Inverse Association Between Coffee Consumption and Risk of Cholecystectomy in Women but Not in Men

Caroline Nordenvall,* Viktor Oskarsson,‡ and Alicja Wolk‡

Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; and ‡Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

BACKGROUND & AIMS: There is conflicting epidemiologic evidence on whether coffee consumption reduces the risk of gallstone disease. We examined the association between coffee consumption and risk of cholecystectomy (as a proxy for symptomatic gallstone disease) in a prospective cohort study.

METHODS: We collected data from 30,989 women (born 1914–1948) and 40,936 men (born 1918–1952) from the Swedish Mammography Cohort and the Cohort of Swedish Men. Baseline information on coffee consumption was collected by using a food-frequency questionnaire; subjects were followed up for procedures of cholecystectomy from 1998 through 2011 by linkage to the Swedish Patient Register. Hazard ratios (HRs) were estimated by using Cox proportional hazard models.

RESULTS: During a total follow-up period of 905,933 person-years, we identified 1057 women and 962 men who had undergone a cholecystectomy. After adjustment for potential confounders, the HR of cholecystectomy was 0.58 (95% confidence interval [CI], 0.44–0.78) for women who drank ≥6 cups of coffee/day compared with women who drank <2 cups/day. In contrast, there was no association in men (HR, 0.96; 95% CI, 0.75–1.24). Because of this sex difference, we examined and found evidence of effect modification by menopausal status and use of hormone replacement therapy (HRT) ($P_{interaction}$ = .026). An inverse association was observed only in women who were premenopausal (HR, 0.17; 95% CI, 0.05–0.55) or used HRT (HR, 0.44; 95% CI, 0.28–0.70).

CONCLUSIONS: We observed an inverse association between coffee consumption and risk of cholecystectomy in women who were premenopausal or used HRT but not in other women or in men.

Keywords: Gallbladder; Surgery; Diet; Sweden.

Coffee, one of the most widely consumed beverages in the world, has been suggested to influence gallstone formation by stimulating cholecystokinin release and gallbladder contractility.[1,2] However, the epidemiologic evidence on whether coffee consumption reduces the risk of gallstone disease is conflicting. In a few studies, a statistically significant inverse association between coffee consumption and risk of gallstone disease has been observed.[3–6] Other studies have not confirmed an association,[7–10] and some have even observed a statistically significant positive association.[11,12]

Because of this conflicting evidence, we examined the association between coffee consumption and risk of cholecystectomy (as a proxy for symptomatic gallstone disease) in 2 prospective cohorts of women and men. Because Sweden is one of the countries with the highest coffee consumption per capita worldwide,[13] these cohorts had a wide distribution of coffee consumption.

Materials and Methods

Participants

The Swedish Mammography Cohort,[14] which was initiated during 1987 to 1990, included 66,651 women (74% of all women born 1914–1948 and living in Västmanland and Uppsala counties in central Sweden) who responded to a questionnaire regarding their diet, weight, height, and parity. Updated information, including additional questions on smoking, medication use, and medical

history, was obtained in 1997 from 39,227 women (70% of all women still alive and living in the study area) who responded to a second questionnaire. The Cohort of Swedish Men,[15] which was initiated simultaneously in 1997, included 48,850 men (49% of all men born 1918–1952 and living in Västmanland and Örebro counties in central Sweden) who responded to a questionnaire that was identical (except for some sex-specific questions) to the second questionnaire in the Swedish Mammography Cohort.

For this study, which was approved by the Regional Ethical Board at Karolinska Institutet (Stockholm, Sweden) (2010/1461-31/3), we used the questionnaire in 1997 as baseline. The return of a completed questionnaire was treated as informed consent of study participation.

Assessment of Coffee Consumption and Dietary Covariates

A food-frequency questionnaire was used to collect dietary information in 1997. Participants reported their average daily or weekly coffee consumption (in cups; 1 cup defined as 150 mL) during the past year with an open-ended question. This question has been validated by comparing it with data from fourteen 24-hour dietary recall interviews during a period of 1 year in a group of 248 men; the Spearman coefficient was 0.71 (Alicja Wolk, unpublished data). Information on dietary covariates (including other beverages) was also obtained from the food-frequency questionnaire.

Assessment of Other Covariates

On the questionnaire in 1997, participants reported their education, smoking status, physical activity, use of aspirin, weight, and height. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). History of hyperlipidemia and diabetes was obtained by linkage to the Swedish Patient Register and the Swedish Diabetes Register, respectively, and complemented with information from the questionnaire. On the female questionnaire, there were also questions on parity, use of oral contraceptives, and menopausal status and use of hormone replacement therapy (HRT).

Case Ascertainment

Via the participants' personal identity numbers, we identified procedures of cholecystectomy by linkage to the Swedish Patient Register. In this register, which has had an almost complete national coverage since 1987,[16] cholecystectomy has been represented by codes 535 (until 1996) and JKA20 and JKA21 (after 1996, according to the Swedish Classification of Operations and Major Procedures).

Participants who had undergone a cholecystectomy between January 1, 1998 and December 31, 2011 were classified as cases. An underlying history of cholelithiasis or cholecystitis was ascertained by International Classification of Diseases-9 codes 574 and 575 and International Classification of Diseases-10 codes K80 and K81.

Information on death and cancer was obtained by linkage to the Swedish Cause of Death Register and the Swedish Cancer Registry, respectively.

Statistical Analysis

At baseline, we excluded participants who had an incorrect personal identity number (n = 540) or a history of cholecystectomy or cancer (except non-melanoma skin cancer) (n = 10,550) as well as participants with missing (n = 4292) or extremely high (>10 cups/day) coffee consumption (n = 288). Also, because symptoms that lead to cholecystectomy may be due to malignancies and not gallstones, we excluded those who developed cancer in the duodenum, liver, gallbladder, biliary ducts, or pancreas during follow-up (n = 482 including 62 cases of cholecystectomy). Thus, of the 39,227 women and 48,850 men who were eligible, 30,989 women and 40,936 men were included in the analysis.

Person-years were calculated from January 1, 1998 to the date of cholecystectomy, date of death, or December 31, 2011, whichever came first.

Cox proportional hazard models, with age as the time scale, were used to estimate hazard ratios (HRs) of cholecystectomy associated with coffee consumption. All analyses were done separately for women and men. No evidence of departure from the proportional hazards assumption was observed when it was tested by using Schoenfeld's residuals. Participants were divided into 4 categories according to their coffee consumption: <2 (reference), 2–3, 4–5, or ≥6 cups/day. A test for trend across categories was conducted by modeling the median coffee consumption in each category as a continuous variable. To examine a potential dose-response association in detail, we used restricted cubic splines with 3 knots at fixed quantiles of the distribution of coffee consumption (0.10, 0.50, and 0.90; a test against the hypothesis of a linear association was conducted by testing the second spline transformation equal to zero).[17]

Multivariable models were adjusted for education (≤12, >12 years), BMI (<25, 25–29, ≥30 kg/m^2), smoking status (never, past, current), alcohol drinking (never, past, current (binary; according to median intake among drinkers [4.6 g/day in women and 10.5 g/day in men]), physical activity (<20, 20–40, >40 minutes of walking/day), use of aspirin (no, yes), history of hyperlipidemia (no, yes), history of diabetes (no, yes), energy intake (kcal/day in sex-specific quartiles), and tea consumption (never, <2, ≥2 cups/day), as well as for use of oral contraceptives (never, ever), parity (nulliparous, parous), and menopausal status and use of HRT (premenopausal, never use, ever use) in women. The