Lead Article

Dietary trans-fatty acid intake in relation to cancer risk: a systematic review and meta-analysis

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Context: *Apart from ruminant fat, trans-fatty acids are produced during the partial hydrogenation of vegetable oils, (eg, in the production of ultraprocessed foods). Harmful cardiovascular effects of trans-fatty acids are already proven, but the link with cancer risk has not yet been summarized.* ***Objective:*** *A systematic review (following PRISMA guidelines) – including observational studies on the association of trans-fatty acid intake with any cancer risk – was conducted, with no limitations on population types.* ***Data Sources:*** *The electronic databases PubMed and Embase were searched to identify relevant studies.* ***Data Extraction:*** *This systematic review included 46 articles. Quality was assessed via the Newcastle-Ottawa scale. Meta-analyses were conducted if at least 4 articles exploring the same transfat-cancer pairings were found.* ***Data analysis:*** *Nineteen cancer types have been researched in cohort and case-control studies on trans-fatty acids, with breast cancer (n = 17), prostate cancer (n = 11), and colorectal cancer (n = 9) as the most researched. The meta-analyses on total trans-fat showed a significant positive association for prostate cancer (odds ratio [OR] 1.49; 95%CI, 1.13–1.95) and colorectal cancer (OR 1.26; 95%CI, 1.08–1.46) but not for breast cancer (OR 1.12; 95%CI, 0.99–1.26), ovarian cancer (OR 1.10; 95%CI, 0.94–1.28), or non-Hodgkin lymphoma (OR 1.32; 95%CI, 0.99–1.76). Results were dependent on the fatty acid subtype, with even cancer-protective associations for some partially hydrogenated vegetable oils. Enhancing moderators in the positive transfat-cancer relation were gender (direction was cancer-site specific), European ancestry, menopause, older age, and overweight.* ***Conclusion:*** *Despite heterogeneity, higher risk of prostate and colorectal cancer by high consumption of trans-fatty acids was found. Future studies need methodological improvements (eg, using long-term follow-up cancer data and intake biomarkers). Owing to the lack of studies testing trans-fatty acid subtypes in standardized ways, it is not clear which subtypes (eg, ruminant sources) are more carcinogenic.* ***Systematic Review Registration:*** *PROSPERO registration no. CRD42018105899*

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INTRODUCTION

Cancer is one of the most common diseases worldwide and diet is probably the key modifiable risk factor.[1,2] In current society, energy-dense ultraprocessed foods are highly consumed[3] but are often less healthy. A 5-year prospective study involving 104 980 participants showed that a 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of more than 10% in risks of overall and breast cancer.[4] As the associations remained significant after adjustment for BMI, energy, and macronutrient content, the authors concluded that further studies are needed to better understand the relative effect of the various dimensions of food processing.

One of the health-deteriorating outcomes of industrial evolutions in food processing are trans-fatty acids (TFAs). TFAs are fatty acids with nonconjugated double bonds (at least one) in transconfiguration and are abundant in ultraprocessed foods.[5,6] During this process of partial hydrogenation of vegetable (and sometimes fish) oils, hydrogen is added to polyunsaturated fatty acids. By using a metal catalyst, the amount of double bonds is reduced so as to create an unsaturated fatty acid with a double bond in transconfiguration, thereby transforming liquid oils to a semisolid state at room temperature, which thus prolongs the shelf life.[7] The major dietary sources of trans-fats can be found in high-fat products such as industry-processed foods (eg, cakes, cookies, crackers, margarine, fried potatoes, potato chips, popcorn, and household shortening) as well as animal products (eg, meat and dairy).[8–12] However, it should be noted that the main sources of trans-fats may differ slightly between cultures and geographical regions. The TFAs of vegetable oils are most likely C18:1Δ9t (elaidic acid) and somewhat less frequently C16:1Δ9t (trans-palmitoleic acid) and C18:2Δ9t12t (linolelaidic acid).[13] TFAs of fish oils are a complex mixture of fatty acids of different chain lengths, mainly varying between 14 and 24 carbon atoms, eg, C20:1, 20:2, 22:1, and 22:2. TFAs can also be found in natural ruminant fat (and milk) as they are formed by enzymes during hydrogenation in the rumen of animals such as cows or sheep. TFAs of animal origin are most likely C18:1Δ11t, called trans-vaccenic acid, and generally represent a lower proportion of TFA intake than industrial TFAs, although this is now changing with the new legislation to limit industrial TFAs.[14]

In the human body, TFAs cannot be synthesized and they are not required in the diet.[15] In fact, TFAs can be involved in disease development such as cardiovascular disease and type 2 diabetes[16–19] but probably also cancer[20–23] owing to their pro-inflammatory properties and their inhibitory effects on the metabolism of the essential omega-3 and omega-6 polyunsaturated fatty acids. Therefore, several countries have already implemented strict rules to limit and/or ban TFAs in the food chain; for example, Denmark was, in 2003, the first country to legislate on the production and importation of foods with fatty acids.[24] Based on a systematic review including studies from 1995 to 2017,[11] 22 out of 29 countries showed a mean TFA intake below the World Health Organization (WHO)-recommended 1% of total energy.[25] Both industrialized countries (eg, Canada and the United States) and less developed countries (eg, Iran and Lebanon) can be found in the group with an intake above 1%. Even after a legislation to limit or ban industrial TFAs, potential long-term health effects may exist as cancer has a long latency period and fat is stored in the body, and still other forms, such as ruminant TFAs, can be present in food.

The aim of this systematic review was to examine the link between TFA intake and cancer development in humans (see Table 1 for PICOS [population, intervention, comparison, outcome, and study design] criteria). Because of the epidemiological viewpoint, this review will not consider cancer progression or survival. Apart from a general overview, this review aims to describe differential effects due to subtypes/origin of TFA, vulnerability factors in the population (moderation), and methodological study quality, as well as implications for future research and public health. A meta-analysis was conducted for those TFA-cancer pairings for which four or more articles were found. The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines were followed (Appendix S1; *please see the Supporting Information online*).

METHODS

Search methods for identification of studies

PudMed and Embase databases were last searched by two researchers on March 22, 2020, with no limitations on language or date of publication. As can be found in Table 2, the two key words used in the searches were neoplasm and TFA. The PubMed search was established using free terms instead of only MeSH (medical subject heading) terms as otherwise relevant articles could be missed (pure MeSH terms resulted in only 32 hits). In Embase, other spelling formats of "trans fatty acids" and the use of "carcinogen" (next to neoplasm) did not result in more hits.

The articles were uploaded into EndNote. After removal of the duplicate articles, two independent authors selected articles, based first on title, then abstract, and

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Criteria
Participants	No limitations in sociodemographic characteristics (eg, age, origin) In cohort studies: participants should have no cancer at the outset as the article's focus of interest is in cancer development In case-control studies: the study population should consist of cancer participants and healthy controls
Intervention/exposure	Dietary TFA intake or TFA blood/tissue levels were considered as predisposing factors. In indicating the position of the trans-bond, the carbon of the carboxyl group was considered first, using the delta system. Conjugated linoleic acid was excluded from the TFA definition.[26]
Comparison	TFA intake as continuous or categorized (eg, tertile, quartile, quintile) variable
Outcome	Cancer diagnosis: overall cancer or specific cancer type Nonmalignant abnormalities (eg, adenomas) were not considered. There was no fixed limit for follow-up length.
Study design	Observational studies such as (nested) case-control studies and prospective cohort studies were included. Interventional studies were not found, probably owing to an ethical conflict. In-vitro studies, animal studies, editorials, and reviews were excluded.

Abbreviation: TFA, trans-fatty acid

Table 2 **Terms used in the PubMed and Embase database searches**

Database	Search terms used
PubMed	("neoplasms"[MeSH Major Topic] OR "neoplasm"[Title/Abstract] OR "cancer"[Title/Abstract]) AND ("trans"[Title/Abstract] AND ("fatty acids"[All Fields] OR "fatty acid"[Title/Abstract] OR "fat"[Title/Abstract]) OR ("vaccenic"[All Fields] OR "elaidic"[All Fields]) OR "trans fatty acids"[Majr])
Embase	"malignant neoplasm"/exp AND "trans fatty acid"/exp

then on full text. When a disagreement occurred, both authors read the full text again and then made a well-considered decision after discussion with a third author (I.H.).

Data collection and risk of bias assessment

The following descriptive data of interest were retrieved by one reviewer: cancer type, study design, country, name of study, method of TFA assessment (and isomer if specified), sample size, age of participants, exclusion criteria, duration of follow-up, and tested confounding factors. Summary measures of interest were odds ratio (OR), hazard ratio, or relative risk. If multiple summary measures were available, the measure with maximal adjustment for confounders was chosen (as there was no standard set of confounders used across the articles).

The Newcastle-Ottawa scale was developed to assess the quality of nonrandomized studies and analyzes risk of bias.[27] Based on 9 multiple-choice questions grouped in the 3 subscales selection, comparability, and exposure (for case-control)/outcome (for cohorts), 9 points could be awarded for a high-quality study. To identify other risks of bias, further information on the principal study (to identify articles originating the same cohort) and split/merged analyses (to identify selective reporting) was noted.

Meta-analysis

A meta-analysis was only performed for TFA-cancer relations that were examined in at least four articles (independent of the TFA measurement methodology adopted). In total, 12 meta-analyses were performed using the most adjusted risk estimate (subpopulation risk estimates were considered if articles did not report an overall risk estimate). Pooled risk estimates were obtained for each cancer site and TFA type individually using random-effects models. Heterogeneity between studies was assessed using the I^2 statistic as a measure of the proportion of total variation in estimates that was due to heterogeneity.[28] I^2 values of 25%, 50%, and 75% corresponded to cutoff points for low, moderate, and high degrees of heterogeneity. For meta-analyses including at least 10 measures, Egger's test results were reported (significant test reflects risk for publication bias).

RESULTS

Results of the search

Figure 1 shows the literature search process. The PubMed and Embase search strings identified 618 articles after exclusion of duplicates, of which 46 articles were included in the final meta-analysis.

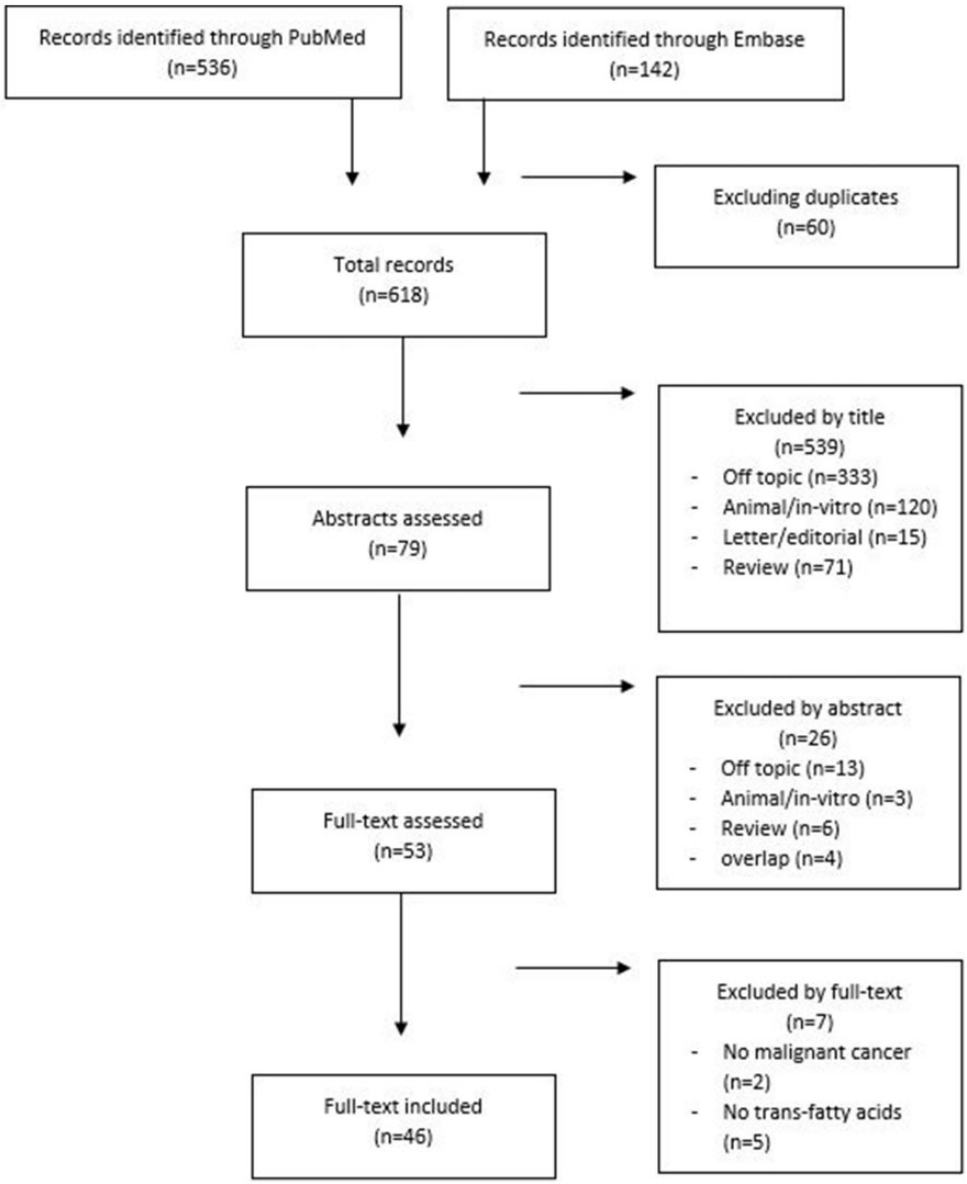

Figure 1 **Flow diagram of the literature search process**

Descriptive data of included studies

Descriptive data of all included studies are shown in Table 3. Articles were published between 1999 and 2020. There were 16 prospective studies, 15 case-control studies, and 15 nested case-control or case-cohort studies. Studies were mainly US or Europe based, but continental ancestry (or "race") was often considered. The Nurses' Health Study was the most often used cohort[29–38] and resulted in partial population overlap between articles with the same TFA-cancer analyses (eg, [29,31,34,38]). Sample sizes mostly ranged between 200 and 2000. The youngest age of participants was 17 years, but studies mostly involved older adults. The follow-up ranged between 3 and 30 years. Most articles examined overall TFA intake, but several articles also considered TFA subtype[20–22,33,39–52] and 1 article distinguished by TFA origin (fish oil, vegetable oil, ruminant fat).[53] TFA intake was most often examined by means of a dietary questionnaire, but 4 studies used erythrocyte concentration (for breast and myeloma),[33,44,47,54] 6 serum (for breast and prostate cancer),[21,39,41,42,45,48] 4 plasma (for breast, pancreatic, and prostate cancer, and myeloma),[40,50,51,55] 1 whole blood (for prostate cancer),[20] and 2 adipose tissue (for breast cancer).[56,57]

Nineteen cancer types were researched from cohort and case-control studies. In descending order, these were as follows: breast cancer (n = 17; 18 192 cases), prostate cancer (n = 11; 9081 cases), colon/rectal cancer

Table 3 **Descriptive data for all 46 included studies**

Cancer	Author,year	Country	Study name	Study design	TFA method	Age (y)mean±SD or min-max(case-controls)	No. of case-controls	NOS score, 0–9	Follow-up years
Bladder Brain Breast Colon Kidney Leukemia Lung NHL Ovarian Pancreatic Prostate Rectal Stomach Testis	Hu (2011)[59]	Canada	Canadian National Enhanced Cancer Surveillance System (NECSS)	CC	FFQ (total)	62.5±9.7 49.9±14.4 55.7±11.4 62.6±9.7 58.7±10.6 57.1±13.2 62.8±8.6 57.3±12.3 55.0±12.3 61.6±9.5 66.3±6.0 61.6±9.6 61.9±9.9 36.9±10.0 57.1±13.4	Bladder: 1029 Brain: 1009 Breast: 2362 Colon: 1727 Kidney: 1345 Leukemia: 1069 Lung: 3341 NHL: 1666 Ovarian: 442 Pancreatic: 628 Prostate: 1799 Rectal: 1447 Stomach: 1182 Testis: 686 Controls: 5039	6	3
All cancer Bladder Breast Central nervous Cervix Colon Endometrial Kidney Leukemia Lung Melanoma Mouth/pharynx Multiple myeloma NHL Nonmelanoma skin Ovarian Pancreatic Prostate Rectal Stomach	Laake (2013)[53]	Norway	Norwegian Counties Study	Pro	FFQ (fish oil, vegetable oil, ruminant fat)	17–49 (mean = 41)	All cancer: 12004 Bladder: 556 Breast: 1397 Central nervous: 464 Cervix: 181 Colon: 990 Endometrial: 449 Kidney: 277 Leukemia: 200 Lung: 1226 Melanoma: 461 Mouth/pharynx: 233 Multiple myeloma: 189 NHL: 431 Nonmelanoma skin: 257 Ovarian: 316 Pancreatic: 320 Prostate: 1848 Rectal: 656 Stomach: 398 Controls: 65 564	8	24.8

(continued)

Table 3 **Continued**

Cancer	Author,year	Country	Study name	Study design	TFA method	Age (y)mean±SD or min-max(case-controls)	No. of case-controls	NOS score, 0–9	Follow-up years
Breast	Byrne (2002)[31]	USA	Nurses' Health Study (NHS)	Pro	FFQ (total)	56.8±5.5	Breast: 1071 Controls: 43 626	5	14
Breast	Farvid (2014)[32]	USA	Nurses' Health Study II (NHSII)	Pro	FFQ (total)	36.4±4.6	Breast: 2830 Controls: 85 974	5	20
Breast	Hirko (2018)[33]	USA	Nurses' Health Study II (NHSII)	Nested CC	Erythrocytes (total, industrial TFA, 16:1Δ9t, 18:1t, 18:2t, 18:2Δ9t12t)	44.7±4.5 44.8±4.4	Breast: 794 Controls: 794	8	8
Breast	Kohlmeier (1997)[56]	Switzerland, Spain, Ireland, Germany, the Netherlands	European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer	CC	Adipose tissue (total)	62.2±6.1 61.7±5.9	Breast: 209 Controls: 407	6	NS
Breast	London (1993)[57]	USA	Postmenopausal women from 5 Boston area hospitals	CC	Adipose tissue (total) FFQ (total)	36–93, median=61	Breast: 402 Controls: 597	8	NS
Breast	Pala (2001)[44]	Italy	Hormones and Diet in the Etiology of Breast Cancer Risk (ORDET) cohort	Nested CC	Erythrocytes (18:1Δ9t)	58.1±5.4 57.1±5.3	Breast: 71 Controls: 141	6	5.5
Breast	Rissanen (2003)[45]	Finland	Mobile Clinic Health Examination Survey	Nested CC	Serum (trans-MUFA, 18:1Δ11t)	49.0±14.3 49.0±14.3	Breast: 127 Controls: 242	6	18
Breast	Sczaniecka (2012)[46]	USA	VITamins And Lifestyle (VITAL) cohort	Pro	FFQ (total, 18:1Δ9t, 18:2t)	50–76	Breast: 772 Controls: 29 480	6	6
Breast	Shannon (2007)[47]	China	Breast self-examination (BSE) cohort	Nested CC	Erythrocytes (18:1Δ11t)	35–63	Breast: 330 Controls: 1038	6	11

(continued)

Table 3 **Continued**

Cancer	Author,year	Country	Study name	Study design	TFA method	Age (y)mean±SD or min-max(case-controls)	No. of case-controls	NOS score, 0–9	Follow-up years
Breast	Takata (2009)[48]	USA	β-Carotene and Retinol Efficacy Trial (CARET) Cohort	Nested CC	Serum (16:1t, 18:1Δ9t, total 18:1t, 18:2Δ9t, 18:2Δ12t, 18:2Δ9t12t, total 18:2t)	58.6±5.1 58.6±5.4	Breast: 130 Controls: 257	7	14
Breast	Voorrips (2002)[81]	The Netherlands	The Netherlands Cohort Study on Diet and Cancer (NLCS)	Case-cohort	FFQ (total, 18:1Δ11t)	55–69	Breast: 941 Controls: 1598	5	6.3
Breast	Chajès (2008)[41]	France	E3N Study (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale) French component of EPIC	Nested CC	serum (16:1Δ9t, 18:1Δ9t, 18:2Δ9t12t, total trans-MUFA)	56.8± 6.356.8±6.3	Breast: 363Controls: 702	7	7
Breast	Chajès (2017)[40]	Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK	European Prospective Investigation into Cancer and Nutrition (EPIC) study	Nested CC	Plasma (16:1Δ9t, 18:1Δ9t, 18:1Δ11t, total ruminant TFA, total industrial TFA)	53.94±8.17 53.95±4.23	Breast: 2982 Controls: 2982	7	11.5
Breast	Linos (2010)[35]	USA	Nurses' Health Study II (NHS II)	Pro	FFQ (total)	34–53	Breast: 455 Controls: 39 268	6	7.8
Breast	Holmes (1999)[34]	USA	Nurses' Health Study (NHS)	Pro	FFQ (total)	30–55	Breast: 2956 Controls: 85 839	7	14

(continued)

Table 3 **Continued**

Cancer	Author,year	Country	Study name	Study design	TFA method	Age (y)mean±SD or min-max(case-controls)	No. of case-controls	NOS score, 0–9	Follow-up years
Colorectal	Kato (2010)[82]	USA	Luminal lipid exposure, genetics and colon cancer risk	CC	FFQ (total)	62 63	Colorectal: 1163 Controls: 1501	6	NS
Colorectal	Theodoratou (2007)[83]	UK	Study Of Colorectal Cancer in Scotland (SOCCS)	CC	FFQ (total)	63.9±9.64 64.7±9.53	Colorectal: 1455 Controls: 1455	6	7
Colorectal	Limburg (2008)[43]	USA	Iowa Women's Health Study	Pro	FFQ (total , 18:1t , 18:2t)	55–69	Colorectal: 1229 Controls: 33 987	7	18
Colorectal	Nkondjock (2003)[84]	Canada	N.S. (5 major francophone teaching hospitals of the Réseau Interhospitalier de Cancérologie de l'Université de Montréal)	CC	FFQ (total)	35–79	Colorectal: 402 Controls: 668	5	NS
Colon	Slattery (2001)[91]	USA	Kaiser Permanente Medical Care Program of Northern California	CC	FFQ (total)	30–79	Colon: 1993 Controls: 2410	5	NS
Colorectal	Vinikoor (2009)[60]	USA	North Carolina Colon Cancer Study I (NCCCS I)	CC	FFQ (total)	Whites: 65.06±9.70 66.16±9.30 African-Americans: 62.04±10.32 65.94±9.63	Whites: colorectal: 341 controls: 606 African-Americans: colorectal: 282 - controls: 414	5	4

(continued)

Table 3 **Continued**

Cancer	Author,year	Country	Study name	Study design	TFA method	Age (y)mean±SD or min-max(case-controls)	No. of case-controls	NOS score, 0–9	Follow-up years
Colorectal (distal)	Vinikoor (2010)[92]	USA	North Carolina Colon Cancer Study II (NCCCS II)	CC	FFQ (total)	Whites: 62.66±10.13 64.12±9.76 African-Americans: 61.28±9.91 63.16±9.63	Whites: distal colorectal: 717 controls: 799 African-Americans: distal colorectal: 233 - controls: 159	5	5
Myeloma	Jurczyszyn (2014)[54]	Poland	N.S. (University Hospital in Krakow)	CC	Erythrocytes (total)	61 52	Myeloma: 43 Controls: 21	4	NS
Myeloma	Jurczyszyn (2015)[55]	Poland	N.S. (University Hospital in Krakow)	CC	Plasma (total)	N.S. 57	Myeloma: 60 Controls: 60	4	NS
Non-Hodgkin lymphoma	Bertrand (2017)[30]	USA	Health Professionals Follow-Up Study (HPFS) and Nurses' Health Study (NHS)	Pro	FFQ (total)	HPFS: 54.3±9.8 NHS: 46.7±7.2	NHL: 1802 Controls: 134 327	6	24-30
Non-Hodgkin lymphoma	Charbonneau (2013)[85]	USA	N.S. (Mayo Clinic)	CC	FFQ (total)	60.9±12.3 60.1±13.7	NHL: 603 Controls: 1007	5	6
Non-Hodgkin lymphoma	Zhang (1999)[37]	USA	Nurses' Health Study (NHS)	Pro	FFQ (total)	30–55	NHL: 199 Controls: 88 211	7	14
Ovarian	Genkinger (2006)[86]	North America and Western Europe	The Pooling Project of Prospective Studies of Diet and Cancer: 12 prospective studies	Pro	FFQ (total)	25–100	Ovarian: 2132 Controls: 551 085	6	7–22
Ovarian	Gilsing (2011)[87]	The Netherlands	Netherlands Cohort Study	Case-cohort	FFQ (total)	61.8±4.3 61.4±4.3	Ovarian: 340 Controls: 2161	5	16.3
Ovarian	Bertone (2002)[29]	USA	Nurses' Health Study (NHS)	Pro	FFQ (total)	30–55 (mean 46.2)	Ovarian: 301 Controls: 79 957	6	12
Ovarian	Merritt (2014)[88]	USA	New England Case-Control (NECC) study	CC	FFQ (total)	52.5±12.3 52.4±12.5	Ovarian: 1872 Controls: 1978	5	14

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Table 3 **Continued**

Cancer	Author,year	Country	Study name	Study design	TFA method	Age (y)mean±SD or min-max(case-controls)	No. of case-controls	NOS score, 0–9	Follow-up years
Ovarian	Rice (2019)[38]	USA	Nurses' Health Study (NHS), Nurses' Health Study II (NHSII)	Pro	FFQ (total)	25–55	Ovarian: 896 Controls: 133 947	8	2820
Pancreatic	Matejcic (2018)[51]	Europe	European Prospective Investigation into Cancer and Nutrition (EPIC) study	Nested CC	Plasma (ruminant, industrial, C18:1Δ9/12t 4, C18:1Δ11t)	35–70	Pancreatic: 375 Controls: 375	7	11.7
Pancreatic	Michaud (2003)[36]	USA	Nurses' Health Study (NHS)	Pro	FFQ (total)	30–55	Pancreatic: 178 Controls: 88 624	5	18
Pancreatic	Thiébaut (2009)[49]	USA	National Institutes of Health–AARP (NIH-AARP) Diet and Health study	Pro	FFQ (total, 16:1t, 18:1t, 18:2t)	50–71	Pancreatic: 1337 Controls: 524 136	6	7.2
Prostate	Chavarro (2008)[20]	USA	Physician Health Study	Nested CC	Whole blood (total, 16:1Δ9t , 18:1Δ6t, 18:1Δ9t, 18:1Δ11t, C18:2Δ9t12t, 18:2Δ9c12t, 18:2Δ9t12c)	58 58	Prostate: 476 Controls: 476	7	13
Prostate	King (2005)[21]	USA	Beta-Carotene and Retinol Efficacy Trial (CARET)	Nested CC	Serum (16:1Δ9t, 16:1Δ7t, 18:1Δ8t, 18:1Δ9t, 18:1Δ10t, 18:1Δ11t, 18:1Δ12t, total 18:1t, 18:2Δ9c12t 18:2Δ9t12c, 18:2Δ9t12t, total 18:2t)	Cases: n =39 <55, n=69 55–59, n=74 60–64, n=90 >65 Controls: n=64 <55, n=113 55–59, n=111 60–64, n=138 >65	Prostate: 272 Controls: 426	8	4

(continued)

Table 3 **Continued**

Cancer	Author,year	Country	Study name	Study design	TFA method	Age (y)mean±SD or min-max(case-controls)	No. of case-controls	NOS score, 0–9	Follow-up years
Prostate	Liss (2019)[52]	USA	San Antonio Biomarkers of Risk for Prostate Cancer (SABOR)	Pro	FFQ (total, 16:1t, 18:1t, 18:2t)	61.7±8.2 58.7±9.3	Prostate: 229 Controls: 1674	8	10
Prostate	Liu (2007)[22]	USA	N.S. (Cleveland, Ohio)	CC	FFQ (total, 16:1t, 18:1t, 18:2t)	65.7±8.2 65.6±8.3	Prostate: 506 Controls: 506	6	NS
Prostate	Brasky (2011)[39]	USA	Prostate Cancer Prevention Trial	Nested CC	Serum (16t, 18:1t, 18:2t,)	Prostate: low-grade: 63.6±5.5 high-grade: 65.0±5.9 Controls: 63.6±5.6	Prostate: 1658 Controls: 1803	8	7
Prostate	Cheng (2013)[42]	USA	Carotene and Retinol Efficacy Trial (CARET)	Nested CC	Serum (16:1t, 18:1t, 18:2t)	60.4±5.7 60.3±5.8	Prostate: 641 Controls : 1398	8	9
Prostate	Neuhouser (2007)[89]	USA	Carotene and Retinol Efficacy Trial (CARET)	Pro	FFQ (total)	60.4± 5.858.0±6.1	Prostate: 890 Controls: 11 110	6	11
Prostate	Schuurman (1999)[90]	The Netherlands	The Netherlands Cohort Study (NLCS)	Case-cohort	FFQ (total)	63.9±3.8 61.4±4.2	Prostate: 642 Controls: 1525	5	6.3
Prostate	Ukoli (2010)[50]	USA-Nigeria	N.S. (Southern Nigeria and the USA)	CC	Plasma (total, 16:1Δ9t, 18:1Δ9t)	African-Americans: 56.9±9.8 Nigerians: 60.1±14.0	African-Americans: Prostate: 48 Controls: 96 Nigerians: Prostate: 66 Controls: 226	7	NS

Abbreviations: CC, case-control; FFQ, food frequency questionnaire; MUFA, monounsaturated fatty acid; NHL, non-Hodgkin lymphoma; NOS, Newcastle-Ottawa-Scale total score (0-9); NS, not specified; pro, prospective cohort; SD, standard deviation; TFA, trans-fatty acids.

(n = 9; 12 635 cases), ovarian cancer (n = 7; 6229 cases), pancreatic cancer (n = 5; 2838 cases), non-Hodgkin lymphoma (NHL) (n = 4; 4701 cases), kidney cancer (n = 2; 1622 cases), lung cancer (n = 2; 4567 cases), bladder cancer (n = 2; 1585 cases), stomach cancer (n = 2; 1580 cases), brain or central nervous system cancer (n = 2; 1473 cases), leukemia (n = 2; 1269 cases), testis cancer (n = 1; 686 cases), melanoma (n = 1; 461 cases), endometrium cancer (n = 1; 449 cases), nonmelanoma skin cancer (n = 1; 257 cases), mouth/pharynx/esophagus cancer (n = 1; 233 cases), multiple myeloma (n = 1; 189 cases), and cervix cancer (n = 1; 181 cases).

Results on the study quality are shown in Table 3 and detailed results in Table S1 (*please see the Supporting Information online*). None of the studies obtained the maximum score of 9 on the Newcastle-Ottawa scale; most studies scored 6 (n = 15) or 5 (n = 12), and the remaining studies scored 7 (n = 10), 8 (n = 7), and 4 (n = 2). The most common bias risks were a low follow-up/response rate (only 12 studies scored a star, increasing attrition bias) and the use of a food frequency questionnaire instead of a biomarker to estimate TFA intake (increasing detection bias). A strength was that almost all studies considered age (n = 41) and many adjusted for BMI/energy intake (n = 36). Occasionally, selective reporting may have occurred as some studies only reported split analyses (eg, on severity of the cancer, on sex, and on origin; Table S2 – *please see the Supporting Information online*) without reporting the overall population effect size or showing significant interaction.

Data on the tested hypothesis

Table S2 (*please see the Supporting Information online*) shows the outcome measures (OR, hazard ratio, relative risk), interpretation, and used confounders for all included studies. In descending order, the most often used confounders in those studies were age, total energy intake, BMI, alcohol consumption, smoking, continental ancestry (ie, race), physical activity, menopause, age at menarche, height, educational level, family history, and parity. A summary of results per cancer-TFA subtype, based on trend values, is shown in Table S3 (*please see the Supporting Information online*). Still, comparisons are difficult because of different TFA exposure assessment methodologies (diet, adipose tissue, different blood compartments), lack of specific TFA isomer descriptions (eg, "C18:1t" with no further specification in the case of elaidic and trans-vaccenic acid), different populations (eg, studies involving only subpopulations based on smoking status, menopausal status, and continental ancestry), and different statistical analyses (eg, predictor categorization cutoffs, summary measures, and confounders).

Significant positive associations with total TFA intake were found in 14 of the 48 analyses (Table S3; *please see the Supporting Information online*). Meta-analysis was only performed for specific TFA-cancer relations that were examined in at least 4 articles. The meta-analyses on total TFA intake showed a significant positive association for prostate (OR 1.49; 95%CI, 1.13–1.95) and colorectal cancer (OR 1.26; 95%CI, 1.08–1.46) but not for breast cancer (OR 1.12; 95%CI, 0.99–1.26), ovarian cancer (OR 1.10; 95%CI, 0.94–1.28), or NHL (OR 1.32; 95%CI, 0.99–1.76) (Figure 2). Based on I^2, heterogeneity was moderate and for NHL even very high. An Egger's *P*-value equal to 0.300 and 0.312 for breast and prostate cancer, respectively, did not suggest publication bias (not examined in associations with fewer than 10 studies).

Differential effects were found when investigating TFA subtypes (Table S3; *please see the Supporting Information online*). Significant positive associations were sometimes found for C16:1t (n = 4/7), C18:2t (n = 5/12), C18:1Δ9t (ie, elaidic acid; n = 3/11), ruminant TFA (n = 5/21 or 2/7 for trans-vaccenic acid specifically, except a significant inverse association with myeloma), and partially hydrogenated fish oil (2/19, except a significant inverse association with bladder and prostate cancer). In contrast, articles that used TFA from partially hydrogenated vegetable oil as a group (without specifying the chemical structure, but which theoretically should mainly contain elaidic acid) found often nonsignificant results (n = 14/19) or even a significant inverse association with cancer risk (n = 5/19).[53] The 7 meta-analyses on TFA subtypes (Figure 3) were in approximate agreement with the meta-analysis results on total TFA intake: some significant findings for prostate cancer but not significant for breast cancer. Indeed, prostate cancer showed a significant positive association with C18:1Δ9t (OR 1.23; 95%CI, 1.11–1.37) and C16:1t (OR 1.21; 95%CI, 1.07–1.37) but not with C18:1t or C18:2t. The level of heterogeneity (I^2) was very low for the 2 significant findings while high for the other 5 analyses. These findings should be interpreted with caution since the number of studies and the sample sizes were low. For the association of C18:1Δ9t with prostate cancer, the results were largely based on one study (with a weight of 86.7%).

Moderation analysis, as tested by significant interaction, is relevant for identifying high-risk groups. Gender is a classic moderator (based on significant interaction): women were found to be more vulnerable to health-deteriorating TFA associations (for nervous system and colon cancer), although health-beneficial associations for fish TFAs (for lung cancer) and ruminant

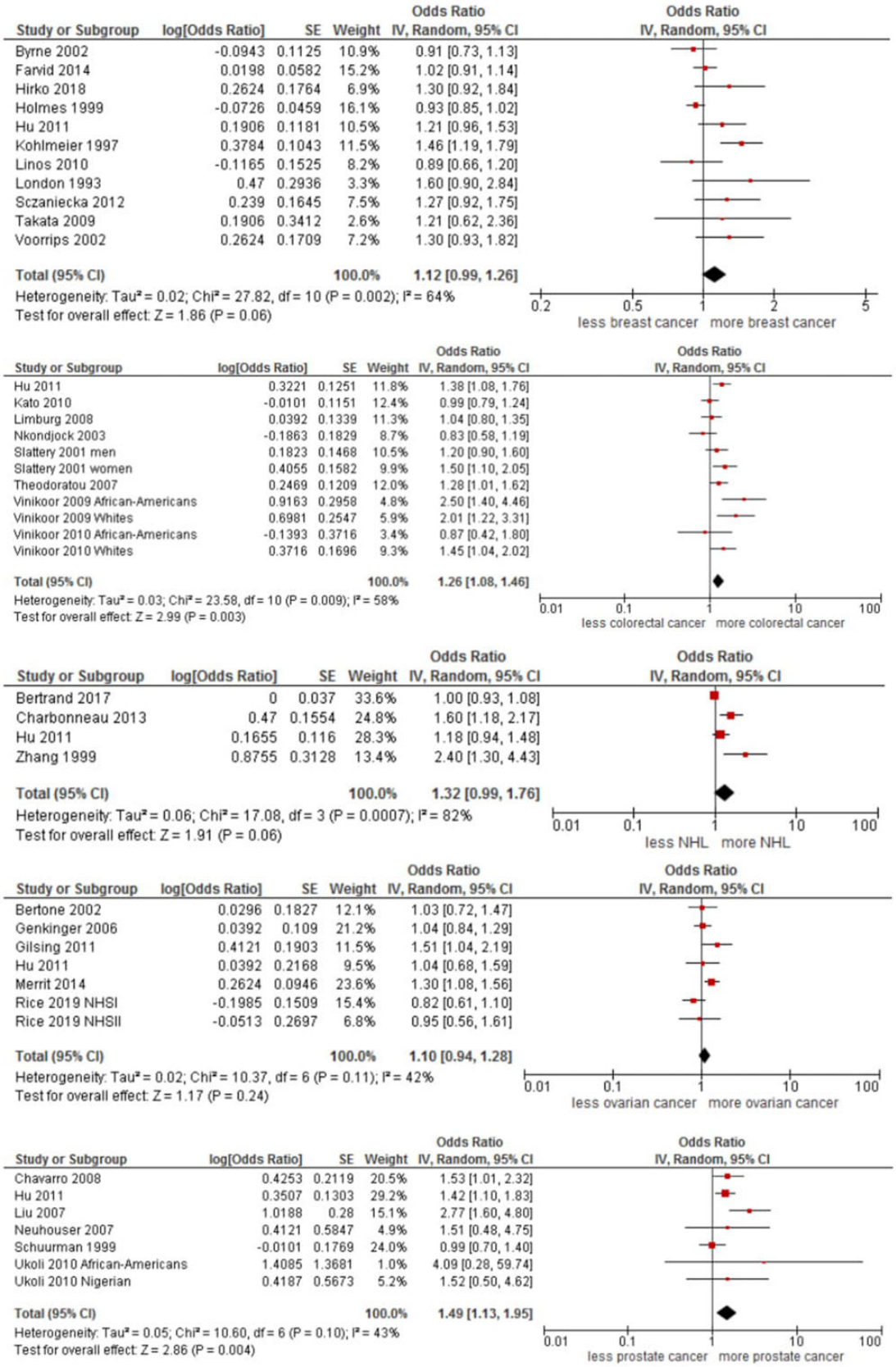

Figure 2 **Meta-analysis for total trans-fatty acids and cancer subtypes: breast cancer, colorectal cancer, non-Hodgkin lymphoma (NHL), ovarian cancer, prostate cancer**

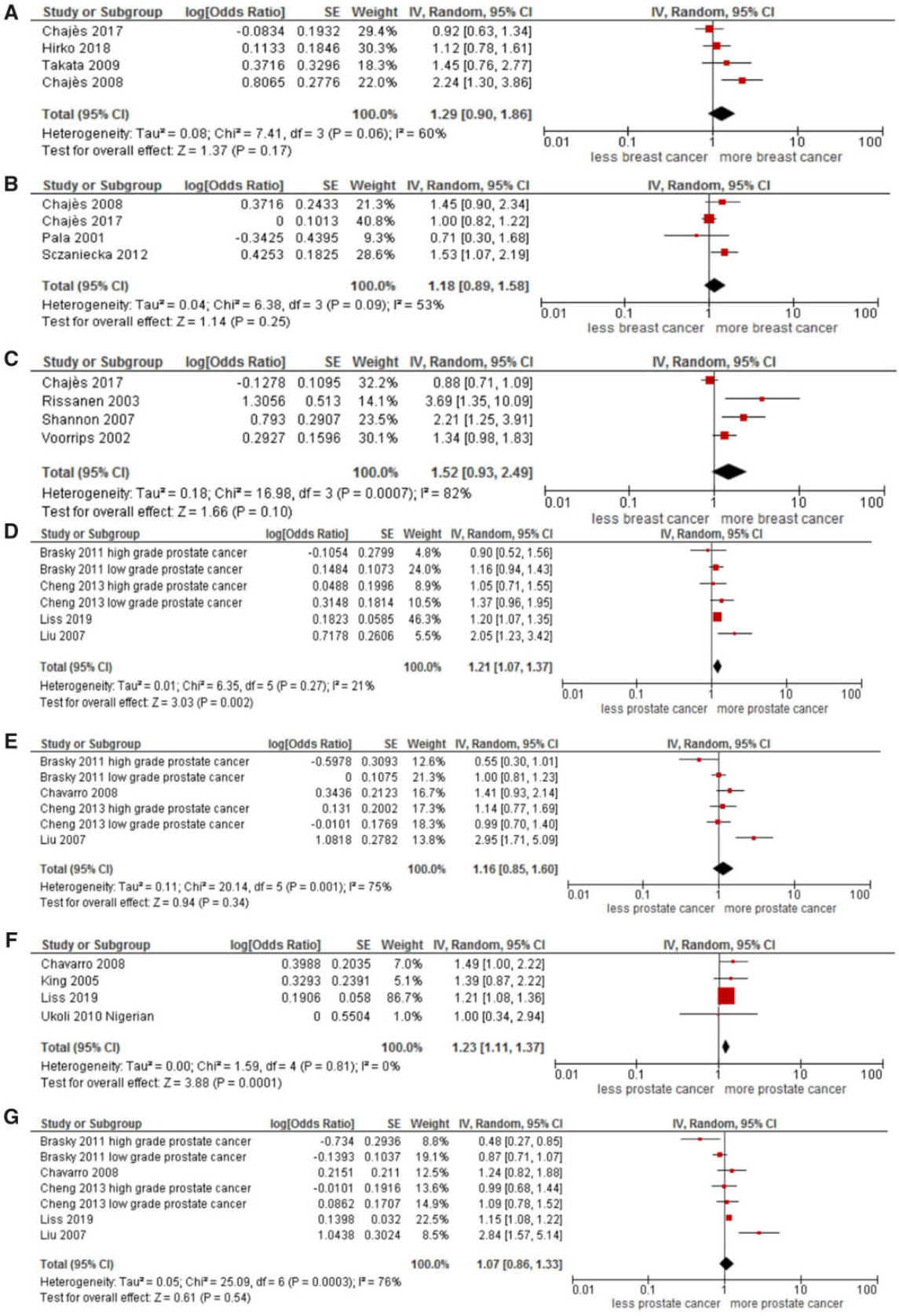

Figure 3 **Meta-analysis for trans-fatty acid subtypes.** A) Breast cancer with C16:1Δ9t; B) breast cancer with C18:1Δ9t; C) breast cancer with C18:1Δ11t; D) prostate cancer with C16:1t; E) prostate cancer with C18:1t; F) prostate cancer with C18:1Δ9t; G) prostate cancer with C18:2t

TFAs (for melanoma) were found only in women and for vegetable oil TFAs (for pancreas cancer) only in men.[53,58] Moreover, the study by Matejcic et al[51] found higher prostate cancer risk by industrial TFAs only in men. Age also acted as a moderator (eg, a positive TFA–colorectal cancer and TFA–prostate cancer link was only found in those above 60 but not below 60 years, although interaction was not significant).[59] Concerning lifestyle, TFAs increased cancer risk only in smokers (for prostate, colon, and breast cancer) and in overweight individuals (for colon cancer), although interaction was not significant.[59] Moreover, continental ancestry affects the risk of developing a neoplasm: Europeans appeared to have a higher risk of developing a distal colorectal cancer or a prostate cancer than Afro-Americans with the same high TFA intake,[22,60] although moderation was not formally tested and the sample size for Afro-Americans was much lower. In another study, Afro-Americans had a significantly positive TFA–prostate cancer association, while Nigerians did not.[50] Menopause may be an important moderator for breast and ovarian cancer risk (not formally tested by interaction): a significant positive TFA–ovarian cancer[38] or ruminant TFA–breast cancer association was found only in postmenopausal women[53] and a stronger TFA–breast cancer association in postmenopausal vs premenopausal women,[45] although a positive TFA–breast cancer association was found, again in just one study,[59] in premenopausal women.[61] Other moderators that were seldom tested included genetics and medication/hormone use.

DISCUSSION

Overall results

Overall, this review to some extent supports the ban of industrial TFAs in food since the meta-analysis for the association between total TFA intake and prostate and colorectal cancer was significantly positive. Nevertheless, there were still inconclusive results, similar to the findings of previous reviews.[23,61] Some studies did indeed find a significant dose-dependent risk between TFA intake and cancer, while others did not.

Cancer types

Breast cancer. Our own meta-analyses of breast cancer risk with total TFA intake or 3 TFA subgroups were not significant, although it should be mentioned that the total TFA meta-analysis was rather borderline (OR 1.12; 95%CI, 0.99–1.26) and that menopause may be a moderator herein. One recent meta-analysis[62] also concluded that there is no overall significant association between dietary or serum TFA and future breast cancer risk. Only in postmenopausal women, a significant higher risk was seen for higher serum TFA.[62] The current systematic review could not find more recent studies, but also included 3 studies on erythrocyte TFA[33,44,47] and 2 on adipose tissue TFA,[56,57] of which only 1 found a significant positive association with total TFA intake[56] and 1 with trans-vaccenic acid.[47]

Prostate cancer. Eleven studies investigated associations with prostate cancer risk, reporting often significant positive associations[21,22,50,52,59] and only in one study contradictory results (inverse association for high-grade prostate cancer[39]) The current meta-analysis confirmed a significant enhanced prostate cancer risk with higher total TFA, C18:1Δ9t, and C16:1t intake with low-to-moderate heterogeneity.

Colorectal cancer. Nine studies investigated associations with colorectal cancers, reporting sometimes significant positive associations,[58–60] with higher risk in women, overweight, and older participants. The current meta-analysis confirmed the significant positive association, with moderate heterogeneity.

Pancreas. Five studies investigated associations with pancreas cancer risk, though with conflicting results. One study found an inverse association among men for partially hydrogenated vegetable oils,[53] while another study reported positive associations with TFA C16:1t (trans-hexadecenoic acid) intake.[49]

Upper digestive system cancers (mouth/pharynx/esophagus, stomach). Only one study investigated associations with mouth, pharynx, and esophagus cancer, and reported a significant positive association with TFA exposures from ruminant fat but not for partially hydrogenated oils.[53] Two studies investigated associations with stomach cancer,[53,59] with a significant positive trend found only for partially hydrogenated fish oils.[53]

Melanoma and nonmelanoma skin cancer. Only one study investigated associations with skin cancer, reporting no associations with melanoma skin cancer, though a significant positive association with TFA derived from ruminant fat was observed in women.[53]

Respiratory system (lung). Only 2 studies investigated the effect of TFA exposures on lung cancer risk, reporting differential results for the different TFA subtypes. A significant inverse association was found with partially hydrogenated fish oils in women only,[53] though the

studies found no significant associations for all other TFA subtypes.[53,59]

Reproductive system (ovarian, endometrium, cervix, testis). The current meta-analysis conducted for 6 articles (giving 7 analyses in total) found no significant association between total TFA intake and ovarian cancer risk. A previous meta-analysis based on 2 case-control and 2 cohort studies showed a significant positive association between TFA intake and ovarian cancer (relative risk = 1.25; 95%CI, 1.06–1.49).[63] This might be explained by the inclusion of 3 additional analyses with nonsignificant associations in the current article.

Only one study investigated associations with endometrium cancer and with cervix cancer, though found no significant associations.[53]

Nervous system (brain and central nervous system). Only 2 studies investigated associations with nervous system cancer: one with brain cancer[59] and another with cancer of the central nervous system.[53] Both found no significant associations with TFA exposures.

Urinary system (bladder, kidney). Only 2 studies investigated associations with bladder and kidney cancers,[53,59] reporting no significant associations between TFA exposures, except for an inverse association between fish TFA and bladder cancer.

Non-Hodgkin lymphoma and leukemia. The current meta-analysis could not confirm an NHL association with total TFA intake and revealed very high heterogeneity. Concerning TFA source, one study observed a lower risk of NHL with a high intake of partially hydrogenated vegetable oil TFAs,[53] while another study found higher NHL risk among individuals with a high intake of ruminant TFA.[53] According to the authors, the different associations between cancer risk and consumption of TFA from different sources (ruminant, fish, and vegetable oil) may be related to the different chemical structures of each TFA, which may lead to a different site-specific carcinogenic effect.[53] However, this was only investigated in this one study and needs confirmation. For leukemia, no significant associations were observed with TFA intake.[53,59]

Pathways

An important underlying mechanism of TFA is the induction of endothelial dysfunction and inflammation. Elevated levels of inflammatory biomarkers (eg, C-reactive protein, interleukin-6, and E-selectin) have been found in those with the highest intakes of TFA.[64–67] Also in one intervention,[19] the group with a 6 g/d TFA diet for 6 weeks had a significantly higher concentration of the oxidative stress marker 8-iso-PGF2alpha. This chronic inflammation and oxidative stress may lead to an induction of cell proliferation and protein/RNA/DNA damage by oxidative free radicals.[68] Damage at protein level can decrease the function of the proteins, while a DNA mutation could lead to increased expression of oncogenes or decreased expression of tumor suppressor genes.[69] For example, chronic prostatic inflammation can lead to the loss of glutathione-S-transferase-π function, which is important in the defense against chemical carcinogenesis.[70] As an example at DNA level, a diet rich in TFAs has been linked to p53 mutations by which p53 loses its tumor-suppressing capacity (induction of apoptosis and cell cycle arrest) and thus allows uncontrolled growth of malignant cells.[58] Also, people with a certain genotype (eg, QQ/RQ genotype of the ribonuclease L gene) may potentially be more vulnerable to TFA-induced carcinogenesis.[22]

Implications for public health

In 2010, trans-fat was estimated to cause still half a million cardiovascular deaths each year, despite data showing immediate and long-lasting health benefits when industrially produced TFAs were removed from the food supply.[71] The current review partly supports a similar health importance of the TFA ban also for cancer prevention. The Global Burden of Diseases Nutrition and Chronic Diseases Expert Group reported important heterogeneity across countries that informs nation-specific clinical, public health, and policy priorities.[71] Following the first national policy to reduce industrially produced TFA in Denmark in 2003, mandatory TFA limits are currently in effect for 2.4 billion people across 28 countries.[71] Nevertheless, a majority of countries do not have such policies. In 2019, the European Commission amended the regulation on TFAs with a maximum TFA limit of 2 g per 100 g fat, for TFAs other than TFAs naturally occurring in fat of animal origin. In May 2018, the WHO launched the REPLACE action package to support governments to eliminate industrially produced TFAs from the global food supply by 2023.[72] The WHO will provide support in overcoming any challenges (eg, by developing and providing regulatory capacity-building training). Implementing healthier replacement oils and fats remains a challenge in low- and middle-income countries since the largest share of edible oils/fats is in the hands of small and medium-sized enterprises that may have limited resources and capacities to reformulate. In these countries, palm oil is often the most available and affordable alternative that meets many of the functional properties of TFAs, but palm oil is high in saturated fatty acids,

which should be avoided. In contrast, one study from Canada[73] found that in this high-income country, food manufacturers/restaurants are generally taking advantage of the costs and efforts involved in reformulation as an opportunity not only to reduce TFAs but also to increase the content of *cis* unsaturated fats, which may provide additional health benefits. The median TFA intake in the articles included in this systematic review was often above the WHO-recommended 1% of daily energy intake. Even after a legislation to limit or ban industrial TFAs, potential long-term health effects may exist as cancer has a long latency period and fat is stored in the body, and still other forms (eg, ruminant TFAs) can be present in food.

Limitations and implications for future research

To investigate TFA intake, questionnaires were often used. This method can be prone to recall bias and measurement inaccuracy owing to substantial TFA differences between products and over time, and thus detection bias. A more objective way to investigate intake is biomarker assessment. As a reflection of dietary intake, TFA concentrations can be measured in blood (short term)[74] and adipose tissue (long term), especially since TFAs are not synthetized endogenously. Adipose tissue concentrations give an indication of the fat intake over the previous 1–3 years since changes are visible after a few months and the half-life is around 1–2 years.[75,76] Thus, even several years after a TFA ban, TFAs would be detectable and would become available in the bloodstream (although in lower concentrations). However, one child cohort[77] found decreased plasma TFA concentrations in parallel with the decreased TFA concentrations in food over the period 2000–2010. One meta-analysis[62] found no association between dietary intake of TFAs (measured by questionnaire) and risk of breast cancer, while the same meta-analysis found a positive association between serum TFAs and breast cancer risk in postmenopausal women. In the included studies in the present review, 8 out of 15 biomarker studies vs 11 out of 30 questionnaire studies found a significant association between TFA intake and cancer incidence.

Since previous research relating TFA intake to cancer risk has mainly focused on colorectal, prostate, and breast cancer, there remains a need for further investigation into the relationship between TFA intake and cancers such as hepatocellular, bladder, or kidney cancer. Moreover, mechanistic research should further examine the underlying pathways and potential remaining cancer risk after an anticipated TFA ban, owing to their storage in organs. A limitation for the meta-analyses was the non-uniformity in use of confounding variables as well as in terminology used for several confounders. For example, several articles incorrectly used the terms "race" and "ethnicity" interchangeably.

To develop targeted prevention strategies aimed at eliminating TFAs, it is important to investigate the relevance of the chemical structure and origin of TFAs (ie, vegetable vs animal origin, the length of the carbon chain [16 vs 18], and the position of the trans-bond, which was often not specified). This heterogeneity in TFA type analyses between articles may cause reporting bias and made standardized meta-analysis difficult. The study by Laake et al[53] investigated different sources of TFA and concluded that TFAs from ruminant fat and partially hydrogenated fish oil had more adverse effects on cancer risk than TFAs from vegetable oil, although there remains a possibility that the higher cancer risk from ruminant fat and partially hydrogenated fish oil TFAs may be linked to the higher saturated fat content of ruminant and fish oil compared with vegetable oil, or to the different carbon chain length. In another study, TFAs from partially hydrogenated fish oil also had a more unfavorable effect on lipid risk indicators for coronary heart disease than TFAs from partially hydrogenated soybean oil.[78]

Another relevant avenue for targeted prevention may be via moderation (ie, identifying which subgroups in the population are more at risk for TFA-induced carcinogenesis). Enhancing moderators in the positive TFA-cancer relation were gender (sometimes men, sometimes women), European ancestry, menopause, older age, and high BMI. Comparative studies on ancestry/race difference included mainly European vs African-American analyses, but not, for example, Asian populations. Genotype as a moderator was only mentioned for prostate cancer; it is not yet known whether such connection also exists for other cancers.[22] To bring the level of confounding to a minimum, confounders should be more often adjusted for in the analyses. For example, including other lifestyle factors linked to cancer risk (eg, physical activity,[79] smoking, BMI, and other nutrients in the adjusted statistical methods) will lead to more reliable results. After all, other nutrients may confound the association since TFA intake was found to be positively significantly associated with total fat intake and negatively with vitamin E, several monounsaturated fatty acids, several saturated fatty acids, and total polyunsaturated fatty acid in an American population.[80]

CONCLUSION

This systematic review suggests some potential harmful effects of high consumptions of TFA through higher cancer risks, with significant meta-analysis results for colorectal and prostate cancer. Thus, this review

provides some support for the ban of industrial TFA in food, despite heterogeneity. Underlying pathways are still not fully known, but chronic inflammation and oxidative stress possibly play a role. Future studies investigating associations between fatty acid intakes and cancer risk should apply methods and study designs of higher methodological quality (eg, adjusting for the principal confounders and using biomarkers of intake). Considering the potential differential effects of the different TFA subtypes, for targeted prevention strategies, future studies should examine which TFA subtypes (including ruminant TFAs) may be more carcinogenic and which populations are at highest risk.

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SUPPORTING INFORMATION

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 **PRISMA checklist**

Table S1 **Newcastle-Ottawa Scale quality scores**

Table S2 **Results of all included studies**

Table S3 **Overview of studied cancer-transfat associations and presence of significant findings**

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