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The association of percentage energy from fat and colon cancer risk among members of the U.S. military

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Abstract

Purpose—Epidemiologic studies have previously reported an association between high fat intake and colon cancer risk. However, findings have generally been inconclusive. This study aimed to investigate the association between fat as a percentage of energy intake and colon cancer risk.

Methods—Study subjects included 215 cases and 215 matched controls identified by the Defense Medical Surveillance System. Percentage energy from fat (Pfat) was estimated using a short dietary screener developed by the National Cancer Institute for two time periods: the year before first blood draw and colon cancer diagnosis. Conditional logistic regression analysis was used to assess the relationship between colon cancer risk and Pfat. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results—Compared with the lowest quartile of Pfat, the adjusted odds of having colon cancer were 2.00 (95% CI 0.96–4.18), 2.83 (95% CI 1.41–5.66) and 3.37 (95% CI 1.58–7.17) for the second, third, and highest quartiles in the year before cancer diagnosis. Similar results were observed for Pfat at an earlier time.

Conclusion—Our findings suggest a positive association between Pfat and colon cancer in the U.S. military population.

Keywords

Dietary fat; Percentage energy from fat; Colon cancer; Epidemiology

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Introduction

Experimental studies have shown that dietary fat intake increases the risk of colorectal cancer by increasing secretion of secondary bile acids, which can promote cell proliferation (Chomchai et al. 1974; Lapre and Van der Meer 1992; Narisawa et al. 1974; Nigro et al. 1973; Park et al. 2012; Tang et al. 2012), alter intestinal microflora (Kim et al. 2012; Reddy and Wynder 1973), and damage colonic membranes (Nagengast et al. 1995; Rafter et al. 1986; Vahouny et al. 1984). While many epidemiologic studies have investigated the relationship between dietary fat and colorectal cancer (Kushi and Giovannucci 2002; Vargas and Thompson 2012), results have been inconsistent.

A pooled analysis of 13 case-control studies found no evidence of any energy-independent effects of total fat and colorectal cancer risk (Howe et al. 1997). In a meta-analysis of 6 prospective cohort studies on the relationship between animal fat consumption and colorectal cancer (Alexander et al. 2009), four observed null associations (Bostick et al. 1994; Goldbohm et al. 1994; Lin et al. 2004; Sanjoaquin et al. 2004) and two reported elevated risk with increased animal fat intake (Giovannucci et al. 1994; Willett et al. 1990). In the Nurses' Health Study (Willett et al. 1990), highest vs. lowest intake of total or animal fat was positively associated with colon cancer after adjusting for total energy intake. A relative risk of 2.00 for total and 1.89 for animal fat was observed when comparing highest vs. lowest consumption of fat intake (Willett et al. 1990). In addition to the studies included in the meta-analyses, some studies (West et al. 1989; Whittemore et al. 1990) have shown increased risk associated with high fat consumption while others show no association (Dahm et al. 2010; Sun et al. 2012). Similar to studies of total dietary and animal fat intake, results from studies that evaluated specific fat constituents are also not entirely clear. While many reported null associations (Zhong et al. 2013; Dahm et al. 2010; Giovannucci et al. 1994; Goldbohm et al. 1994; Lin et al. 2004; Stemmermann et al. 1984), some observed positive associations with saturated (Whittemore et al. 1990; Willett et al. 1990) and monounsaturated (Willett et al. 1990) fats and others reported inverse associations for polyunsaturated fat (Theodoratou et al. 2007; Levi et al. 2002; Howe et al. 1997; Williams et al. 2010).

Despite the inconsistency in research, a comprehensive review provided by the World Cancer Research Fund and American Institute for Cancer Research (2007) reported that there is limited evidence that foods containing animal fats increase colorectal cancer risk. Thus, current federal dietary guidelines recommend between 20–35% of energy intake from fat for adults (U.S. Department of Agriculture 2010; Institute of Medicine 2002). Percentage energy from fat (Pfat) reflects the amount of fat consumed relative to total energy intake. A high intake of Pfat (>35%) generally relates to increased consumption of saturated fat (U.S. Department of Agriculture 2005). However, research on Pfat in relation to colorectal cancer risk is sparse and results have been inconsistent. Null (Sun et al. 2012, Lin et al. 2004; Flood et al. 2003; Williams et al. 2010), positive (West et al. 1989), and inverse (Stemmermann et al. 1984) associations between Pfat and colorectal cancer risk have all been reported.

Previous studies on Pfat included both colon and rectal cancers. If the relationship between Pfat and risk differs between colon and rectal cancers, association with a specific site might

be diluted. In addition, while Pfat at diagnosis was usually used in these studies Pfat at an earlier time may be more important for etiologic research due to a long latent period of cancer occurrence. This study aimed to assess the relationship between percentage energy from fat and colon cancer risk in the U.S. military population. We investigated Pfat in the year prior to diagnosis and earlier in life.

Methods

Study subjects

We conducted a case-control study among U.S. active duty military members. Study subjects were identified through the Defense Medical Surveillance System (DMSS). DMSS hosts a central repository of longitudinal medical data for all active duty members and the Department of Defense Serum Repository (DoDSR) that collects blood samples from all members approximately every other year (Rubertone and Brundage 2002). This study was approved by the Uniformed Services University of the Health Sciences and the Walter Reed National Military Medical Center Institutional Review Boards.

Eligible cases consisted of men and women diagnosed with colon cancer between January 1, 2001 and December 31, 2009 who were between 17 and 79 years of age at diagnosis of colon cancer, active duty at time of diagnosis, and had at least one pre-diagnostic serum sample of 1mL. We used a lower age bound of 17 years because that is the minimum age for entry into the U.S. military and an upper age bound of 79 years to minimize incorrect recall of information. Serum samples were a study criterion because the original purpose of this study was to identify serum biomarkers. Controls were men and women who did not have colon cancer, were active duty in the reference year (corresponding to diagnosis year of matched case), had at least one serum sample 1mL, and were alive at the start of the study. They were matched to cases on gender, age (within one year of birth), racial background (European-American, African-American, and Other), and time points at which serum samples were collected (within ± 60 days of requested case sample).

At the first step of study subject enrollment, DMSS identified and provided a list of all eligible cases according to the 9th Revision International Classification of Diseases (ICD-9) coding system. Before contacting eligible cases, we verified survival status through the Defense Manpower Data Center (DMDC), which manages and updates all personnel information, as well as CDC's National Death Index and the Social Security Administration. An informative letter describing the study purpose and procedures, informed consent document, and questionnaire packet were mailed to all surviving cases. After 3 weeks, subjects who provided no response or incomplete information were followed up with reminder emails, phone calls, or letters. For each case who participated, a matched control was contacted using procedures similar to cases. Five potential controls were identified and randomly selected by DMSS based on matching criteria. If the person did not respond or did not want to participate, the next control was contacted until successful enrollment.

There were 593 eligible colon cancer cases after excluding individuals who reported that they did not have the disease. Of these individuals, 138 were unreachable and 162 were deceased. Out of the remaining 293 cases who responded, 234 participated (82%). We then

contacted 532 controls who were matched to case participants according to the procedures described above. Out of the contacted controls, 5 were deceased and 162 were unreachable or did not respond. Of the remaining 365 controls, 215 ultimately participated (59%). A matched control was successfully recruited for 92% (215/234) of the participating cases. Informed consent was obtained from all eligible study subjects.

Data collection

Self-administered questionnaires were utilized to collect epidemiologic data. Telephone interviews were conducted for those who preferred to provide information over the phone (cases, N=23; controls, N=12). Epidemiologic data included demographic variables, personal habits and lifestyle characteristics, medical history, personal feelings and health, family histories of cancer and colorectal polyps, menstrual/contraceptive/reproductive histories (for women only), and dietary intake. When applicable, questions on exposures at the time before first blood draw for military duty (**time 1**) and in the year before cancer diagnosis for cases or reference date for controls (**time 2**) were asked. These data allowed us to assess risk factors at both time points. The mean length of time between the two time periods was 10.4 years, which did not significantly differ between cases and controls.

Information on fat intake was collected using a validated Short Percentage Energy from Fat Screener developed by the National Cancer Institute (NCI) (Applied Research Program 1996), which consisted of 16 questions about frequency of usual consumption for 15 food groups and use of reduced-fat margarine (Thompson et al. 2007). Detailed information on food items included in the screener can be found at <http://riskfactor.cancer.gov/diet/screeners/fat>. At time 2, frequency was designated using 8 possible response categories that ranged from 'never' to '2 or more times per day.' For time 1, possible responses included "lower," "same," or "higher" consumption at time 1 compared with time 2 for the same 16 questions.

Additional tumor and clinical characteristics were obtained from the Automated Central Tumor Registry (ACTUR), the DoD cancer registry. Out of 234 cases, information was available for 182 individuals. Although all participating cases understood that this was a colon cancer study, a colon cancer diagnosis was documented in the cancer registry for only 135 cases.

Statistical analysis

We first described the distribution of demographic variables by case-control status and then compared Pfat of cases and controls at time 1 and time 2, separately. Pfat was estimated using SAS programs developed by NCI (Applied Research Program 1996). For time 2, age-/gender-specific portion sizes were determined through dietary intake data in the United States using the U.S. Department of Agriculture's 1989–91 Continuing Survey of Food Intakes by Individuals (CSFII) (1996). Portion size information and gender-specific regression coefficients relating Pfat and each food group were subsequently applied to subject responses about frequency of consumption. Pfat was then calculated based on these measures from all food items. For time 1, we developed a scoring procedure to quantify responses into a measure of relative intake based on subject responses from time 2. For each

food item, responses at time 1 (lower=1, same=2, and higher=3) were multiplied by each of the 16 responses at time 2. These measures were subsequently combined with age-/gender-specific portion sizes and gender-specific regression coefficients according to NCI procedures. A relative Pfat score was then formed based on all food items.

In data analysis, Pfat was categorized into quartiles based on the distribution of controls, separately for time 1 and time 2. We defined lowest and highest consumers of total fat as a percentage of energy to be in the first (Q1) and fourth (Q4) quartile, respectively. Pfat was assessed as both a continuous and categorical variable.

Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using conditional logistic regression analysis to assess the relationship between Pfat and colon cancer. In unadjusted analyses, results were further stratified by gender to account for potential differences in dietary fat intake. The following potential confounders were considered for inclusion in our multivariate models: race/ethnicity, highest education, service branch, marital status, religion, household income, number of people living in household, personal history of colon and rectal polyps, family history of cancer, physical activity, history of alcohol, history of smoking, deployment status, BMI (classified according to World Health Organization (2014)), other health conditions (family polyposis, ulcerative colitis/crohn's disease, duodenal ulcer, stomach ulcer, gallstone disease, lactose intolerance, diabetes mellitus, hypertension, coronary artery disease, and pancreatitis), and medications (nsaids and aspirin). The combined race-ethnicity covariate was considered a potential confounder although race (not ethnicity) was one of the matching factors. Covariates that altered the OR of pfat by 10% for time 1 or time 2 were selected as potential confounders and included in multivariate models. These covariates were smoking status, ever drinker, service branch, and deployment status. Since we collected data for two time periods, variables at corresponding time points were respectively used in the models. In order to confirm results, we repeated multivariate analyses using cases that were colon cancer confirmed by both DMSS and ACTUR, and their matched controls. P-values for trend were also calculated. Multivariate analysis stratified by gender was not possible due to the small number of female participants.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). We defined statistical significance at a p -value<0.05.

Results

In the present study, average age was about 41 years and the proportion of males was 82.3% for both cases and controls. Table 1 presents the distribution of selected demographic characteristics at time 2 by case-control status. Cases and controls were similar across all demographic variables except for service branch where cases were more likely to be in the Air Force (26.1%) and less likely to be in the Navy (30.2%) compared with controls.

Table 2 illustrates the relationship between Pfat and colon cancer risk by time and gender. At time 1, individuals in the second highest (Q3) and highest (Q4) quartiles of Pfat had a higher odds of colon cancer (Q3: OR 2.42; CI 1.31, 4.48 and Q4: OR 1.96; CI 1.03, 3.71)

compared with those in the lowest quartile (Q1). Similar results were observed at time 2 for Q3 (OR 2.18; CI 1.24, 3.83) and Q4 (OR 1.91; CI 1.05, 3.46). Additionally, risk was found to increase with Pfat at time 1 (p -trend=0.029) and time 2 (p -trend=0.007). When data were stratified by gender, corresponding ORs (Q4 vs. Q1) and p -values for trend were 9.06 (CI 1.57, 52.23) and 0.010 at time 1 and 7.35 (CI 1.17, 46.12) and 0.009 at time 2 for females. Among males, we observed increased risk; however, none were significant.

After adjusting for smoking, alcohol, deployment, and service branch (Table 3), individuals in Q3 and Q4 had a higher odds of colon cancer compared with those in Q1 at time 1 (Q3: OR 2.54; CI 1.18, 5.46 and Q4: OR 3.08; CI 1.33, 7.11) and at time 2 (Q3: OR 2.83; CI 1.41, 5.66 and Q4: OR 3.37 (CI 1.58, 7.17). P -values for trend were 0.007 at time 1 and 0.001 at time 2, respectively. When analyses were confined to cases with confirmed colon cancer in both DMSS and ACTUR databases and their matched controls, the direction and magnitude of the ORs were similar at time 1 and time 2.

Discussion

Our study found that percentage energy from fat both in the year prior to cancer diagnosis and before first blood draw was associated with increased colon cancer risk. Compared to individuals with the lowest percentage of energy intake from fat, those with higher intake at diagnosis (>31.8% Pfat) and at an earlier time had a significantly increased risk of colon cancer. These associations might exist primarily among females.

While there are few studies on Pfat in relation to colon cancer, results from previous case-control studies on fat intake have not been consistent. An OR of 2.0 (CI 1.0–4.0) for males and 1.9 (CI 1.0–3.7) for females was observed when comparing highest vs. lowest fat intake in a colon cancer study conducted in Utah (West et al. 1989). Additionally, a matched case-control study of colon and rectal cancer in Chinese Americans located in North America showed an OR of 1.8 (CI 1.3–2.5) for males and 2.0 (CI 1.2–3.5) for females from saturated fat (Whittemore et al. 1990). In contrast, a combined analysis of 13 case-control studies did not observe any associations with total fat or fat constituents (Howe et al. 1997). Among cohort studies, both positive (Giovannucci et al. 1994; Willett et al. 1990) and null (Lin et al. 2004; Dahm et al. 2010; Sun et al. 2012) associations of total fat and colon cancer have been reported. While the differences in results may be due to variability in measurement of fat intake, fat source, and whether specific fat constituents were considered, baseline study design and population may be important related factors.

In this study, we used another measurement of fat intake (Pfat) to assess its relation to colon cancer risk and observed a more than a 3-fold increase in risk among highest consumers of fat. Percentage energy from fat reflects the relative intake of total fat and is positively related to the consumption of saturated fat (U.S. Department of Agriculture 2005). While we were unable to specify individual fat constituents, we provided some insight into whether total fat or saturated fat intake may be related to colon cancer risk. Furthermore, many studies assessed fat intake based on time at cancer diagnosis for cases and corresponding reference date for controls (Sun et al. 2012; Potter and McMichael 1986; West et al. 1989; Whittemore et al. 1990). Because of a long latent period for cancer occurrence, exposure at

an earlier time is a desired measurement. Results from our study suggest that Pfat is positively associated with colon cancer not only at cancer diagnosis but also at an earlier time (average of 10 years earlier).

When data were stratified by gender, the difference in Pfat among cases and controls seemed to be primarily driven by females. Because we were not able to perform multivariable analyses by gender due to small sample size, our results are only suggestive of the possible effects of gender. This finding is supported by positive associations previously reported in an all-female cohort (Willett et al. 1990) as well as case-control studies (Potter and McMichael 1986; West et al. 1989; Whittemore et al. 1990) on fat intake and colon cancer. While it is not clear why the association might exist primarily among women in our study, recent literature suggests that it may be related to estrogen profiles, which may increase colon cancer risk (Liang 2007). Animal models showed that high fat diets may downregulate estrogen receptors in adipose tissue, which subsequently increases inflammation and insulin resistance while decreasing glucose metabolism (Giovannucci et al. 2001; Purim et al. 2013; Riant et al. 2009) – all of which are associated with increased risk of carcinogenesis.

While our study is the first one of its kind that measures percentage of energy intake from fat at two time points and assesses its relation to colon cancer risk, it has limitations. The number of study subjects was relatively small overall, which prevented us from performing multivariate analysis by gender. Like many other studies, there may be errors in recalling dietary intake. If errors were differential between cases and controls, the results might be biased. Additionally, the participation rates were relatively low and varied between cases and controls. We cannot exclude the possibility that differential participation may have affected the results. The percentage energy from fat screener is a short dietary screener intended for broad comparisons of fat intake and is, thus, limited in its ability to assess detailed dietary information accurately. Furthermore, Pfat score at time 1 was a weighted relative measure, rather than a direct measure based on reported frequencies of food consumption. Thus, it was not as accurate as the measure at time 2. Finally, study subjects were active-duty members, who may differ from the general population in many aspects including dietary intake and physical activity. Therefore, our results may not be readily generalizable.

In summary, these data suggest that increased fat consumption as a percentage of total energy intake is associated with increased colon cancer risk at both cancer diagnosis and at an earlier time that may be mainly observed among females. Confirmation in a larger study is warranted.

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Table 1

Selected demographic characteristics among colon cancer cases and matched controls in the U.S. military

	Cases n(%)	Controls n(%)
Race/Ethnicity		
Non-Hispanic White	158 (73.5)	166 (77.2)
Non-Hispanic Black	34 (15.8)	35 (16.3)
Hispanic	10 (4.7)	7 (3.3)
Other/Unknown	13 (6.1)	7 (3.3)
Highest Education^a		
High School or Less	20 (9.3)	22 (10.2)
Some College, Technical, Vocational	82 (38.1)	72 (33.5)
College	46 (21.4)	49 (22.8)
Graduate, Professional	66 (30.7)	70 (32.6)
Unknown	1 (0.5)	2 (0.9)
Service Branch^a		
Army	65 (30.2)	49 (22.8)
Navy	65 (30.2)	108 (50.2)
Air Force	56 (26.1)	24 (11.2)
Marines	16 (7.4)	31 (14.4)
Other/Unknown	13 (6.1)	3 (1.4)
Marital Status^a		
Married	160 (74.4)	164 (76.3)
Not Married	54 (25.1)	50 (23.3)
Unknown	1 (0.5)	1 (0.5)
Religion		
None	31 (14.4)	40 (18.6)
Protestant	122 (56.7)	106 (49.3)
Jewish	2 (0.9)	4 (1.9)
Catholic	51 (23.7)	57 (26.5)
Other	5 (2.3)	5 (2.3)
Unknown	4 (1.9)	3 (1.4)
Household Income^a		
<\$29,999	16 (7.4)	11 (5.1)
\$30,000 to \$44,999	36 (16.7)	38 (17.7)
\$45,000 to \$59,999	59 (27.4)	45 (20.9)
>\$60,000	101 (47.0)	119 (55.4)
Unknown	3 (1.4)	2 (0.9)
People in Household^a		
1	44 (20.5)	43 (20.0)
2	43 (20.0)	43 (20.0)
3	53 (24.7)	45 (20.9)

	Cases n(%)	Controls n(%)
4	47 (21.9)	52 (24.2)
>4	26 (12.1)	32 (14.9)
Unknown	2 (0.9)	0

Note: Not all column totals add up to 100% due to rounding

^aRefers to the year before date of diagnosis/reference

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Table 2
Unadjusted odds of colon cancer among subjects in the U.S. military, separately by time period

Quartiles of total fat (% energy)					
	Q1	Q2	Q3	Q4	P trend
Time 1: Before date of first blood draw					
All					0.0288
Median, IQR	25.84, 4.50	31.77, 2.05	36.83, 3.26	47.22, 11.02	
Cases/Controls	24/45	43/42	63/46	47/44	
OR	Reference	1.72	2.42	1.96	
95% CI	Reference	0.93, 3.18	1.31, 4.48	1.03, 3.71	
Females					0.0103
Median, IQR	25.04, 7.55	31.50, 0.90	36.72, 4.12	51.33, 12.31	
Cases/Controls	4/16	9/6	9/5	9/4	
OR	Reference	4.1	5.18	9.06	
95% CI	Reference	1.00, 16.84	1.15, 23.42	1.57, 52.23	
Males					0.3081
Median, IQR	27.46, 4.29	31.88, 2.13	36.83, 3.26	46.55, 10.45	
Cases/Controls	20/29	34/36	54/41	38/40	
OR	Reference	1.32	1.88	1.38	
95% CI	Reference	0.65, 2.66	0.94, 3.75	0.68, 2.80	
Time 2: Before date of diagnosis/reference					
All					0.0073
Median, IQR	28.05, 2.65	30.82, 0.80	33.07, 1.29	37.43, 3.32	
Cases/Controls	35/54	40/52	75/54	63/53	
OR	Reference	1.22	2.18	1.91	
95% CI	Reference	0.68, 2.22	1.24, 3.83	1.05, 3.46	
Females					0.0086
Median, IQR	27.06, 4.20	30.74, 0.57	32.68, 0.70	37.81, 3.52	
Cases/Controls	9/18	6/10	12/5	11/5	
OR	Reference	1.43	5.63	7.35	
95% CI	Reference	0.37, 5.60	1.19, 26.69	1.17, 46.12	

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Quartiles of total fat (% energy)					P trend
	Q1	Q2	Q3	Q4	
Males					0.1090
Median, IQR	28.31, 2.38	30.91, 0.80	33.13, 1.32	37.39, 3.30	
Cases/Controls	26/36	34/42	63/49	52/48	
OR	Reference	1.12	1.75	1.50	
95% CI	Reference	0.57, 2.19	0.94, 3.28	0.78, 2.87	

Note: OR=Odds Ratio; CI=Confidence Interval; IQR=Interquartile Range

Table 3

Adjusted odds of colon cancer among subjects in the U.S. military, separately by time period

	Time 1: Before date of first blood draw		Time 2: Before date of diagnosis/reference	
	Cases/Controls	OR (95%CI)	Cases/Controls	OR (95%CI)
Total fat (% energy)				
Q1	23/45	Reference	33/54	Reference
Q2	41/41	1.76 (0.83, 3.72)	39/48	2.00 (0.96, 4.18)
Q3	63/46	2.54 (1.18, 5.46)	73/53	2.83 (1.41, 5.66)
Q4	47/42	3.08 (1.33, 7.11)	61/51	3.37 (1.58, 7.17)
Ever drinker				
No	60/47	Reference	59/43	Reference
Yes	114/127	0.66 (0.36, 1.21)	147/163	0.59 (0.34, 1.02)
Ever smoker				
No	143/133	Reference	175/173	Reference
Yes	31/41	0.59 (0.29, 1.21)	31/33	0.89 (0.46, 1.69)
Service branch				
Army	53/43	Reference	62/48	Reference
Navy	51/86	0.27 (0.13, 0.58)	63/104	0.23 (0.11, 0.47)
Air Force	49/17	2.83 (1.21, 6.63)	56/23	1.94 (0.92, 4.10)
Marines	11/26	0.18 (0.06, 0.56)	14/29	0.18 (0.07, 0.50)
Other	10/2	4.59 (0.83, 25.44)	11/2	5.23 (1.02, 26.70)
Deployed				
No	116/98	Reference	63/48	Reference
Yes	58/76	0.68 (0.38, 1.23)	143/158	0.88 (0.47, 1.64)