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Original Research

Healthy dietary patterns and incidence of biliary tract and gallbladder cancer in a prospective study of women and men

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Abstract ***Background:*** Whether diet influences the risk of biliary tract cancer (BTC) is unknown. We examined the associations of two healthy dietary patterns, including a modified Dietary Approach to Stop Hypertension (mDASH) diet and a modified Mediterranean (mMED) diet, with the incidence of BTC in a population-based prospective study.
Methods: The study population comprised 76,014 Swedish adults who were 45–83 years of age and cancer-free at baseline. The mDASH and mMED diets were calculated from self-reported dietary data collected by a validated food-frequency questionnaire. Cox proportional hazards regression models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI) adjusted for potential confounders.
Results: Over 1,010,777 person-years (mean 13.3 years) of follow-up, 140 extrahepatic BTC cases (including 77 gallbladder cancers) and 23 intrahepatic BTC cases were ascertained by linkage with the Swedish Cancer Register. Adherence to the mDASH and mMED diets was statistically significantly inversely associated with risk of extrahepatic BTC ($P_{trend} \leq 0.0003$) and gallbladder cancer ($P_{trend} \leq 0.005$) but not intrahepatic BTC ($P_{trend} \geq 0.11$). The multivariable HRs (95% CI) for the highest versus lowest tertile of the mDASH diet were 0.41 (0.26–0.64) for extrahepatic BTC and 0.36 (0.20–0.64) for gallbladder cancer. The corresponding HRs (95% CI) for the mMED diet were respectively 0.41 (0.25–0.67) and 0.42 (0.23–0.79).
Conclusion: Adherence to a healthy diet may play a role in reducing the risk of extrahepatic BTC.

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1. Introduction

Biliary tract cancers (BTC) include carcinomas of the gallbladder and bile ducts. Gallbladder cancer, which is the most common malignant tumour of the biliary tract, is usually diagnosed at an advanced stage, is difficult to treat, and often has a poor survival [1]. Few risk factors have been identified but gallstone disease [2], obesity [3–5] and type 2 diabetes [6] have been associated with increased risk of gallbladder cancer. The incidence of gallbladder cancer has declined strikingly over the last three decades [7]. This trend is possibly related to increasing number of cholecystectomies for gallstones as well as the efficient treatment of Helicobacter pylori infections [7]. Improved diet, with increased consumption of fresh fruits and vegetables and decreased consumption of salted and preserved foods, may also have played a role in the declining incidence. Diet could potentially influence the risk of gallbladder cancer and BTC directly (e.g. through anti-oxidative, anti-inflammatory or other anti-carcinogenic effects) or indirectly through gallstones, obesity and type 2 diabetes. Yet, the possible role of diet in the development of gallbladder cancer and BTC is unknown. To the best of our knowledge, no previous epidemiologic study has examined the association between overall dietary patterns and risk of gallbladder cancer or BTC.

We sought to investigate the association between two healthy dietary patterns, including the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean (MED) diets, and the incidence of BTC. For this purpose, we used data from two population-based prospective cohorts of Swedish adults.

2. Methods

2.1. Study population

The Swedish Mammography Cohort was initiated in 1987–1990 when all women born in 1914–1948 and residing in central Sweden (Västmanland and Uppsala counties) were invited to participate in a mammography-screening program and to complete a dietary questionnaire. Completed questionnaires were obtained from 74% of the source population. Between mid-September 1997 and January 1998, 39,227 participants (70% response rate) who were still alive and living in the study area answered an expanded questionnaire regarding diet, lifestyle and other risk factors for cancer. Simultaneously, all men born in 1918–1952 and residing in central Sweden (Västmanland and Örebro counties) received an identical dietary and lifestyle questionnaire; 48,850 men (49% of the source population) returned a completed questionnaire and agreed to participate in the Cohort of Swedish Men. The two cohorts are representative of the Swedish population in the same age range in terms of age distribution, educational level and prevalence of overweight [8].

Eligible for inclusion in the present study were participants who adequately completed the 1997 dietary questionnaire without having an implausible total energy intake. After exclusion of participants with an incorrect or a missing personal identification number and those who died, had a cancer diagnosis (other than non-melanoma skin cancer) in the Swedish Cancer Register or had undergone a cholecystectomy (data from the Swedish Patient Register) before baseline, 76,014 participants (32,588 women [49–83 years of age] and 43,426 men [45–79 years of age]), with follow-up from 1998 through 2012, remained for analysis. The Regional Ethical Review Board at Karolinska Institutet in Stockholm, Sweden, approved the study.

2.2. Dietary assessment and diet scores

A 96-item food-frequency questionnaire (FFQ), designed to measure the Swedish diet, was used to assess average food consumption over the preceding year. Eight predefined frequency categories that ranged from never to $\geq$3 times/week were provided for most food items. For commonly consumed foods (e.g. milk and bread), participants were asked to indicate their exact consumption per day or per week. Participants were also asked to report their average consumption of alcoholic beverages during the past year. The reproducibility and validity of the FFQ with regard to nutrient intake have been described previously [9]. For example, the mean correlation coefficient between FFQ-based estimates and 14 24-hour recall interviews was 0.65 for macronutrients.

The DASH diet calculated in this study was adapted from the DASH diet score of Fung *et al.* [10]. The original score included vegetables, fruits, legumes and nuts, whole-grains, low-fat dairy products, red meat and processed meat, sweetened beverages and sodium. We modified the original score by excluding sodium intake because dietary sodium could not be adequately estimated from our FFQ due to lack of information on salt used in cooking and at the table. Participants were classified into quintiles by their intake of each food component. For the first five components, participants were provided a score from 1 to 5 for being in the lowest to the highest quintiles of intake. Scores were reversed (5–1 for lowest to highest quintiles) for red meat and processed meat and sweetened beverages for which low intake was desired. Possible scores on the modified DASH (mDASH) diet ranged from 7 to 35.

The modified Mediterranean (mMED) diet was based on the Mediterranean diet scale constructed by Trichopoulou *et al.* [11] and later revised to include fish [12]. We modified the original scale concerning the included food components by 1) replacing cereals with whole-grain cereals (because whole-grain cereals, unlike