



Meta-Analysis

Dietary fat intake and risk of bladder cancer: Evidence from a meta-analysis of observational studies

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Abstract: The association between dietary fat intake and bladder cancer had been inconsistent in the previous epidemiological studies. The aim of this study was to investigate the difference between fat intake and bladder cancer risk. Databases of PubMed, Embase, and Web of Science were systematically searched for suitable studies from inception to June 2018. A meta-analysis was performed to analyze the efficacy of dietary fat intake on bladder cancer risk. A Forest plot was prepared to indicate the relationship. Ten citations were used in this study. The Funnel plot suggested highest category of dietary fat intake could increase the risk of bladder cancer (summarized relative risk (RR)= 1.279, 95% confidence interval (CI)= 1.036-1.577, $I^2= 53.2\%$, $P_{\text{for heterogeneity}} = 0.019$). A positive association was found among European populations (summarized RR= 1.359, 95%CI= 1.027-1.798), but not in North American populations. The association was not significant in the subgroup analysis by fat type on bladder cancer risk. Egger test ($P= 0.239$) and Funnel plot showed there was no significant publication bias in the included publications. In conclusions, compared with the lowest category of dietary fat intake, the highest category could significantly increase the bladder cancer risk, especially among European populations. As some limitations existed in our analysis, large scale studies with detailed amount of dietary fat intake are needed to verify our results.

Key words: Dietary; Fat; Bladder cancer; Meta-analysis.

Introduction

Bladder cancer, which is one of the most common malignant tumors of the urinary system, accounted for 90%-95% of all urothelial cancers (1). It was estimated that there were 430,000 new cases and 165,000 bladder cancer deaths in 2012 (2). Risk factors such as genetic factors (3, 4), secondhand smoking (5), diabetes mellitus (6), vitamin A (7), fruits and vegetables (8) and so on had been well documented. Previous paper had been suggested that dietary may be an important factors in the development of bladder cancer because many diet-related metabolites were in direct contacting with the bladder epithelium during excretion (9).

High dietary fat intake had been confirmed the relationship with ovarian cancer (10), breast cancer (11), lung cancer (12), endometrial cancer (13) and so on in the recent meta-analyses. So far, numerous researchers had examined potential effects of dietary fat intake on bladder cancer risk (14-20). Meanwhile, some studies had demonstrated that people with highest fat intake had a higher risk of developing bladder cancer, compared to those with lowest fat intake (21-23). However, no consistent results were found in the publications. Hence, this meta-analysis was conducted to obtain a compendium of the current understanding of dietary fat intake and bladder cancer risk.

Materials and Methods

Search strategy and inclusion criteria

We conducted a systematic search of PubMed, Embase, and Web of Science databases for observational studies published from inception to June 2018 in English using the search terms: 'fat' OR 'saturated fat' OR 'monounsaturated fat' OR 'polyunsaturated fat' OR 'animal fat' OR 'vegetable fat' combined with 'bladder cancer'. All the studies enrolled using this strategy was checked independently by two authors; the articles that met all inclusion criteria were enrolled in the meta-analysis. The inclusion criteria were as following: (1) patients were diagnosed of bladder cancer; (2) observational studies; (3) the interested association about fat intake and bladder cancer; (4) available relative risk (RR) and 95% confidence interval (CI) for bladder cancer in fat intake.

Data extraction

In our systematic review of the literature, the following variables were extracted from included studies: study, year, country, ages, study type, fat type, number of cases and participants, RR and 95%CI for bladder cancer. Two authors independently extracted the above mentioned data, and disagreements were resolved by discussion and consensus.

Statistical analysis

The overall summary effect sizes were estimated using a random-effects model. Forest plots and data analyses were performed using Stata version 12.0. A Q and I² test were performed to analysis the heterogeneity of the studies that included in this meta-analysis (24). The Egger’s test (25) and Begg’s funnel plots method was used to evaluate the risk of publication bias. A two-sided P<0.05 was defined as statistically significant, except for heterogeneity testing, which had a boundary level of 0.10.

Results

Study selection and study characterization

A search of the PubMed, Embase, and Web of Science databases was conducted, and 10 observational studies (14-23) were enrolled, after excluding duplicated, irrelevant and non-full text articles. The flow diagram for the identified studies is shown in Figure 1. All studies were published in English.

This meta-analysis included 4,302 bladder cancer patients. Eight of the 10 included articles were case-control studies, and the others were cohort studies. Six articles came from Europe and the other four came from North America. Vena et al. assessed the risk of bladder cancer by subgroup analysis under 65 and over 65 years of age, respectively. We considered this report as two independent studies. Therefore, there were 11 studies from the 10 articles used in our meta-analysis. The characteristics of the observational studies are shown in Table 1.

Meta-analysis

In our meta-analysis, the summarized RR was 1.279 (95%CI= 1.036-1.577, P= 0.022), suggesting a higher developing of bladder cancer with dietary fat intake (Figure 2). Significant heterogeneity (I²= 53.2%, P= 0.019) was found in the overall analysis. A meta-regression analysis was performed to assess the high between-study heterogeneity. Results from meta-regression suggested that study design (P= 0.023) was significantly associated with this high heterogeneity. The I² reduced to 0.0% for cohort studies and 29.2% for case-control studies while we performed subgroup analysis by study design.

A subgroup analysis was performed to determine the relationship between fat type and bladder cancer risk. The results were negative for bladder cancer risk with highest category of saturated fat, monounsaturated fat, polyunsaturated fat or animal fat intake. When we performed subgroup analysis by study design, positive association was found in case-control studies (summarized RR= 1.432, 95%CI= 1.153-1.778), but not in cohort studies. A further analysis was performed to evaluate the geographic locations and risk of bladder cancer. Significant association was found among European populations (summarized RR= 1.359, 95%CI= 1.027-1.798), but not in North American populations.

Risk of bias and sensitivity analysis

Results from Egger test (P= 0.239) and Funnel plot (Figure 3) showed no significant publication bias in the included publications. A sensitivity analysis plot

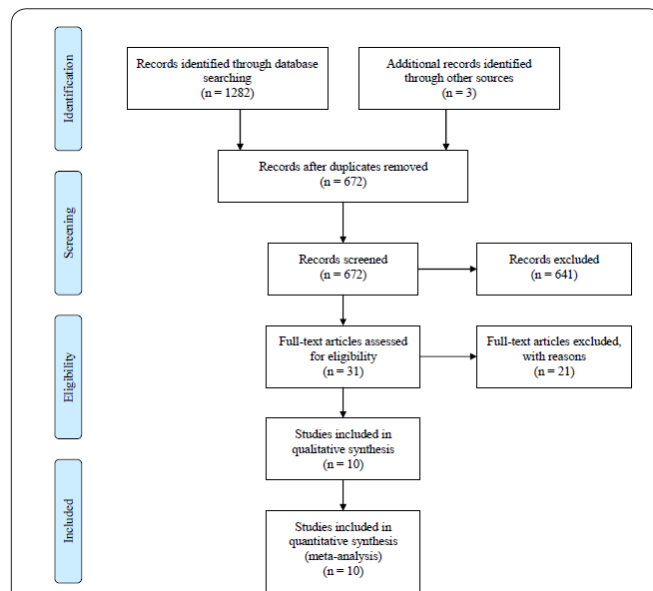


Figure 1. Flow chart of meta-analysis for exclusion/inclusion of studies.

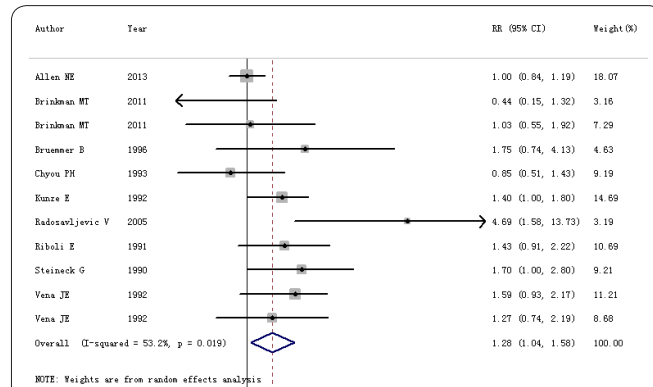


Figure 2. The forest plot of the relationship between dietary fat intake and bladder cancer risk.

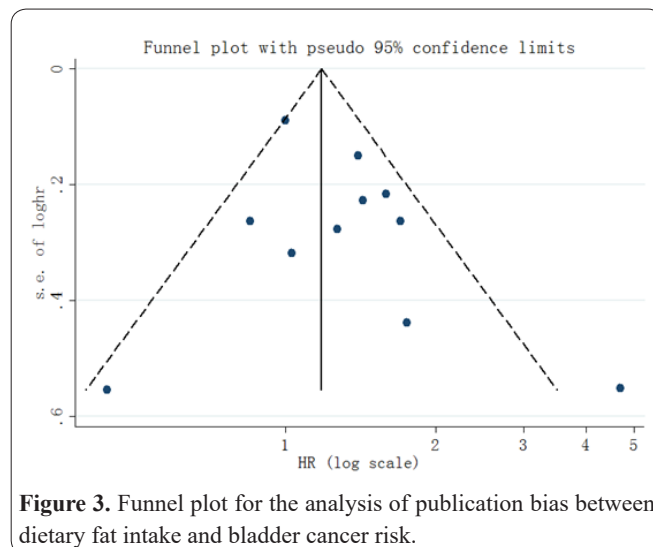


Figure 3. Funnel plot for the analysis of publication bias between dietary fat intake and bladder cancer risk.

was performed to analyze the sensitivity of the studies included in this meta-analysis, which indicated that no observational studies needed to be excluded (Figure 4).

Discussion

Although numbers of papers had published to assess the relationship between fat intake and bladder cancer risk, no specific evidence was detected based on the

Table 1. Characteristics of the included studies about the association of dietary fat intake on bladder cancer risk.

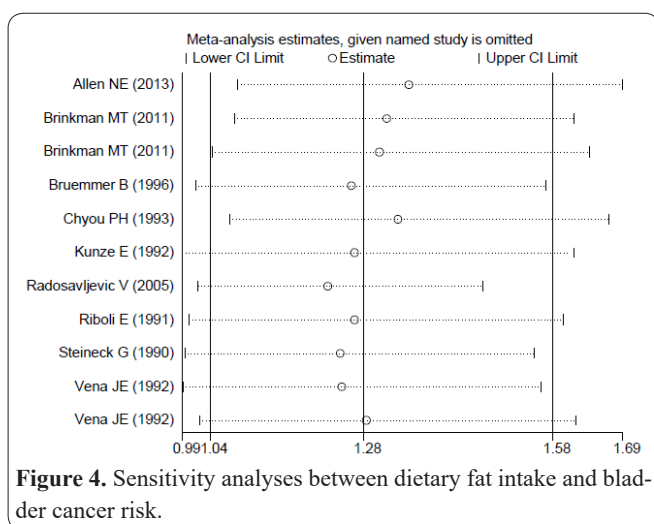
| Study, year | Design | Age | Participants, Cases | Country | Fat type | RR (95%CI) Highest vs. lowest | Adjustment |
|-----------------------|--------|-------|---------------------|---|--|--|--|
| Allen NE, 2013 | Cohort | 50-69 | 469339, 1416 | Netherlands, Norway, Spain, Sweden and United Kingdom | Total fat Saturated fat Monounsaturated fat Polyunsaturated fat | Total fat 1.00(0.84-1.19) Saturated fat 0.95(0.79-1.14) Monounsaturated fat 0.93(0.76-1.15) Polyunsaturated fat 1.19(0.99-1.42) | Adjusted for sex, age at recruitment and centre and adjusted for age (as the underlying time variable), smoking history, smoking duration, BMI and total energy intake, where appropriate. |
| Brinkman MT, 2011 | PBCC | >50 | 586, 200 | Belgium | Total fat Saturated fat Monounsaturated fat Polyunsaturated fat | Total fat 1.03(0.55-1.92) Saturated fat 1.17(0.65-2.11) Monounsaturated fat 1.02(0.55-1.89) Polyunsaturated fat 0.80(0.45-1.42) | Adjusted for sex, age, smoking status (current/non-current), number of cigarettes smoked per day, number of years smoking, occupational exposure to PAHs or aromatic amines and energy intake (kcal). |
| Brinkman MT, 2011 | PBCC | 25-74 | 561, 322 | United States | Total fat Animal fat Vegetable fat Saturated fat Monounsaturated fat | Total fat 0.44(0.15-1.32) Animal fat 0.52(0.20-1.33) Vegetable fat 0.39(0.18-0.86) Saturated fat 0.41(0.16-1.09) Monounsaturated fat 0.69(0.25-1.88) | Adjusted for age, sex, smoking status (current v. non-current smoker; pack-years smoked (categories: 0-10, 10-20, 20-30, 30-40, 40-50 and 50+)), cholesterol intake and total energy intake (Q, kJ/d). |
| Bruemmer B, 1996 | PBCC | 45-65 | 667, 262 | United States | Total fat Polyunsaturated fat Saturated fat | Total fat 1.75(0.74-4.13) Polyunsaturated fat 1.12(0.53-2.35) Saturated fat 1.49(0.69-3.21) | Adjusted for age, sex, county, smoking, and calories |
| Chyou PH, 1993 | Cohort | 46-68 | 7995, 96 | United States | Total fat | 0.85(0.51-1.43) | Adjusted for age and smoking. |
| Kunze E, 1992 | HBCC | 55-84 | 1350, 675 | Germany | Total fat | 1.4(1-1.8) | Adjusted for age and smoking. |
| Radosavljevic V, 2005 | HBCC | 64.92 | 260, 130 | Serbia | Animal fat | 4.69(1.58-13.73) | Adjusted for age and smoking. |
| Riboli E, 1991 | HBCC | <80 | 1224, 432 | Spain | Total fat Saturated fat Monounsaturated fat Polyunsaturated fat | Total fat 1.43(0.91-2.22) Saturated fat 2.25(1.42-3.55) Monounsaturated fat 1.48(0.98-2.23) Polyunsaturated fat 0.87(0.57-1.31) | Adjusted for calories minus calories from fat |
| Steineck G, 1990 | PBCC | 40-76 | 929, 418 | Sweden | Total fat | 1.7(1.0-2.8) | Adjusted for gender, year of birth and smoking. |
| Vena JE, 1992 | HBCC | 35-90 | 1206, 351 | United States | Total fat | <65 years 1.59(0.93-2.17) >65 years 1.27(0.74-2.19) | Adjusted for age, education, and cigarette smoking (pack-years) by use of continuous variables. |

Abbreviation: RR: relative risk; CI: Confidence Intervals; PBCC: Population-based case-control study; HBCC: Hospital-based case-control study.

Table 2. Summary RR and 95%CI of the association between dietary fat intake and bladder cancer risk.

| Subgroups | Number of studies | Number of cases | RR(95% CI) | P for trend | Heterogeneity test | |
|----------------------|-------------------|-----------------|---------------------|-------------|--------------------|-------|
| | | | | | I ² (%) | P |
| Overall | 11 | 4302 | 1.279(1.036-1.577) | 0.022 | 53.2 | 0.019 |
| Fat type | | | | | | |
| Saturated fat | 5 | 2632 | 1.163(0.735-1.842) | 0.519 | 75.6 | 0.003 |
| Monounsaturated fat | 4 | 2370 | 1.049(0.801-1.373) | 0.727 | 33.0 | 0.214 |
| Polyunsaturated fat | 5 | 2632 | 0.926(0.686-1.248) | 0.612 | 50.2 | 0.091 |
| Animal fat | 2 | 452 | 1.537(0.178-13.261) | 0.696 | 88.9 | 0.003 |
| Study design | | | | | | |
| Cohort | 2 | 1512 | 0.983(0.834-1.160) | 0.843 | 0.0 | 0.558 |
| Case-control | 9 | 2790 | 1.432(1.153-1.778) | 0.001 | 29.2 | 0.185 |
| PBCC | 4 | 1202 | 1.198(0.721-1.992) | 0.485 | 48.7 | 0.119 |
| HBCC | 5 | 1588 | 1.501(1.196-1.883) | <0.001 | 19.2 | 0.293 |
| Geographic locations | | | | | | |
| Europe | 6 | 3271 | 1.359(1.027-1.798) | 0.032 | 63.9 | 0.017 |
| North America | 5 | 1031 | 1.159(0.794-1.692) | 0.445 | 46.4 | 0.113 |

RR: relative risk; CI: confidence interval; PBCC: population-based case-control studies; HBCC: hospital-based case-control studies.

**Figure 4.** Sensitivity analyses between dietary fat intake and bladder cancer risk.

observational studies. In this study, 11 independent observational studies were used involving 4302 bladder cancer patients and 484,117 participants. Our results revealed that people with highest intake of dietary fat could increase the risk of bladder cancer. Subgroup meta-analyses by different fat type, different study design (including different source of controls in case-control studies) and different geographic locations were also performed.

In fat type subgroups, there was no significant association between saturated fat, monounsaturated fat, polyunsaturated fat or animal fat intake and bladder cancer risk. Nevertheless, the results might not be very conclusive, because of the relatively small number of participants and studies used in the subgroups analysis. In geographic locations subgroups, significant association between dietary fat intake and bladder cancer appeared in European populations, instead of North American populations. Therefore, our results were more suitable for European populations, not in all population. In the subgroup analysis by study design, statistical significance about such association was also observed in case-control studies, not in cohort studies while only 2 cohort studies included in this meta-analysis. Therefore, it is necessary to have a larger sample size of the relevant

cohort researches.

We found significant between-study heterogeneity on the association between fat intake and bladder cancer risk. A paper had said that between-study heterogeneity in the meta-analysis is common (26), and it is an essential component to explore the heterogeneity existed in the between-study. Meta-regression was used to explore the causes of heterogeneity for covariates of publication year, fat types, study design, ethnicity and number of cases. Results from meta-regression suggested that study design was significantly associated with this high heterogeneity. The I^2 was reduced to 0.0% for cohort studies and 29.2% for case-control studies.

There were some limitations in our analysis. Firstly, the sample size in each stratified analyses was relatively small and might potentially limit the enough statistical power to explore the real relationship. Therefore, further studies, especially cohort studies, with a larger sample size were still needed to be further validated. Secondly, only English language articles were included, which may omit other languages studies. However, we did not detect any publication bias. Thirdly, nine of the 11 studies were case-control studies and only 2 were cohort studies. The selection bias, recall bias and some other confounding factors cannot be excluded; for example, some subjects may change their dietary fat intake after the baseline assessment. However, case-control design was a very important epidemiological approach in the observational study. Therefore, it is requirement for evidence from prospective cohort studies.

In summary, our results concluded that highest dietary fat intake compared with the lowest intake may be associated with the development of bladder cancer. As some limitations existed in our analysis, large scale studies with detailed amount of dietary fat intake are needed to verify our results.

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Competing interests

None.

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