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ORIGINAL CONTRIBUTION

Is dietary fat associated with the risk of colorectal cancer? A meta-analysis of 13 prospective cohort studies

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Abstract
Background The results of animal studies suggest there is a significant role for dietary fat in the development of colorectal cancer (CRC). However, inconsistent results have been reported by epidemiological studies.
Aim of study To evaluate the association between total dietary fat and risk of colorectal cancer development using a meta-analysis based on prospective cohort studies.
Methods Published literature was retrieved from Medline, Embase and CNKI (China Knowledge Resource Integrated Database) databases updated to 1st May, 2009. Overall, thirteen prospective cohort studies with 3,635 cases and 459,910 participants were included.
Results The combined relative risk (RR) [95% confidence interval (95%CI)] for the risk of CRC was 0.99 (0.89,1.09) when the highest level of total dietary fat was versus (vs.) the lowest level. Stratified analyses according to gender, ethnicity, country and age showed that the highest level of total dietary fat did not increase the risk of CRC [RR (95%CI): 0.89 (0.77,1.03) for males; 1.09 (0.94,1.26) for females; 1.08 (0.94,1.25) for Caucasians; 0.90 (0.77,1.04) for Asians; 1.13 (0.94,1.36) for Americans; 0.92 (0.81,1.04) for individuals older than 40]. Besides those, the highest level of total fat diet also did not increase the risk of neither colon cancer [RR (95%CI): 0.96 (0.82,1.13)] nor rectal cancer [RR (95%CI):1.07 (0.63,1.82)]. Furthermore, neither animal fat nor plant fat were associated with the risk of CRC [RR (95%CI): 1.05 (0.91–1.22) for animal fat and 0.96 (0.82–1.11) for plant fat].
Conclusions This meta-analysis suggests that dietary fat may not be associated with the increased risk of CRC. More well-designed studies with larger population performed among Asians are needed to further evaluate the associations. In addition, probable bias caused by measurement error should be noticed in this meta-analysis, and measurement error needs to be adjusted in the future studies.

Keywords Colorectal cancer · Dietary fat · Cohort study · Meta-analysis

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Introduction

Colorectal cancer (CRC) is the third most common cancer in males and the second most common cancer in females [1, 2]. The development of CRC is a multistep process with

multiple risk factors involved, which are still requiring further elucidation. Indeed, many studies have suggested the importance of environmental factors in the development of CRC, especially diet [2, 3]. Recently, several meta-analyses have suggested that a diet rich in fruit, vegetables [4] or fish oil [5] is associated with a decreased risk of CRC, while a diet rich in meat is associated with an increased risk of CRC [6]. At the annual meeting of the Nutrition Society and the British association for parenteral and enteral Nutrition in 2007 [7], the Second World Cancer Research Fund/American Institute for Cancer Research Expert Report produced headline recommendations that physical activity, limited energy-dense food consumption, limited alcohol drinking, limited red and processed meat consumption were all of benefit for general health, including cancer prevention. However, the effect of dietary fat on the pathogenesis of CRC remains unclear.

Animal studies [8–10] confirmed that dietary fat could stimulate the secretion of bile acids, which can damage the colonic mucosa and lead to the regression of epithelium, eventually increasing the risk of CRC. However, inconsistent results were reported by epidemiological studies. Many prospective cohort studies [11–26] demonstrated that there was no association between total dietary fat and the risk of CRC except in one study [27]. A meta-analysis [28] performed in 1997 based on thirteen case–control studies also reported the absence of impact of total dietary fat on the risk of CRC.

Prospective cohort studies, which allow avoidance of recall and selection bias [6] in general, would be regarded as a more powerful method than case–control studies to examine the influence of dietary fat on the risk of CRC. A meta-analysis based on prospective cohort studies is unavailable at present, and thus we felt it necessary to perform such a study.

Materials and methods

Literature search strategy

To identify the cohort studies that evaluate the association between dietary fat and the risk of CRC, we searched the databases of Medline (up to 1st May, 2009), Embase (up to 1st May, 2009) and CNKI (China Knowledge Resource Integrated Database, up to 1st May, 2009) using the following key words: 'diet*' OR 'fat*', 'colo*' OR 'rect*' OR 'large bowel', 'cancer' OR 'tumor' OR 'carcinoma'. We also searched the references manually to identify suitable studies.

Inclusion and exclusion criteria

The studies included in this analysis had to meet the following inclusion criteria: (a) The studies reported the association between total dietary fat and the risk of CRC as the main aim of this meta-analysis was to primarily evaluate this influence. (b) The studies reported the relative risk (RR) and its 95% confidence interval (95%CI) according to the highest level of fat intake vs. the lowest level; (c) Only prospective cohort studies were considered. When the studies used the same data series, the earliest published article or the article with the largest population was included. The following were the major reasons for exclusion of papers: (a) Details of inclusion and exclusion criteria for participants were not stated in the study. (b) Data were repeatedly reported. (c) The study was a review, comment, editorial or letter.

Study selection

Overall, 121,537 studies were returned with the search key words. After excluding obviously irrelevant studies through reviewing the titles and abstracts, 17 studies [11–27] were finally identified to be potentially suitable for this meta-analysis. Through reviewing the full texts, the relative risks (95% confidence intervals) of 2 studies [11, 19] could not be available though an effort to connect with authors was made; 3 studies [14, 22, 25] used the same data series, and the study [14] with the largest population was included according to the statement above. Hazard Ratio (95% confidence interval, 95%CI) was used as effect size in one paper published in 2008 [26]. However, when the highest level of dietary fat vs. the lowest level was examined, hazard ratio and 95%CI were considered to be equal to a relative risk and 95% confidence interval. Overall, thirteen prospective cohort studies [12–18, 20, 21, 23, 24, 26, 27] were selected. The details of the study selection are shown in Fig. 1.

Data extraction

Two authors (Liu L and Chen Z) extracted data from the 13 prospective cohort studies independently. Disagreements were solved by discussion with coauthors. The following data were extracted: the cohort size, the ethnicity of participant, gender, the period of follow-up, dietary questionnaire, adjusted confounders, relative risks and 95% confidence intervals for the highest level of total fat vs. the lowest level and the types of fatty acids.

Statistical analysis

Combined relative risk (RR) and 95% confidence intervals (95%CI) were used to measure the impact of the highest level of dietary fat on the risk of CRC [the highest vs. the lowest level of dietary fat]. RR and corresponding 95%CI were transferred into logarithm from individual study for

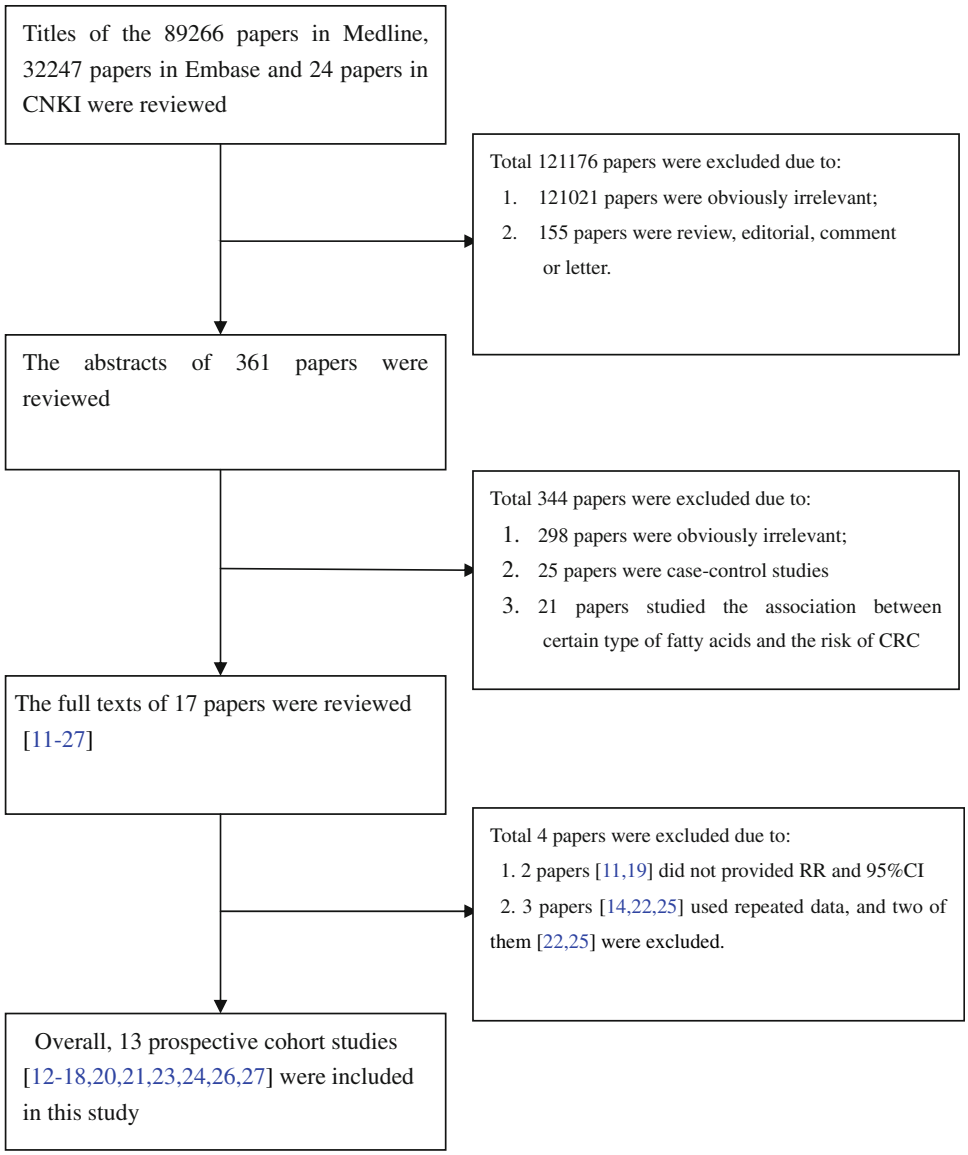

Fig. 1 Flow chart of selection of studies and specific reasons for exclusion from the meta-analysis

combined analysis, and standard error of logRR was calculated for analysis for publication bias. The method of random effects model [29] was used to analyze the statistical significance. When separate RR and 95%CI were provided for colon and rectum, early and advanced stage, males and females, we combined the RRs and 95%CIs to get a single RR and corresponding 95%CI for further analysis. Stratified analyses were performed according to the gender, ethnicity, age, country, confounders, tumor location, types of fatty acids and sources of fatty acids. Confounders were defined as smoking, alcohol drinking and physical activity, which all have been proven to be associated with the risk of CRC [7].

The statistic analysis was performed by STATA 8.2 software (Stata-Corp, College Station, Tex), and $P < 0.05$ was considered to be statistically significant. Tests for heterogeneity were carried out using Q-test and *I*-square (I^2) test. $P < 0.1$ was considered to be statistically significant for heterogeneity. *I*-square (I^2) was used to estimate total variation across studies due to heterogeneity in percentage. I^2 less than 25% was considered as low level of heterogeneity, 25–50% as moderate level, and higher than 50% as high level [30].

Several methods were used to evaluate the publication bias. Visual inspection of asymmetry in funnel plots was performed. The Begg rank correlation method and the Egger weighted regression method were also used to statistically assess publication bias ($P < 0.05$ was considered representative of statistically significant publication bias). All statistical tests were two sided.

Results

Study characteristics

Overall, thirteen prospective cohort studies [12–18, 20, 21, 23, 24, 26, 27] with 3,635 cases of CRC and 459,910 participants were included. Among those 13 studies, 5 studies [12, 13, 21, 23, 27] were performed in America, 5 studies [14, 15, 17, 18, 20] in European countries (two in Finland, one in England, one in Norway and one in Netherlands), and 3 studies [22, 24, 26] in Asian countries (two in Japan and one in Singapore).

There were seven studies whose participants were older than 40 [12–14, 16, 18, 23, 26]. Food frequency questionnaires varied from 50 to 276 items were used to assess various types of food consumption in the studies. All of the studies stated explicit inclusion and exclusion criteria. Diagnoses of colorectal cancer, death, migration or completion of follow-up were all commonly used as endpoints according to whichever occurred first. When analyzing the association between dietary variables and the risk of CRC, Cox proportional hazards model was commonly used, and many confounders, such as energy, age, smoking and alcohol, were adjusted in the studies. All of the studies [12–18, 20, 21, 23, 24, 26] reported no relationship between dietary fat and risk of CRC except for one study [27], which reported a positive association. Thus, we performed this meta-analysis to quantitatively analyze the association between dietary fat and the risk of CRC. The basic characteristics of the studies are listed in Table 1.

Meta-analysis

Single RR and its corresponding 95%CI were combined from separate RRs and 95%CIs in four articles [15, 16, 24, 26]. Combined analyses indicated that there were no associations between total dietary fat, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and cholesterol and the risk of CRC, and combined RRs (95%CI) were 0.99 (0.89,1.09) for total dietary fat, 1.00 (0.90,1.12) for SFA, 1.04 (0.93,1.16) for MUFA, 1.10 (0.91 1.34) for PUFA and 1.10 (0.92,1.32) for cholesterol (Figs. 2, 3, 4, 5, 6).

Stratified analyses according to gender, ethnicity, country, period of follow-up, food frequency questionnaire (FFQ) and age showed that total dietary fat was not associated with the risk of CRC [RR (95%CI): 0.89 (0.77,1.03) for males; 1.09 (0.94,1.26) for females; 1.08 (0.94,1.25) for Caucasians; 0.90 (0.77,1.04) for Asians; 1.13 (0.94,1.36) for Americans; 1.01 (0.88,1.15) for period of follow-up = <10 years, 1.03 (0.91,1.17) for FFQ $<$ 100 items, 0.89 (0.74,1.07) for FFQ $\geq$ 100 items and 0.92 (0.81,1.04) for individuals older than 40] (Table 2). After adjusting confounders of smoking, alcohol drinking and physical activity, the result was persistent [RR (95%CI): 0.97 (0.83,1.12)]. According to the sources of fatty acids, both animal fat and plant fat were certified no associations with the risk of CRC [RR (95%CI): 1.05 (0.91,1.22) for animal fat; 0.96 (0.83,1.12) for plant fat]. In addition, we also found there were no associations between total dietary fat and the risk of colon cancer [RR (95%CI): 0.96 (0.82,1.13)] and rectal cancer [RR (95%CI): 1.07 (0.63,1.82)]. Furthermore, stratified analyses showed that diet rich in SFA, MUFA, PUFA and cholesterol also did not increase the incidence of colon and rectum cancer. The details are shown in Tables 2 and 3.

Stratified analyses for the risk of CRC for Caucasians and for the risk of colon cancer according to gender were performed, and the results were similar. Indeed, the results suggested that total dietary fat did not increase either the risk of CRC for Caucasians or the risk of colon cancer among males and females. Details are shown in Table 4.

Heterogeneity among these studies was not evident (Tables 2, 3 and 4). Potential publication bias was not ruled out (Figs. 7, 8) except combined analyses for the associations between total dietary fat and the risk of CRC for males (P of Begg for bias = 0.13; P of Egger for bias $<$ 0.01), between saturated fatty acid and the risk of CRC (P of Begg for bias = 0.05; P of Egger for bias = 0.04).

Discussion

Diet and lifestyle are thought to be closely associated with the development of CRC [31, 32]. Particularly consumption of large amounts of calcium, dairy food and vegetables [4, 33] is suggested to be associated with a decreased risk of CRC. In contrast, processed meat and alcohol drinking may play an important role in the tumorigenesis of CRC [6, 34]. Dietary fat, a common component of most foods, has been suggested to be a risk factor for tumor formation [35, 36], but inconsistent results have been reported [27, 28]. The Second World Cancer Research Fund/American Institute for Cancer Research Expert Report did not reach an ultimate conclusion about the influence of dietary fat on the risk of CRC in 2007 [7]. Recently, meta-analyses have been performed and have indicated a modest effect [37]. Therefore, we performed this meta-analysis based on the 13 prospective cohort studies to examine the relationship more rigorously.

The possible mechanism for dietary fat increasing the risk of CRC based on animal models is that increasing secretion of bile acids caused by dietary fat can lead to chronic damage to the mucosa of the colorectal tract, which in turn can cause aberrant gene mutation, eventually

Table 1 Characteristics of the 13 prospective cohort studies

Author (reference)	Ethnicity (country)	No. of cases/ cohort sizes	Follow-up (median years)	Methods of diagnosing CRC	Food Frequency Questionnaire (items)	Adjusted RR (95%CI)[a]	Confounder adjustments
Willett [27]	Caucasian (U.S.A)	150/88751	1980–1986 (NA)	Self-report, medical record	61	2.00 (1.10,3.63)	Age and total energy
Bostick [13]	Caucasian (U.S.A.)	212/35216	1989–1992 (NA)	Cancer registry	127	0.86 (0.54,1.33)	Age, energy, height; parity, vitamin E and vitamin A
Giovannucci [12]	Caucasian (U.S.A)	205/47949	1986–1992 (NA)	Self-report, medical record	131	1.19 (0.74,1.90)	Age and energy
Jarvinen [20]	Caucasian (Finland)	109/9959	1967–1999 (NA)	Cancer registry	More than 100	1.47 (0.52,4.2)	Age, gender, BMI, occupation, smoking, geographical area, energy intake, consumption of vegetables, fruits and cereals
Flood [21]	Caucasian (U.S.A.)	487/45496	1989–1998 (median 8.5)	Self-report, cancer registry	62	1.14 (0.86,1.53)	Energy
Lin [23]	Caucasian (U.S.A)	202/37547	1993–2003 (median 8.7)	Self-report, medical record	131	1.00 (0.63,1.58)	Ag, random treatment assignment, BMI; family history of colorectal cancer, history of colorectal Polyps, physical activity, smoking; alcohol consumption, hormone therapy and total energy intake
Oba [24]	Asian (Japan)	213/30221	1993–2000 (NA)	Cancer registry	169	1.02 (0.72,1.45)[b]	Age, height, BMI, smoking, alcohol and physical activity
Goldbohm [14]	Caucasian (Netherlands)	215/3123	1986–1989 (median 3.3)	Cancer registry	150	1.07 (0.70–1.64)	Age, energy and fiber intake
Butler [26]	Asian (Singapore)	961/61321	1993–2005 (median 9.8)	Cancer registry	165	0.96 (0.79–1.17)[b,c]	Age, interview year, dialect group, smoking, alcohol consumption, BMI, education, familial history of colorectal cancer, diabetes and physical activity
Pietinen [18]	Caucasian (Finland)	185/27111	NA (median 8)	Cancer registry	276	0.90 (0.6 ± 1.3)	Smoking, BMI, alcohol consumption, education, physical activity and calcium intake
Chyou [16]	Asian (Japan)	453/7954	1965–1995 (NA)	Cancer registry	54	0.74 (0.57–0.96)[d]	Age
Kato [17]	Caucasian (England)	100/14727	1985–1994 (median 7.1)	Self-report and cancer registry	70	1.05 (0.60–1.84)	Age, place at enrollment, energy and education
Gaard [15]	Caucasian (Norway)	143/50535	1977–1991 (median 11.4)	Cancer registry	80	0.80 (0.50–1.3)[b]	Age, height, BMI and smoking

NA not available

[a] Adjusted RR (95%CI) was based on the highest quintile versus the lowest quintile of total dietary fat

[b] Single RR and 95%CI were combined from the RRs and 95%CIs of gender (male and female)

[c] Tumor stage (Dukes A&B and C&D)

[d] Or sites (colon and rectum)

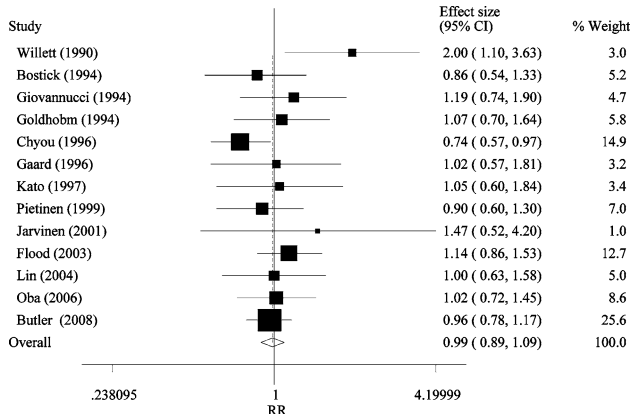

Fig. 2 Forest plot showed that absence of impact of total dietary fat on the risk of colorectal cancer. Random effects model was used

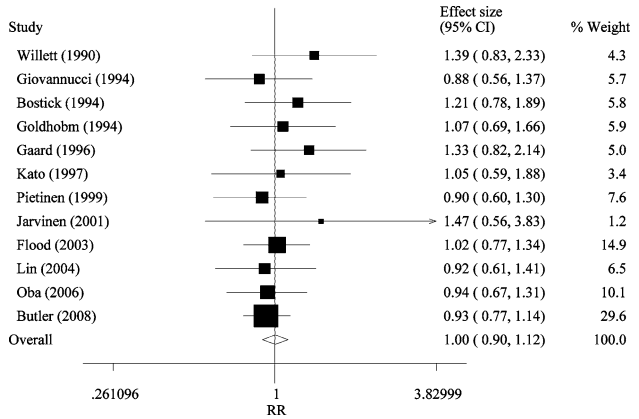

Fig. 3 Forest plot showed that absence of impact of saturated fatty acids on the risk of colorectal cancer. Random effects model was used

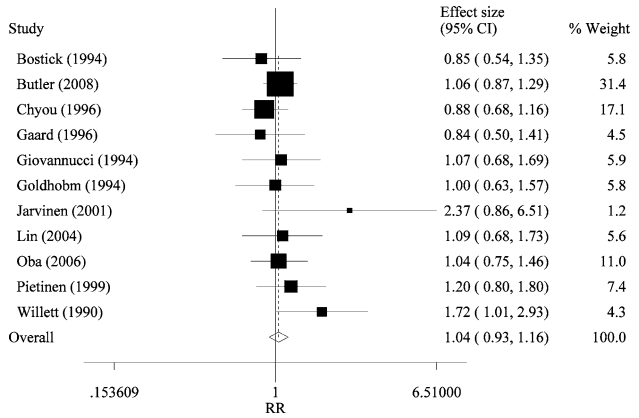

Fig. 4 Forest plot showed that absence of impact of monounsaturated fatty acids on the risk of colorectal cancer. Random effects model was used

leading to the formation of CRC [8–10, 38]. However, this hypothesized effect is not supported by epidemiological studies [15–18]. In addition, it is assumed that dietary fat can lead to a high level of energy intake, which increases

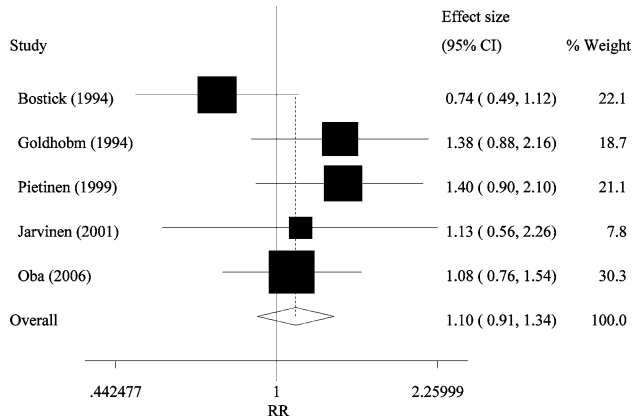

Fig. 5 Forest plot showed that absence of impact of polyunsaturated fatty acids on the risk of colorectal cancer. Random effects model was used

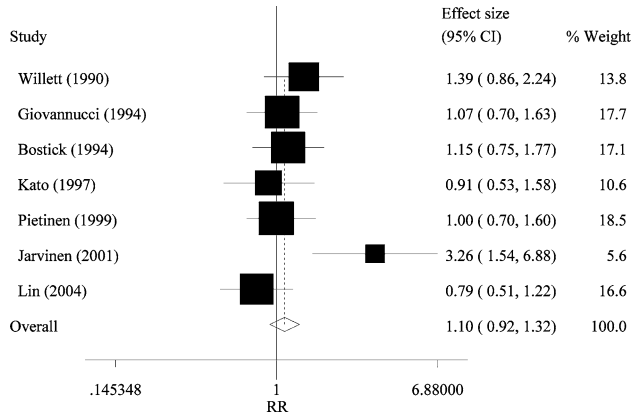

Fig. 6 Forest plot showed that absence of impact of cholesterol on the risk of colorectal cancer. Random effects model was used

the risk of CRC [39]. However, after adjusting for energy intake, dietary fat still does not increase the risk of CRC [40]. This meta-analysis suggests that dietary fat is not associated with increased risk of CRC, which is consistent with the result of a previous meta-analysis [28] based on 13 case–control studies. Furthermore, the result is supported by a randomized controlled trial [41] despite the fact that the intervention group in the study was given a relatively low level of dietary fat.

Different types of fatty acids may have different functions in the development of CRC. Restricting the analyses to the types of fatty acids, SFA, MUFA, PUFA and cholesterol were all not associated with the increased risk of CRC. Following on from this, as the main aim of this meta-analysis was to assess the impact of total dietary fat on the risk of CRC, these results have to be interpreted with caution. Omega-3 and Omega-6 PUFAs have enzymatic competition for their metabolism and have different effects in the process of tumorigenesis [42, 43]. Omega-3 PUFA is assumed to carry a decreased risk of CRC. However,

Table 2 Meta-analysis the association between total dietary fat and the risk of CRC

Indexes	No. of studies	RR (95%CI)	Test for heterogeneity		Test for publication bias	
			P value	I^2 (%)	P of Begg[d]	P of Egger[e]
Gender						
Males	7	0.89 (0.77,1.03)	0.23	26.3	0.13	<0.01
Females	9	1.09 (0.94,1.26)	0.36	9.4	1.00	0.44
Mixed[a]	1	1.47 (0.52,4.20)	NA	NA	NA	NA
Ethnicity						
Caucasians	10	1.08 (0.94,1.25)	0.67	0	0.21	0.38
Asians	3	0.90 (0.77,1.04)	0.23	32.4	1.00	0.97
Country						
U.S.A	5	1.13 (0.94,1.36)	0.26	23.7	0.22	0.58
European countries	5	1.01 (0.81,1.27)	0.92	0	0.46	0.09
Asian countries	3	0.90 (0.77,1.04)	0.23	32.4	1.00	0.97
Source of fat						
Animal fat	5	1.05 (0.91–1.22)	0.22	28.6	1.00	0.78
Plant fat	5	0.96 (0.82–1.11)	0.49	0	0.71	0.68
Tumor location						
Colon	8	0.96 (0.82,1.13)	0.06	48.7	0.11	0.06
Rectum	2	1.07 (0.63,1.82)	0.98	0	NA	NA
Follow-up						
Period ≤ 10 years	6	1.01 (0.88,1.15)	0.93	0	0.71	0.70
Period > 10 years	1	1.02 (0.57,1.82)	NA	NA	NA	NA
Confounders adjusted[b]						
Adjusted	4	0.97 (0.83,1.12)	0.97	0	1.00	0.87
Not adjusted	9	1.00 (0.87,1.16)	0.13	36	0.47	0.11
FFQ[c]						
<100 items	8	1.03 (0.91,1.17)	0.52	0	0.17	0.25
≥100 items	5	0.89 (0.74,1.07)	0.29	19	0.22	0.09
Age of participants ≥ 40 years	7	0.92 (0.81,1.04)	0.60	0	0.37	0.47
Total	13	0.99 (0.89,1.09)	0.38	6.9	0.13	0.09

NA not applicable

[a] Mixed, participants including males and females

[b] Confounders adjusted, confounders of smoking, alcohol drinking and physical activity were adjusted

[c] FFQ, Food Frequency Questionnaire

[d] P of Begg, P value of Begg rank correlation method for testing publication bias

[e] P of Egger, P value of Egger rank correlation method for testing publication bias

Omega-6 PUFA [44] has an inverse relationship with the risk of CRC. Interestingly, our stratified analysis showed that there was no association between PUFA and the risk of CRC. This result might be modified by the different functions of Omega-3 and Omega-6 PUFA in the process of carcinogenesis. Some studies reported increased risk of CRC with a high level of SFA intake [26, 45]. However, this meta-analysis and other studies do not suggest the positive association between SFA and the risk of CRC [19] (Tables 2 and 3). Therefore, this relationship needs to be further studied. We also examined the relationships between animal fatty acids and plant fatty acids and the risk of CRC. The results, persistently, did not reach significance.

The incidence of CRC varies globally [1–3]. It is well established that CRC is the second most common cancer in the European countries and the United States [1, 2, 46]. However, the incidence of CRC in Asian countries is significantly lower [47]. One of the explanations for the difference may be different dietary patterns between Caucasians and Asians [48, 49]. Compared to Asians, Caucasians tend to have a diet that is rich in meat, which may be also rich in fat. However, subgroup analyses of the meta-analysis did not find any association between dietary fat and the risk of CRC in Caucasian women and men. It might suggest that other risk factors but dietary fat contributed to the risk of CRC, for example, dietary pattern, high level of meat, alcohol drinking and smoking [6, 34, 49, 50] (Table 4).

As with all meta-analyses, this study is open to potential bias because of systematic and random errors [51]. First, most of included studies (ten of the 13 studies) were performed in Europe and America so it is difficult to say how well the findings can be extrapolated to Asian populations. Second, even though a standardized searching strategy was decided on before initiating the study, using a thorough computerized and manual searching method, it is still possible that articles that may have potentially fitted the inclusion criteria have not been included. Third, the definition of the highest level of dietary fat was from median 75 g/d–150 g/d, and the lowest level of dietary fat was from 40 g/d to 95 g/d, which indicates that some potential

Table 3 Meta-analysis the associations between types of dietary fat and the risk of CRC

Indexes	No. of studies	Adjusted RR (95%CI)[d]	Test for heterogeneity		Test for publication bias	
			P value	I^2(%)	P of Begg[d]	P of Egger[e]
Saturated fatty acid						
Gender						
Males	6	0.92 (0.78,1.09)	0.40	4	0.26	0.11
Females	9	1.06 (0.92,1.22)	0.65	0	0.60	0.77
Mixed[a]	1	1.39 (0.31,6.14)	NA	NA	NA	NA
Ethnicity						
Caucasians	10	1.05 (0.92,1.21)	0.87	0	0.07	0.16
Asians	2	0.93 (0.79,1.10)	0.96	0	NA	NA
Country						
U.S.A	5	1.04 (0.87,1.24)	0.64	0	0.81	0.58
European countries	5	1.07 (0.86,1.34)	0.74	0	0.46	0.25
Asian countries	2	0.93 (0.79,1.10)	0.96	0	NA	NA
Tumor location						
Colon	7	1.09 (0.92,1.30)	0.72	0	0.55	0.31
Rectum	1	1.39 (0.31,6.14)	NA	NA	NA	NA
Follow-up						
Period $\leq$ 10 years	6	0.96 (0.85,1.10)	0.98	0	0.19	0.41
Period $>$ 10 years	1	1.33 (0.82,2.15)	NA	NA	NA	NA
Confounders adjusted[b]						
Adjusted	4	0.93 (0.80,1.07)	1.00	0	0.73	0.52
Not adjusted	8	1.10 (0.94,1.29)	0.87	0	0.27	0.19
FFQ[c]						
$<$100 items	8	0.99 (0.88,1.11)	0.78	0	0.17	0.12
$\geq$100 items	4	1.07 (0.84,1.37)	0.69	0	0.73	0.46
Age of participants $\geq$ 40 years	6	0.96 (0.83,1.10)	0.89	0	0.71	0.51
Total	12	1.00 (0.90,1.12)	0.89	0	0.05	0.04
Monounsaturated fatty acid						
Gender						
Males	7	0.99 (0.86,1.14)	0.70	0	0.55	0.08
Females	7	1.10 (0.93,1.31)	0.28	19.1	1.00	0.27
Mixed[a]	1	2.37 (0.86,6.51)	NA	NA	NA	NA
Ethnicity						
Caucasians	8	1.10 (0.92,1.31)	0.47	0	0.92	0.61
Asians	3	1.00 (0.87,1.16)	0.22	30.2	0.81	0.75
Country						
U.S.A	4	1.11 (0.88,1.41)	0.27	23.7	0.31	0.08
European countries	4	1.09 (0.84,1.40)	0.44	0	0.81	0.81
Asian countries	3	1.00 (0.87,1.16)	0.22	30.2	0.81	0.75
Tumor location						
Colon	8	0.97 (0.83,1.13)	0.24	21.6	0.47	0.15
Rectum	2	1.55 (0.95,2.52)	0.56	0	NA	NA
Follow-up						
Period $<$ 10 years	4	1.08 (0.92–1.26)	0.45	0	1.00	0.79
Period $>$ 10 years	1	0.84 (0.50–1.41)	NA	NA	NA	NA
Confounders adjusted[b]						
Adjusted	4	1.08 (0.93,1.25)	0.45	0	1.00	0.81
Not adjusted	7	1.00 (0.84,1.18)	0.27	20.5	0.71	0.24

Table 3 continued

Indexes	No. of studies	Adjusted RR (95%CI)[d]	Test for heterogeneity		Test for publication bias	
			P value	I^2(%)	P of Begg[d]	P of Egger[e]
FFQ[c]						
<100 items	6	1.09 (0.95,1.25)	0.37	7.5	0.92	0.98
≥100 items	5	0.95 (0.79,1.15)	0.41	0	0.46	0.06
Age of participants ≥ 40 years	7	1.01 (0.90,1.15)	0.54	0	0.90	0.68
Total	11	1.04 (0.93,1.16)	0.37	7.5	0.38	0.32
Cholesterol						
Gender						
Males	2	1.03 (0.77,1.39)	0.82	0	NA	NA
Females	4	1.04 (0.82,1.31)	0.34	11.2	1.00	0.98
Mixed[a]	1	3.26 (1.54,6.88)	NA	NA	NA	NA
Country						
U.S.A	4	1.07 (0.86,1.33)	0.38	3.1	0.73	0.46
European countries	3	1.18 (0.87,1.59)	0.01	76.7	0.30	0.38
Confounders adjusted[b]						
Adjusted	2	0.89 (0.66,1.21)	0.44	0	NA	NA
Not adjusted	5	1.24 (0.99,1.54)	0.08	52.6	0.46	0.15
FFQ[c]						
<100 items	4	0.99 (0.79,1.25)	0.38	1.7	1.00	0.84
≥100 items	3	1.29 (0.97,1.70)	0.03	71.0	0.30	0.04
Age of participants ≥ 40 years	4	1.00 (0.80–1.23)	0.65	0	1.00	0.56
Total	7	1.10 (0.92,1.32)	0.06	49.8	0.37	0.06
Polyunsaturated fatty acid	5	1.10 (0.91,1.34)	0.05	54.9	0.71	0.84

NA not applicable

[a] Mixed, participants including males and females

[b] Confounders adjusted, confounders of smoking, alcohol drinking and physical activity were adjusted

[c] FFQ, Food Frequency Questionnaire

[d] P of Begg, P value of Begg rank correlation method for testing publication bias

[e] P of Egger, P value of Egger rank correlation method for testing publication bias

Table 4 Stratified analyses of the impact of total dietary fat on the risk of CRC according to site (colon) and ethnicity (Caucasians)

Indexes	No. of studies	Adjusted RR (95%CI)	Test for heterogeneity		Test for publication bias	
			P value	I^2(%)	P of Begg[a]	P of Egger[b]
Colon						
Males	5	0.93 (0.76,1.14)	0.07	53.9	1.00	0.07
Females	5	1.01 (0.78,1.31)	0.10	48.6	0.81	0.89
Total	8	0.97 (0.83,1.13)	0.06	43.1	0.53	0.17
Caucasians						
Males	4	1.06 (0.82,1.36)	0.83	0	1.00	0.42
Females	7	1.10 (0.92,1.32)	0.37	7	0.76	0.70
Total	10	1.09 (0.94–1.26)	0.69	0	0.88	0.75

[a] P of Begg, P value of Begg rank correlation method for testing publication bias

[b] P of Egger, P value of Egger rank correlation method for testing publication bias

bias caused by imbalance of baseline may exist. As a result we can not rule out the influence of potential bias. Fourth, although publication bias was not observed by visual inspection of funnel plots, Begger rank correlation method and the Egger weighted regression method, potential publication bias might exist. Fifth, nested case-cohort study,

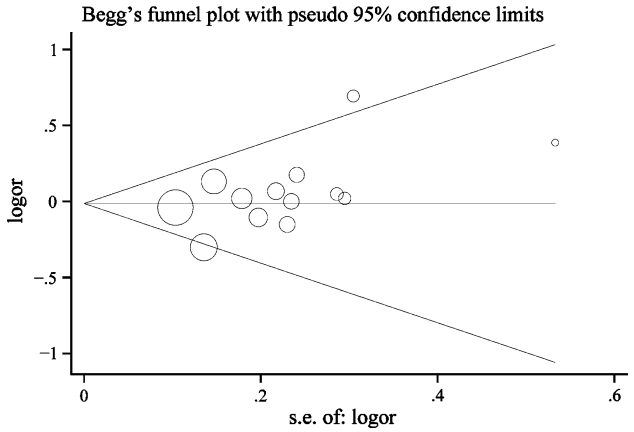

Fig. 7 Begg's funnel plot was used to evaluate the potential publication bias for total dietary fat and colorectal cancer risk. Each point represents a separate study for the indicated association. Horizontal line indicates mean effect size

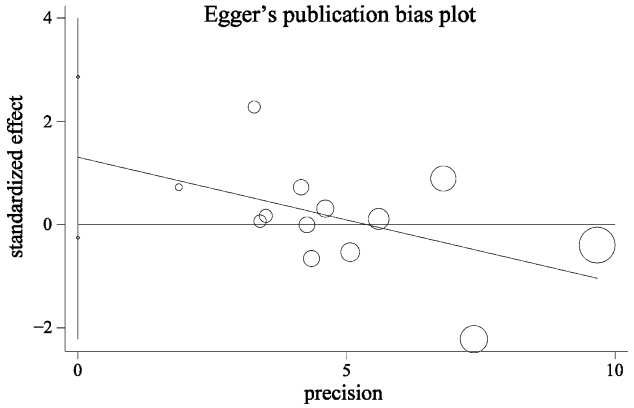

Fig. 8 Egger's publication bias plot was used to evaluate the potential publication bias for total dietary fat and colorectal cancer risk. Each point represents a separate study for the indicated association. Oblique line indicates mean effect size

which is originated from prospective cohort study, can avoid the recall bias and is deemed to same efficacy as prospective cohort study [52]. However, to the best of our knowledge, there is just one nested case–control study about the relationship between dietary fat and risk of CRC published, and hence not included in this study [40]. Finally, although the results of stratified analysis according to items of food frequency questionnaires were consistent with a null association, the measurement error caused by food frequency questionnaires still may exist in some studies, finally influencing the result of this meta-analysis. However, taking all these criticisms into account, we feel the result of this meta-analysis is consistent with the previous meta-analysis and randomized controlled study [28, 41], and thus powerful enough to illustrate the null relationship between total dietary fat and the risk of CRC. In order to minimize the potential bias, we designed explicit methods for data extraction and study evaluation and were thorough in retrieving suitable studies. Further strength in our study lies in the fact that data from prospective cohort studies were collected before the occurrence of CRC, thus avoiding selection bias and recall bias, which are more vulnerable to affect case–control studies. Therefore, only prospective cohort studies were selected in order to effectively reflect an association between dietary fat and the risk of CRC.

In conclusion, this meta-analysis suggests that there may be no associations between total dietary fat and the risk of CRC for males and females. Stratified analyses may indicate no relationships between total dietary fat and the risk of colon cancer and rectal cancer. In addition, we observe that there may be no associations between SFA, MUFA, PUFA and cholesterol and risk of CRC. More well-designed studies with larger population performed among Asians are needed to further evaluate the associations. In addition, probable bias caused by measurement error should be noticed in this meta-analysis, and measurement error needs to be adjusted in the future studies.

Conflict of interest None.

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