*

To date the association between prostate cancer and TFA intake has been reported in six human studies (Table 2). Four studies show that TFA increased prostate cancer risk and two studies showed no relationship. The European Antioxidant Myocardial Infarction and Breast Cancer (EURAMIC) ecological study measured total TFA in adipose tissue biopsies from 690 subjects and found a positive correlation between TFA levels and prostate cancer risk in the subset male population (r 0·50; 95 % CI −0·15, 0·85)[34]. This study also observed a positive association between TFA levels and both colon cancer (n 1058) and postmenopausal breast cancer (n 358) risk (r 0·93 (95 % CI 0·74, 0·98); r 0·89 (95 % CI 0·62, 0·97), respectively). It should be noted that ecological studies are weak and provide limited evidence about actual exposure and cancer incidence.

Using FFQ as a tool to measure TFA, two human studies have shown that TFA intake was not associated with prostate cancer risk. The prospective Netherlands Cohort Study (6·3 years) of 58 279 men found 642 cases and did not observe an association between total TFA intake measured by FFQ and prostate cancer risk. However, prostate cancer risk was increased after adjustment for energy from fat[35]. In a case–control study of 858 men with aggressive prostate cancer (Gleason scores of grade 5 or greater), total 18 : 1 and 18 : 2 TFA were not associated with prostate cancer risk[36].

In contrast to FFQ-based studies, using a direct measure of serum TFA has been associated with increased prostate cancer risk. In a nested case–control study (272 cases, 426 controls) designed to evaluate the association between serum TFA concentration and prostate cancer risk, VA and *cis*, *trans*-18 : 2*n*-6 TFA were both significantly (OR 1·69 and 1·79, respectively) associated with an increased risk for prostate cancer[37]. EA and *trans*-12-18 : 1 were both non-significantly associated with an increase in prostate cancer risk. The authors also report a stronger non-significant relationship between TFA levels and low-grade prostate cancer. Another nested case–control study (476 cases, 476 controls) observed non-significant trends between quintiles of EA, *cis*, *trans*-18 : 2*n*-6 and total 18 : 2 TFA as measured via blood samples[5]. When the TFA levels were investigated in non-aggressive tumours

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Table 3. Human colon cancer studies and *trans*-fatty acids (TFA)

Type of study	Subjects (*n*)	Subject characteristics	Method of assessment	Main finding	Reference
Ecological	1748	From eleven different centres across Europe and Israel, aged ≤ 70 years	Adipose tissue	TFA, ↑ risk	Bakker *et al.* (1997)[34]
Case–control	234 cases, 407 controls	Colonoscopy-referred men and women, aged 30–89 years	FFQ	TFA, ↑ risk	McKelvey *et al.* (2000)[40]
Case–control	1993 cases, 2410 controls	Men and women, aged 30–79 years	FFQ	TFA and oestrogen-negative status, ↑ risk ↑ NSAIDS, ↓ risk when consuming high-TFA diet	Slattery *et al.* (2001)[41]
Case–control	173 cases, 449 controls	Colonoscopy-referred men and women, aged 30–80 years	FFQ	TFA, ↑ risk	Vinikoor *et al.* (2008)[45]
Case–control	1455 cases, 1455 controls	Men and women, aged 16–79 years	FFQ	Total TFA and 18 : 1 TFA intake, ↑ risk	Theodoratou *et al.* (2007)[42]
Case–control	1656 cases, 2292 controls	Men and women, aged 16–79 years	FFQ	TFA, ↑ risk	Theodoratou *et al.* (2008)[43]
Prospective	35 216 subjects, 1229 cases	Women, aged 55–69 years	FFQ	No relationship	Limburg *et al.* (2008)[44]

↑, Increase; NSAIDS, non-steroidal anti-inflammatory drugs; ↓, decrease.

only (Gleason score < 7; *n* 209), EA was non-significantly associated and total TFA, total 18 : 2 TFA, *trans*, *trans*-18 : 2*n*-6, *cis*, *trans*-18 : 2*n*-6 and *trans*, *cis*-18 : 2*n*-6 were all significantly associated with increased prostate cancer risk.

Genetic variation may also be an important modifier of prostate cancer risk. A recent case–control study (*n* 1012) investigated the association between TFA intake (assessed via FFQ), genetic predisposition and risk of prostate cancer[6]. Specifically, the link between the R462Q polymorphism of the immune function gene *RNASEL*, and the risk for prostate cancer development when combined with TFA intake was examined in this study. *RNASEL* encodes the interferon system involved in regulating the anti-viral and pro-apoptotic functions of the cell and the R462Q polymorphism decreases *RNASEL* activity 3-fold[38]. A significant positive association between total *trans*-16 : 1, total *trans*-18 : 1, total *trans*-18 : 2 and total TFA and the risk of prostate cancer was found when examining the lowest to highest quartiles of TFA intake in Caucasians. This negative effect of TFA intake on prostate cancer risk was further modulated by the R462Q polymorphism ($P \leq 0{\cdot}0003$). Although energy intake was also significantly associated with prostate cancer risk, these results demonstrate that TFA intake, independently, and when combined with the *RNASEL* R462Q variant, is positively associated with an increased risk for prostate cancer.

In summary, the results from studies using adipose tissue biopsies and blood serum measurements of TFA have shown a positive association between TFA content and prostate cancer risk. In contrast, studies using a FFQ have not found a positive association. Genetic predisposition is also reported to modulate the risk for prostate cancer when consuming a diet high in TFA.

Effect of trans*-fatty acids in human colon cancer studies*

It has been suggested that 50–80 % of colorectal cancer cases are a result of environmental factors[39]. One adipose tissue biopsy, one prospective and five FFQ case–control studies have been conducted to evaluate the relationship between TFA intake and colon cancer[34,40–45] (Table 3). Five studies showed an increased risk with TFA and one study observed no relationship between dietary TFA and colon cancer risk.

In colonoscopy-referred men and women 234 cases and 407 controls were used to evaluate the potential association between TFA intake and colorectal cancer[40]. TFA intake was determined by FFQ using over-the-counter foods known to contain specific amounts of TFA as markers for TFA exposure. This study found that increased consumption of sweetened baked goods and oils and condiments that are high in TFA significantly increased the risk of colorectal cancer (OR 1·9 (95 % CI 0·95, 3·8) and OR 2·4 (95 % CI 1·3, 4·2), respectively). In men and women, a case–control study (cases, *n* 1993; controls, *n* 2410) study showed that increased total TFA consumption, as assessed by a FFQ, increased the risk of colon cancer (OR 1·5; 95 % CI 1·1, 2·0)[41]. Women who were oestrogen-negative were at a 2-fold greater risk for the development of colon cancer, suggesting that hormonal balance may be a potential variable in the association between colon cancer risk and TFA consumption. This study adjusted for variables such as age, height and use of non-steroidal anti-inflammatory drugs.

Table 4. Human breast cancer studies and *trans*-fatty acids (TFA)

Type of study	Subjects (*n*)	Subject characteristics	Method of Assessment	Main finding	Reference
Ecological	358	From five different centres across Europe and Israel, aged 50–74 years	Adipose tissue	TFA, ↑ risk	Bakker *et al.* (1997)[34]
Case–control	380 cases, 573 controls	Postmenopausal, aged 36–93 years	Adipose tissue	*Trans*-9-16 : 1, ↑ BBD risk	London *et al.* (1993)[49]
Case–control	154 cases, 125 control	Cases aged 52 (SD 11·8) years, controls aged 48·0 ± 4·4 years	Adipose tissue	No relationship	Petrek *et al.* (1994)[60]
Prospective	161 cases	Stage 1 or 2 invasive breast cancer	Adipose tissue	TFA, ↓ positive lymph node status	Petrek *et al.* (1997)[50]
Case–control	209 cases, 407 controls	Postmenopausal, aged 50–74 years	Adipose tissue	↑ TFA, ↑ risk EA carried highest risk Low PUFA intake, ↑ risk	Kohlmeier *et al.* (1997)[48]
Two cohort studies pooled	58 404 subjects, 1071 cases	Postmenopausal, no history of BBD, aged 56·8 (SD 5·5) years	FFQ	No relationship	Byrne *et al.* (2002)[52]
Population-based case–control	1703 cases, 2045 controls	Multi-ethnic, aged 35–79 years	FFQ	Use of hydrogenated cooking oil, ↑ risk	Wang *et al.* (2008)[59]
Prospective-cohort	62 573 subjects, 941 cases, 1598 subcohort	Postmenopausal, aged 55–69 years	FFQ	VA, ↑ risk	Voorrips *et al.* (2002)[58]
Nested case–control	127 cases, 242 controls	Seventy-three premenopausal and fifty-four postmenopausal cases, aged 19–89 years	Serum total lipids	VA, ↑ risk Association stronger in postmenopausal women	Rissanen *et al.* (2003)[56]
Case–control	195 cases, 208 controls	Sixty-eight premenopausal and 127 postmenopausal cases, aged 25–75 years	Serum total lipids	VA, ↓ risk	Aro *et al.* (2000)[51]
Incident case–control	196 cases, 388 controls	Postmenopausal, mean age 55 years	Serum phospholipids	No relationship	Chajès *et al.* (1999)[53]
Prospective case–control	4052 subjects, seventy-one cases, 141 controls	Postmenopausal, aged 42–69 years	Erythrocyte phospholipids	No relationship	Pala *et al.* (2001)[55]
Nested case–control	197 cases, 197 controls	Cases and controls: ninety-one premenopausal and 106 postmenopausal, aged 34–65 years	Serum phospholipids	No relationship	Saadatian-Elahi *et al.* (2002)[57]
Prospective case–control	19 934 subjects, 363 cases, 702 controls	Cases: eighty-four premenopausal and 279 postmenopausal, aged 56·8 (SD 6·3) years	Serum phospholipids	*Trans*-9-16 : 1, *trans*-18 : 2*n*-6, EA, ↑ risk	Chajès *et al.* (2008)[54]

↑, Increase; BBD, benign breast disease; ↓, decrease; EA, elaidic acid; VA, vaccenic acid.

Interestingly, subjects who did not use non-steroidal anti-inflammatory drugs were at a 50 % greater risk for developing colon cancer when consuming a high-TFA diet. As with prostate cancer, this suggests a potential role for chronic inflammation, a situation related to high TFA consumption, in cancer pathology[46]. A recent FFQ study in men and women (173 cases and 449 controls) recruited colonoscopy out-patients and found an increased risk (OR 1·86; 95 % CI 1·04, 3·33) for colorectal adenomas in the highest quartile of total TFA consumption[45]. Non-steroidal anti-inflammatory drug use, family history, BMI, physical activity, smoking status, alcohol consumption, Ca consumption, red meat consumption, and total vegetable serving consumption were all controlled for. The authors suggest a 'threshold effect' to explain the increased risk at the higher levels of TFA intake.

A case–control study involving men and women (cases, *n* 1455; controls, *n* 1455) did not find a significant association between total TFA intake as measured by a FFQ and increased risk of colon cancer[42]. However, after adjusting for family history of colorectal cancer, total energy intake, total fibre intake, alcohol intake, use of non-steroidal anti-inflammatory drugs, smoking, BMI and physical activity, a significant positive association was found between total TFA and total 18 : 1 TFA isomer intake and the risk of colorectal cancer in women. A follow-up study (1656 cases, 2292 controls) examining adenomatous polyposis coli (APC) tumour-suppressor gene mutations, TFA intake (by FFQ) and colorectal cancer risk found that the risk of colorectal cancer was lower (OR 0·78; 95 % CI 0·67, 0·92) in participants who consumed a diet low in TFA regardless of APC mutations[43].

A recent prospective study in women (*n* 35 216; 18-year follow-up) evaluated the relationship between total TFA consumption (by FFQ) and colon cancer risk. This study identified 1229 cases and after controlling for age and total energy, TFA consumption was not associated with an increased risk for colon cancer[44].

To date, studies examining the relationship between TFA intake and human colon cancer have all observed a positive association except the most recent prospective study. Hormonal balance in women and non-steroidal anti-inflammatory drugs appear to influence the risk of colon cancer, but the role of different gene polymorphisms remains to be elucidated[47]. More targeted studies using blood serum or adipose tissue as markers of TFA exposure are warranted to confirm these results.

Effect of trans*-fatty acids in human breast cancer studies*

The effect of TFA on breast cancer development has been investigated more extensively than other cancers. Four of five studies that used adipose tissue as a marker for TFA exposure observed a positive relationship with breast cancer[34,48–50]. The results from both FFQ and blood sample studies are less consistent and somewhat contradictory[34,51–59]. These studies are summarised in Table 4.

An early case–control study (cases, *n* 380; controls, *n* 573) in postmenopausal women examined the relationship between specific TFA isomers in subcutaneous adipose tissue and the risk of breast cancer and proliferative benign breast disease[49]. Interestingly, the *trans*-9-16 : 1 fatty acid isomer was significantly associated with breast cancer, although both EA and VA were not. Another early case–control study (cases, *n* 154; controls, *n* 125) analysed specific TFA isomers and found no relationship between adipose tissue TFA content and breast cancer risk[60]. A study by the same group (*n* 161) with stage 1 or 2 invasive breast cancer supplied adipose tissue biopsies at diagnostic surgery to examine the relationship between total TFA levels and lymph node status after a 7·3-year follow-up[50]. This study observed a negative relationship between adipose tissue TFA content and positive lymph node status (OR 0·24; 95 % CI 0·07, 0·77). This negative relationship is not surprising and potentially suggests a change in lifestyle that included decreased TFA intake.

A case–control study using gluteal fat biopsies as a marker for TFA intake demonstrated that elevated adipose tissue content of TFA was positively associated with an increased risk for breast cancer in postmenopausal women (*n* 698)[48]. Interestingly, EA as 1·02 % of dietary fat carried the highest risk for breast cancer (OR 1·45) and in the lowest tertile of PUFA intake, breast cancer risk increased by 3·6-fold. This suggests that a diet high in TFA and low in PUFA may compound the risk for breast cancer. However, the GLC column used in this study has been criticised as being too short to accurately separate out the individual fatty acid isomers[61].

Data from the Nurses' Health Study found no association between TFA intake quantified via FFQ and the risk of breast cancer in postmenopausal registered nurses[52,62]. Women working in the human health field tend to be healthier than a typical woman in the rest of the population, suggesting that the Nurses' Health Study sample population may have affected the results[52]. Also, results from Holmes *et al.* [62] suggest that a low-fat diet and increased intake of *n*-3 will increase the risk for postmenopausal breast cancer which is in contrast to many other studies and may be a result of the potential limitations of FFQ[63,64]. Another FFQ-based study in a multi-ethnic population (cases, *n* 1703; controls, *n* 2045) found an increased risk for breast cancer in subjects using hydrogenated fat cooking oils[59]. It is important to note that only the use of cooking with hydrogenated oil was measured and that no direct measurements of TFA intake were obtained from the subjects. The Netherlands Cohort Study (941 cases) found that postmenopausal women with higher VA intake as assessed by FFQ had higher breast cancer incidence (OR 1·30; 95 % CI 0·93, 1·80)[58]. Moreover, serum VA levels in a nested case–control study (127 cases, 242 controls), were associated with an elevated risk for postmenopausal breast cancer (OR 4·23; 95 % CI 1·36, 13·2) after controlling for BMI, serum cholesterol, alcohol consumption, education, leisure-time exercise and parity[56]. In contrast, the serum levels of VA in sixty-eight premenopausal and 127 postmenopausal women were associated with a decreased risk for breast cancer (OR 0·3; 95 % CI 0·1, 0·7)[51]. The divergent data regarding VA and its effects on breast cancer may be related to the formation of CLA. As mentioned, VA is a precursor to CLA and CLA has been shown to have anti-carcinogenic properties[65]. The Δ-9-desaturase enzyme is responsible for the conversion of VA to CLA and this conversion reduces mammary carcinogenesis in rats[66,67]. Differences in Δ-9-desaturase function may account for the variation found in these studies. Indeed, polymorphisms of this enzyme have been identified and a number of different transcription factors including PPAR are involved in the regulation of this

Table 5. Potential *trans*-fatty acids (TFA) cancer-promoting mechanisms

Mechanism of action	Study design	Outcome measure	Reference
Oxidant stress	C57Bl/6J mice fed high-EA diet	↑ F_2-isoprostanes ↓ Plasma vitamin E	Cassagno *et al.* (2005)[28]
Oxidant stress	6-week ↑ VA and *trans*-12-18 : 1 diet in men and women	↑ F_2-isoprostanes	Kuhnt *et al.* (2006)[85]
Oxidant stress	Longitudinal study in women aged 42–52 years (*n* 1610)	↑ TFA ↑ F_2-isoprostanes	Tomey *et al.* (2007)[86]
Systemic inflammation	Women of NHS population (*n* 823)	↑ *Trans*-18 : 1 and *trans*-18 : 2 ↑ TNF-R1, TNF-R Total TFA in obese women ↑ IL-6, CRP	Mozaffarian *et al.* (2004)[91]
Systemic inflammation	Randomised cross-over study in men (*n* 50)	↑ Total TFA ↑ CRP, E-selectin	Baer *et al.* (2004)[94]
Systemic inflammation	Double-blind, cross-over study in men and women (*n* 19)	↑ Total TFA ↑ IL-6, TNFα	Han *et al.* (2002)[33]
Systemic inflammation	Prospective cohort study in men and women (*n* 86)	↑ Erythrocyte 18 : 1 and 18 : 2 TFA levels ↑ TNFα and IL-6	Mozaffarian *et al.* (2004)[95]
Systemic inflammation	TFA-supplemented diet in mice	↑ Resistin mRNA ↓ Adiponectin and PPARγ	Saravanan *et al.* (2005)[74]

EA, elaidic acid; ↑, increase; ↓, decrease; VA, vaccenic acid; NHS, Nurses' Health Study; CRP, C-reactive protein.

enzyme[68,69]. It is speculated that a decrease in the functionality of the Δ-9-desaturase enzyme will decrease the conversion of VA to the anticancer fatty acid, CLA[56,58].

Evidence indicating no association between total and specific TFA isomer intake and breast cancer is presented in three case–control studies from Sweden, Italy and the USA[53,55,57]. These studies examined blood biomarkers of total and TFA isomers, including EA, but did not observe a relationship with breast cancer incidence in both pre- and postmenopausal women. In contrast, a recent case–control study (cases, *n* 363; controls, *n* 702) from the same group[53] found an increased risk for breast cancer with elevated serum phospholipid levels of *trans*-9-16 : 1 and *trans*, *trans*-18 : 2*n*-6[54].

The inconsistent findings suggest that many different factors including hormonal balance, intake of PUFA, genetic predisposition and Δ-9-desaturase function may play a role in modulating the effect of TFA on breast cancer development.

Potential mechanisms of action

The mechanism by which TFA may increase cancer risk is not established, but the incorporation of TFA into cell membrane phospholipids (PL) is a likely candidate. At the molecular level, changes in membrane composition may alter membrane-associated function[70]. Dietary TFA incorporated into the PL bilayer induces a structural change that alters cellular function[71–74]. A decrease in levels of *n*-3 PUFA in the plasma membrane of adipose tissue has been reported in mice fed TFA as 3 % of energy for 12 weeks[71]. A decrease in membrane content of *n*-3 PUFA including DHA (22 : 6*n*-3) is associated with an increase in cancer risk and a decline in membrane fluidity[71,75,76]. Reducing membrane fluidity has been associated with an increase in the activity of free radicals in the PL bilayer resulting in oxidative stress[77]. Also, TFA incorporation into adipocyte and endothelial cell membranes may alter the function of membrane-bound receptors and affect signalling cascades associated with inflammatory pathways[78,79]. Several studies have examined the effect of TFA exposure on oxidative stress and systemic inflammation (Table 5).

Trans-*fatty acids, oxidative stress and cancer development*

Oxidant stress and the generation of reactive oxygen species can interfere with various cellular mechanisms including those important in cell growth and regulation[80]. Reactive oxygen species can cause mutations in DNA, increase oncogene expression and markers of oxidative stress have been associated with cancerous tissue[81,82]. The mechanisms by which oxidative stress may influence carcinogenesis are discussed in greater detail by Klaunig & Kamendulis[83].

As mentioned, TFA may increase oxidant stress via their incorporation into cellular membrane PL[77]. Urinary and plasma F_2-isoprostanes are markers of oxidant stress[84]. In mice, a 7-week diet containing EA as 3 % energy resulted in an 18 % increase in plasma F_2-isoprostane levels and a significantly lowered (30 %) plasma vitamin E concentration[28]. The decrease in vitamin E is probably a response to the increase in oxidative stress from the high-TFA diet. Indeed, the elevated F_2-isoprostane levels agree with this speculation. In men and women (*n* 24), significantly elevated urinary F_2-isoprostane levels were observed after a 6-week, high-TFA diet (VA + *trans*-12-18 : 1; 2·56 % of energy) when compared with a placebo control group[85]. This dietary exposure is not outside of the predicted US consumption range[10,11]. Moreover, a recent study investigating lifestyle factors and their effect on oxidant stress collected TFA intake data via a FFQ from 1610 women and found that in both smokers and non-smokers, urinary F_2-isoprostane levels were positively associated with an increase in TFA intake[86]. Interestingly, a number of recent studies have observed the endogenous production of TFA via a radical stress-modulated pathway[87–89]. In rats challenged with carbon tetrachloride or 2,2′-azobis(2-amidinopropane) dihydrochloride to induce oxidative stress, formation of TFA was observed despite being fed a purified non-TFA diet. The authors point out that repeated free radical insults, such as those seen in

ageing, can cause endogenous isomerisation of *cis*-fatty acids to the *trans* formation. Indeed, in 30-month-old rats on a purified non-TFA diet, significant accumulation of TFA in the heart and kidney, but not erythrocytes and liver, was observed when compared with 4-month-old rats. In light of this novel endogenous TFA synthesis pathway, TFA cannot be avoided by simply removing them from the diet. As such, TFA tissue content may in fact reflect two pools from the diet and *de novo* synthesis. Whether dietary TFA exacerbates the effects of *de novo* synthesised TFA on oxidative damage requires further study.

Trans-*fatty acids, inflammation and cancer development*

Systemic inflammation is characterised by elevated plasma concentrations of cytokines such as TNFα and its associated receptors (TNF-R1 and TNF-R2), IL-6 and related inflammatory proteins such as C-reactive protein and E-selectin[46]. These markers of inflammation have been linked to many different types of cancer and a recent review examined this correlation and the potential mechanisms by which inflammation may increase cancer incidence[90]. Briefly, these cytokines have been shown to induce cellular transformation, and promote tumour growth, metastasis and angiogenesis. These effects are probably mediated through the transcription factors NF-κB and possibly PPARγ. Indeed, TFA intake is positively associated with biomarkers of inflammation but the specific mechanism of action is poorly understood (Table 5).

In the Nurses' Health Study, the average of two FFQ from 823 women was used to analyse intake of total TFA[91]. The relationship between TFA intake and markers of systemic inflammation was examined after adjusting for variables such as BMI, and *n*-6, *n*-3 and SFA intake. This study found that *trans*-18 : 1 and *trans*-18 : 2 fatty acids were positively associated ($P \leq 0{\cdot}001$) with serum levels of TNF-R1 and TNF-R2 when compared with the lowest quintile of TFA intake. Also, serum levels of C-reactive protein and IL-6 were positively associated with TFA intake in women with a high BMI. Of note, obesity is correlated with markers of systemic inflammation regardless of TFA intake[92]. Another study examining the Nurses' Health Study population used linear regression models to find that total TFA intake was significantly and positively correlated with plasma concentrations of C-reactive protein, IL-6, TNF-R2 and E-selectin[93]. This study also investigated the effect of specific TFA isomers on plasma markers of systemic inflammation and found that EA and *trans*, *trans*-18 : 2*n*-6 were both significantly and positively associated with TNF-R2 and E-selectin concentrations.

A diet-controlled, randomised, cross-over study in men (*n* 50) examining the effects of 8 % of energy from TFA on markers of systemic inflammation found significantly higher levels of C-reactive protein when compared with a carbohydrate diet (8·5 % of energy from fat replaced by carbohydrate)[94]. Although no significant effect was observed, E-selectin levels increased 5·6 % during the 5-week TFA treatment, suggesting that a longer study period may have allowed the investigators to observe a significant effect of the TFA diet on E-selectin levels[94]. A double-blind, 32 d, cross-over study (*n* 19) compared a stick-margarine diet at 6·7 % of energy from TFA *v.* a soyabean oil diet containing 0·6 % energy from TFA and found that TNFα and IL-6 were 58 and 36 % higher, respectively, in the high-TFA diet[33]. Considering the average intake of TFA in the USA, Canada and UK is 1–4 %, but may be as high as 10 %, the relative importance to the general population needs to be carefully considered[10–12].

In a prospective cohort study, the erythrocyte membrane content of TFA was used as a reflection of dietary intake in eighty-six men and women with established heart disease to investigate the effect of TFA consumption on markers of systemic inflammation[95]. After adjustment for variables including age, sex, BMI and smoking, erythrocyte membrane contents of 18 : 1 and 18 : 2 TFA isomers were both positively associated with elevated levels of TNFα and IL-6.

The mechanism behind the induction of systemic inflammation by TFA may be related to a number of factors. A recent study using human aortic endothelial cells observed a 2-fold higher incorporation of *trans*, *trans*-18 : 2*n*-6 into the vessel wall[96]. The increased incorporation of TFA resulted in an increase in monocyte and neutrophil adhesion producing an increase in the expression of proteins associated with inflammatory pathways. A study in rats fed either TFA diet 1 (3 % TFA + 2 % linoleic acid) or TFA diet 2 (3 % TFA + 4 % linoleic acid) observed a marked reduction in PPARγ and adiponectin (anti-inflammatory) and an increase in resistin (pro-inflammatory) mRNA, suggesting that effects of TFA may be mediated through transcriptional regulation of PPAR[74].

Overall, a high TFA intake is positively associated with markers of systemic inflammation and may promote cancer development via the modulation of transcription factors such as NF-κB and PPARγ.

Discussion

It should be noted that the present review is based on the published literature and does not include any unpublished results. There is the possibility of publication bias in which null or undesirable results are not reported. However, this may be unlikely given the range of publications that have reported positive and negative outcomes or no relationship related to TFA intake and cancer risk (Tables 2–4).

Out of nineteen case–control studies involving prostate, colon and breast cancers, thirteen studies observed that TFA was associated with increased cancer risk (three out of four prostate, five out of five colon and five out of ten breast). Although the findings from these case–control studies might suggest an association, case–control studies lack the ability to demonstrate whether exposure preceded cancer development. In contrast, the strongest evidence from large prospective studies, the 'gold standard', does not support the findings from the case–control studies. Three large (>10 000 subjects) prospective cancer studies of the prostate[35], colon[44] and breast[52] showed no relationship between TFA exposure and cancer risk; however, two large breast cancer cohort studies[54,56] observed a positive association between a specific TFA and cancer risk. The variability of findings may be attributed to methodology. Both FFQ and direct measurement of tissue or blood were used in the smaller case–control studies. However, only FFQ were used in the large cohort studies.

To investigate the relationship between TFA intake and human cancer risk, measures of food intake including FFQ and biochemical markers including adipose tissue biopsies, serum PL, erythrocyte PL and whole-blood TFA content were used as surrogate markers. There are a number of limitations associated with FFQ and the accurate quantification of TFA intake. First, considering there is no 'gold standard' for TFA exposure, a 'validated' FFQ cannot be properly validated. Although some FFQ have been verified as accurate when subjects are properly trained, changes in TFA content of different foods over time may result in errors of estimated TFA intake[97,98]. It is likely that food composition databases are incomplete and do not contain the levels of all TFA isomers. A FFQ also lacks the sensitivity to account for all variations in TFA levels even in the same product. For example, cooking oils used in several fast food restaurants in the USA contain up to 25 % TFA. In contrast, the oils used in the same restaurant in a European country may contain less that 10 % TFA[99]. Variation is also evident in naturally occurring *trans*-fats. Alterations in the ruminant diet can change the TFA profile of the resultant beef and dairy products[100,101]. Therefore it is difficult to estimate total and individual dietary TFA intakes with great accuracy when the TFA content in the food supply is variable. In addition, it is well known that the use of FFQ is potentially susceptible to potential interviewer bias, incorrect reporting of portion size, computational errors, incomplete food composition databases and alterations in dietary habits of subjects during the study[102,103].

Due to limitations associated with FFQ, analysis of adipose tissue and blood serum or plasma provides a more direct and accurate means of elucidating dietary TFA exposure[102]. Direct measurement by GC using long (100 m), highly polar capillary columns provides sensitive detection and quantification of individual *trans* isomers, but has only been used in two studies[98,104]. Most studies report the detection and quantification of total TFA or a limited number of TFA using simple GC methods and short capillary columns incapable of resolving the numerous TFA. Findings from studies that only report total TFA should be cautiously interpreted, as it may be potentially naive to assume all TFA have similar biological effects[13]. Although direct measurement of TFA in tissues and blood provides a quantitative measure of exposure, tissue levels of total or individual TFA cannot be used to establish causality. Therefore it is not possible to differentiate potential biological effects of individual TFA which may have independent, synergistic, or antagonistic effects relative to each other.

Approximately half of the studies (thirteen of twenty-seven human studies; Tables 2–4) investigated the relationship between specific TFA isomers and cancer risk using both FFQ and direct measurement by GC. The majority (nine out of thirteen) reported isomeric effects of TFA, suggesting that individual TFA may enhance cancer risk[5,37,41,48,49,51,53–58,60]. Specifically, EA, *trans*-9-16 : 1 and some polyunsaturated 18 : 2 *trans* isomers were associated with enhanced cancer risk. VA was associated with increased risk in one prostate[37] and two breast cancer studies[56,58] but was associated with decreased risk in one breast cancer study[51]. These studies demonstrate the need to distinguish between individual TFA in order to detect their effects on cancer risk. However, it is also clear that there is limited evidence from which to base any strong conclusions.

Another important consideration is the generalisability of the study results to humans. In particular, animal studies have utilised diets with wide-ranging levels of TFA from < 1 % to $+ 30$ % of energy (Table 1). However, average consumption of TFA in Europe, USA and Canada ranges from < 1 % to 4 % of energy[10–12]. Similarly, human studies have reported individuals with TFA intakes > 10 % of energy. However, such high intakes in these individuals probably reflect only a small proportion of the total population. For example, in Canadian men between the ages of 6 and 18 years, with the highest estimated intake of 11·6 g/d, this only represents 5 % of energy (based on an 8·4 MJ (2000 kcal) diet). At this level, this represents the 95th percentile of intake, in other words only 5 % of the population exceeds levels in excess of 11·6 g/d.

A potential interaction between TFA and genetic polymorphisms has been reported in only one study to date, but has shown the potential implication of understanding the genotype of patient populations[6]. If TFA are in fact shown to have an effect on cancer risk, genetic genotyping may have the potential to identify specific individuals who are susceptible to the effects of TFA. The consideration of genetic polymorphisms may help shed light on how varying TFA exposure affects cancer risk and also the variability of results in human studies. For example, at low levels of TFA, genotype may not affect cancer risk. However, the potential deleterious effects of TFA may be unmasked for a specific genotype at a higher level of intake. Therefore, genotyping provides the means to better stratify populations or groups of individuals who are responders or non-responders at specific exposure levels of TFA to properly assess risk. Without such prior stratification, and by random chance, several possibilities could occur including the recruitment of: (1) a mix of both non-responders and hyper-responders; (2) non-responders; or (3) hyper-responders resulting in no effect, no effect or a positive association, respectively.

If there is indeed a risk associated with TFA intake, there is also the need to establish causality. Although there are some mechanistic reports suggesting that TFA may affect gene expression, cell membrane function and inflammation, there is clearly an insufficient amount of evidence to make any conclusions (Table 5).

Conclusion and future directions

The role of TFA in prostate, breast and colon cancer across different experimental models and human studies remains inconclusive. Although a number of studies have evaluated the individual effects of individual TFA, human and animal studies have shown both positive and negative associations with specific and total TFA exposure. Therefore it is not possible to determine whether this effect is truly real and whether in fact a specific TFA enhances or protects against cancer. These conflicting results are difficult to reconcile given the variability of animal experimental designs and methodological approaches used in human studies. Furthermore, it cannot be ruled out that TFA intake or tissue levels is simply a marker of an unhealthy lifestyle, which increases the risk for cancer[105–108].

The accumulation of experimental data and approaches has helped to frame future studies to better understand the role of TFA in health and disease. Studies in which total TFA is measured by FFQ or simple GC methods are not useful and future studies require careful analytical analysis of individual TFA using long GC columns. Studies have also focused primarily on monoene isomers of TFA and there is a need to better understand the role of polyunsaturated TFA which have been correlated with prostate cancer and breast cancer incidence as well as systemic inflammation. Recent human studies in prostate cancer highlight the need to consider the potential interaction between genetic polymorphisms and TFA on cancer risk. There is also the need to better understand the true risk to the general population consuming 1–4 % of energy and the small segment of the population consuming > 10 % of energy from TFA. Mechanistic studies are needed to substantiate the effects of TFA leading to enhanced cancer risk. The present review has focused on TFA and the risk associated with developing cancer; however, the present review does not address whether there are any potential effects of TFA on pre-existing cancers for which there is very limited information[109–111] and another important area for further research.

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