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Prospective evaluation of *trans*-fatty acid intake and colorectal cancer risk in the Iowa Women's Health Study

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Abstract

Concerns regarding the safety of dietary *trans*-fatty acids (*t*FAs) have generated recent public interest, scientific discussion and legislative action. Although most widely recognized as a risk factor for cardiovascular disease, associations between *t*FA intake and incident cancer have also been proposed. With respect to colorectal cancer (CRC), existing observational data remain limited and inconclusive. Therefore, we conducted a prospective evaluation of *t*FA intake and CRC risk, overall and by anatomic subsite, among participants in the Iowa Women's Health Study, a population-based cohort of older women (ages 55–69 years at enrollment). Exposure data were collected at baseline using a semi-quantitative food-frequency questionnaire. Incident CRC cases were identified through annual linkage to the Iowa Cancer Registry. CRC risks were estimated using Cox proportional hazards regression models. In total, 35,216 women met our inclusion criteria and 1229 CRC cases (631 proximal, 571 distal, 27 site not specified) were observed through 18 years of follow-up. Adjusting for age and total energy consumption, *t*FA intake in the fourth versus first quartile was not significantly associated with overall CRC risk (relative risk [RR] = 1.12; 95% confidence interval [CI] = 0.96–1.32). Similarly, risk estimates based on proximal (RR = 1.09; 95% CI = 0.87–1.37) and distal (RR = 1.18; 95% CI = 0.93–1.49) CRC subsites did not differ from unity. Multivariable adjustment yielded slightly attenuated risk estimates, but the observed associations were not meaningfully altered. Given these findings, *t*FA intake does not appear to be a major CRC risk factor, at least among older women.

Keywords

Colorectal cancer; *trans* fatty acids; dietary fat; cohort study

Introduction

Over the past several decades, dietary fat has been extensively investigated as a potentially modifiable cancer risk factor.1 Yet, for colorectal cancer (CRC), dietary fat-related risk associations remain inconsistent and incompletely defined. Further, two recent randomized,

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Novelty and Impact Statements: Dietary *trans*-fatty acids have been associated with several chronic diseases, but data regarding *trans*-fatty acid intake as a risk factor for colorectal cancer remain limited and inconclusive. In this prospective, cohort study, we evaluated associations between *trans*-fatty acid intake and incident colorectal cancer, overall and by anatomic subsite, in the Iowa Women's Health Study.

controlled trials failed to demonstrate a statistically significant benefit from reduced total dietary fat with respect to risks for either recurrent adenoma2 or incident CRC.3 Since dietary fat represents a heterogeneous mixture of diverse macronutrients, it may be more relevant to consider intake levels of specific fatty acid subtypes, rather than total dietary fat, as indicators of CRC risk.

Trans-fatty acids (*t*FAs), which refer to unsaturated fatty acids with one or more double bonds in the *trans* configuration, are formed during partial hydrogenation of naturally-occurring vegetable or marine oils. Although elevated *t*FA intake has been associated with increased risks for a variety of chronic health conditions, including obesity, hyperlipidemia, type 2 diabetes mellitus and cardiovascular disease4, 5, the underlying biologic mechanisms remain incompletely defined.6 Dietary sources with relatively high *t*FA content include table spreads, bakery goods, and fast foods.4, 7 Limited observational data suggest that at least some tFA-rich foods may be associated with increased colorectal neoplasia risk.8, 9 However, to date, relatively few studies have directly examined *t*FA intake as a potential CRC risk factor, with mixed results.8, 10–12 In the present study, we sought to prospectively evaluate the association between *t*FA intake and incident CRC, overall and by anatomic subsite, in the Iowa Women's Health Study (IWHS).

Material and Methods

Full details regarding the IWHS study design have been published elsewhere.13 In brief, 41,836 older women, ages 55–69 years, were enrolled in 1986. Participants completed a semi-quantitative food frequency questionnaire at baseline, adapted from the 126-item instrument developed by Willett and colleagues.14 Daily intake of *t*FA and other nutrients were calculated by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portions, using the Harvard Food Composition Database, which is based on U.S. Department of Agriculture data.15 Incident cancer cases were identified through annual linkage with the Iowa Cancer Registry (a Surveillance, Epidemiology and End Results program member) and deaths were identified through annual linkage to Iowa death certificates, supplemented by periodic mailed surveys (1987, 1989, 1992, and 1997 and 2004) and for non-respondents, linkage to the National Death Index. We have estimated that less than 1% of the cohort has been lost to follow-up.16

Women with ≤ 1 day of follow-up (n=10); history of cancer prior to baseline, except non-melanoma skin cancer (n=3,830); or extreme energy intake (< 600 kcal or ≥ 5000 kcal per day) or incomplete dietary data (≥30 items blank) on the food frequency questionnaire (n=3,096) were excluded from the present study, yielding a final sample size of 35,216 study participants (exclusions were not mutually exclusive).

Dietary fat was analyzed with respect to total, saturated, polyunsaturated and major *trans*-isomer (C18:1 and C18:2) intake levels. CRC risks by quartiles of fat intake were assessed overall and by proximal (ICD-O codes 18.0, 18.2–18.5) and distal (ICD-O codes 18.6–18.7, 19.9, 20.9) subsites. Person-years were accumulated from baseline until first CRC diagnosis, move from Iowa, death, or administrative censoring on 12/31/2003. Relative risks and 95% confidence intervals (RR; 95% CI) were estimated using Cox proportional hazards regression models, modeling age as the time variable17 and accounting for total energy intake (using the residual method proposed by Willett and Stampfer18, which regresses the nutrient intakes of individuals on their total caloric intake. The resulting residuals are then added to the predicted nutrient intake at the population mean caloric intake, producing an adjusted nutrient value that is uncorrelated with total calories. Other potential confounding factors incorporated into the multivariate models included body mass index, physical activity level, estrogen use, self-reported diabetes mellitus, smoking status, and intake of

total fat, red meat, fruits and vegetables, calcium, folate, vitamin E and alcohol. Family history of CRC and nonsteroidal anti-inflammatory drug use were not available at baseline and were not included in the multivariate risk models. Tests for trend were carried out by ordering the intake quartiles from lowest to highest and including the resulting variable as a one degree-of-freedom linear term in the Cox regression models.

Statistical tests were performed two-sided using the SAS (SAS Institute Inc., Cary, NC) and S-Plus (Insightful, Seattle, WA) software systems. Power analyses were based on the observed number of events in the IWHS cohort using pairwise comparisons of risk across fat intake quartiles. Assuming a two-sided test of hypothesis with a type I error rate of 0.05, and assuming half of all observed events fall into the two quartiles of interest for a given pairwise comparison, our study had 80% power to detect quartile-specific RRs as low as 1.26, 1.38, and 1.40 for overall, proximal and distal CRCs, respectively.

Results

Following exclusions, the final analytic cohort consisted of 35,216 women (550,109 person-years), with a mean (SD) value for *t*FA intake of 2.90 (1.59) g/day. Baseline characteristics are provided in Table 1, by *t*FA intake quartiles. During the follow-up period, a total of 1229 incident CRCs were identified, including 631 proximal, 571 distal and 27 subsite-unspecified cases.

After adjusting for age and total energy consumption, *t*FA intake in the fourth versus first quartiles was associated with a minimally increased risk for CRC overall (RR=1.12; 95% CI = 0.96–1.32), which was not statistically significant. Similar findings were observed for proximal (RR = 1.09; 95% CI = 0.87–1.37) and distal (RR = 1.18; 95% CI 0.93–1.49) CRCs. Multivariable adjustment resulted in slightly attenuated risk estimates (Table 2). Consideration of *t*FA intake by C18:1 (RR=1.05; 95% CI = 0.87–1.26) and C18:2 (RR=1.02; 95% CI = 0.85–1.23) isomers did not appreciably alter the observed risk associations with CRC overall, nor did analyses based on *t*FA-rich foods such as margarine (RR=1.03; 95% CI = 0.88–1.22). Further, excluding incident CRCs diagnosed within the first 5 years of cohort follow-up did not appreciably affect the reported risk estimates (data not shown).

Analyses of other dietary fat subtypes yielded null associations with incident CRC as well, with multivariable-adjusted RRs for comparisons of extreme quartiles of 1.03 (95% CI=0.84–1.25) for total fat, 0.95 (95% CI=0.78–1.15) for saturated fat and 1.05 (95% CI=0.87–1.25) for polyunsaturated fat.

Discussion

In this large, population-based cohort study, baseline *t*FA intake did not predict incident CRC among IWHS participants. Strengths of the present study include: prospective data collection with extended follow-up, near-complete case ascertainment, adjustment for multiple potential confounding factors, and consideration of CRC risks overall and by anatomic subsite, with adequate statistical power to detect relevant differences across quartiles of *t*FA intake. One recognized limitation is that *t*FA intake was characterized from a single baseline survey. However, without specific intervention, adult dietary patterns appear to stay relatively stable over time.19 Also, other cohort studies have observed that updated dietary information has a minimal effect on estimated CRC risk.20 Thus, the null associations observed in our study are unlikely attributable solely to non-differential misclassification bias in the exposure assessment.

Trans fatty acids can promote systemic inflammation and reduce insulin sensitivity5, which represent biologically plausible mechanisms for increased CRC risk.21 However, in animal studies, *t*FA administration has not been shown to enhance colorectal tumorigenesis.22 Human observational data are also limited and inconclusive. Two prior retrospective studies reported statistically significant, positive associations between *t*FA intake and CRC risk. In a multi-center, case-control study involving participants from Minnesota, Northern California and Utah (n=4,403), Slattery et al. found that women in the highest *t*FA quintile had a 50% increase in colon cancer risk, compared to women in the lowest *t*FA quintile (odds ratio [OR] = 1.5; 95% CI = 1.1–2.0; p trend = 0.04).10 However, *t*FA intake was not associated with colon cancer risk among men (OR = 1.2; 95% CI = 0.9–1.7; p trend = 0.34). Similarly, in a national case-control study from Scotland12, Theodoratou, et al. found that CRC risk was 57% higher among women in the fourth versus first quartiles of monounsaturated *t*FA intake (OR = 1.57; 95% CI = 1.05–2.36; p trend = 0.017), whereas no association was detected among men (OR = 0.95; 95% CI = 0.69–1.31; p trend = 0.446). In contrast, secondary data analyses from a prospective study of women (n=37,547) enrolled in a randomized, clinical trial of aspirin and vitamin E failed to demonstrate an association between *t*FA intake and incident CRC (RR = 1.30; 95% CI = 0.89–2.05; p trend = 0.18).11 Further analyses based on proximal and distal CRC subsites were apparently unremarkable, although the subsite-specific risk estimates were not reported. One additional case-control study, conducted by McKelvey and colleagues8, described a null association between *t*FA intake and distal colorectal adenoma risk among subjects (n=1,072) recruited from two screening sigmoidoscopy clinics in southern California (OR = 0.90; 95% CI = 0.40–2.0 for comparison of daily *t*FA intake > 6 grams versus < 2 grams). Risk associations stratified by gender were not reported.

Estimated *t*FA intake ranges from 1.4–5.4 g/person/day in industrialized countries.23 In the United States, average *t*FA intake represents about 2–3% of total calories consumed, which may confer increased risk for cardiovascular disease even at this relatively low level.7 To protect the public health, Denmark24 and New York City25 recently passed legislation to markedly reduce the *t*FA content in commercial food supplies. While the benefits of decreased tFA intake will likely be substantial, data from our large, prospective cohort study argue against an appreciable effect on CRC risk resulting from this dietary modification.

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Abbreviations

CRC	colorectal cancer
***t*FA**	*trans*-fatty acid
IWHS	Iowa Women's Health Study
RR	relative risk
CI	confidence interval
OR	odds ratio

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Table 1

Baseline Subject Characteristics by *Trans*-Fatty Acid (*t*FA) Intake

	Energy Adjusted Total *t*FA Intake, gm/day[1,2]			
	Quartile 1 (≤ 1.96)	**Quartile 2 (1.97– 2.55)**	**Quartile 3 (2.56– 3.28)**	**Quartile 4 (> 3.28)**
Subjects, N	8804	8804	8804	8804
Age, years[3]	62.1 (4.2)	61.9 (4.2)	62.0 (4.2)	62.0 (4.2)
Body mass index, kg/m2[3]	26.8 (5.1)	27.1 (5.1)	27.1 (5.0)	26.9 (5.2)
Physical activity, low, N (%)[4]	3289 (38.1%)	4001 (46.0%)	4297 (49.5%)	4877 (56.3%)
Estrogen use, ever, N (%)	3564 (40.9%)	3358 (38.5%)	3284 (37.6%)	3212 (36.8%)
Self-reported diabetes mellitus, N (%)	684 (7.8%)	566 (6.4%)	440 (5.0%)	382 (4.3%)
Smoking status, current or former, N (%)	3292 (37.9%)	2973 (34.3%)	2807 (32.2%)	2858 (32.9%)
Total energy intake, kcal/d[3]	1772.2 (615.4)	1822.1 (609.5)	1824.5 (599.2)	1775.0 (600.9)
Total fat intake, g/day[3]	59.5 (26.2)	68.6 (27.4)	72.0 (27.3)	73.6 (27.7)
Red meat intake, g/day[3]	25.9 (19.7)	33.7 (22.4)	34.7 (21.9)	32.7 (20.4)
Fruit and vegetable intake, g/day[3]	680.0 (363.1)	571.9 (285.2)	509.1 (246.6)	426.4 (216.7)
Calcium intake, mg/day[3]	1244.9 (598.2)	1130.4 (550.2)	1066.7 (532.6)	941.2 (488.2)
Folate intake, g/d[3]	498.8 (278.9)	442.4 (245.9)	405.7 (226.0)	366.0 (217.5)
Vitamin E intake, mg/day[3]	83.2 (168.8)	68.3 (150.6)	60.6 (142.0)	54.9 (133.6)
Alcohol g/day[3]	5.7 (12.2)	3.9 (8.7)	3.2 (7.2)	2.2 (5.7)

[1] energy adjusted *t*FA intake using the residual method as proposed by Willett and Stampfer;

[2] $p < 0.01$ for comparison across quartiles for all variables except age, for which p=0.35;

[3] mean (standard deviation);

[4] no physical activity or moderate activity less than once per week.

Table 2

Trans-Fatty Acid (*t*FA) Intake and Incident Colorectal Cancer Risk, Overall and by Anatomic Subsite

		CRC RISK					
		Overall		Proximal		Distal	
	Person-Years	Events	RR (95% CI)[1]	Events	RR (95% CI)[1]	Events	RR (95% CI)[1]
***t*FA, total**[3]							
≤1.96	135279	275	1.00 (referent)	140	1.00(Ref)	127	1.00 (referent)
1.97–2.55	137465	311	1.06(0.90,1.26)	167	1.13(0.89,1.43)	138	1.00(0.78,1.29)
2.56–3.28	138416	325	1.15(0.96,1.36)	166	1.16(0.91,1.47)	152	1.14(0.89,1.47)
> 3.28	138949	318	1.06(0.88,1.28)	158	1.04(0.8,1.35)	154	1.09(0.84,1.43)
p trend			0.40		0.78		0.36
***t*FA, C18:1 isomers**[3]							
≤1.83	135156	278	1.00 (referent)	140	1.00 (referent)	130	1.00 (referent)
1.84–2.40	137509	309	1.04(0.88,1.23)	169	1.14(0.9,1.44)	134	0.95(0.74,1.22)
2.41–3.10	138661	323	1.12(0.94,1.33)	165	1.14(0.89,1.45)	151	1.10(0.86,1.41)
> 3.10	138782	319	1.05(0.87,1.26)	157	1.03(0.79,1.33)	156	1.08(0.83,1.41)
p trend			0.47		0.89		0.37
***t*FA, C18:2 isomers**[3]							
≤ 0.12	135521	293	1.00 (referent)	155	1.00 (referent)	131	1.00 (referent)
0.13–0.15	137324	301	1.00(0.85,1.19)	151	0.96(0.75,1.21)	141	1.03(0.80,1.33)
0.16–0.18	138629	327	1.09(0.92,1.3)	173	1.10(0.86,1.4)	151	1.11(0.86,1.43)
> 0.18	138635	308	1.02(0.85,1.23)	152	0.96(0.74,1.25)	148	1.06(0.81,1.39)
p trend			0.63		0.94		0.57

[1] hazard ratio (95% confidence interval) adjusting for age, total energy intake, body mass index, physical activity level, estrogen use, self-reported diabetes mellitus, smoking status, and intake of total fat, red meat, fruits and vegetables, calcium, folate, vitamin E and alcohol;

[3] energy adjusted values using the residual method as proposed by Willett and Stampfer (see Methods section).