Gallstone Disease Is Associated With Increased Mortality in the United States

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BACKGROUND & AIMS: Gallstones are common and contribute to morbidity and health care costs, but their effects on mortality are unclear. We examined whether gallstone disease was associated with overall and cause-specific mortalities in a prospective national population-based sample. **METHODS:** We analyzed data from 14,228 participants in the third US National Health and Nutrition Examination Survey (20–74 years old) who underwent gallbladder ultrasonography from 1988 to 1994. Gallstone disease was defined as ultrasound-documented gallstones or evidence of cholecystectomy. The underlying cause of death was identified from death certificates collected through 2006 (mean follow-up, 14.3 years). Mortality hazard ratios (HR) were calculated using Cox proportional hazards regression analysis to adjust for multiple demographic and cardiovascular disease risk factors. **RESULTS:** The prevalence of gallstones was 7.1% and of cholecystectomy was 5.3%. During a follow-up period of 18 years or more, the cumulative mortality was 16.5% from all causes (2389 deaths), 6.7% from cardiovascular disease (886 deaths), and 4.9% from cancer (651 deaths). Participants with gallstone disease had higher all-cause mortality in age-adjusted (HR = 1.3; 95% confidence interval [CI]: 1.2–1.5) and multivariate-adjusted analysis (HR = 1.3; 95% CI: 1.1–1.5). A similar increase was observed for cardiovascular disease mortality (multivariate-adjusted HR = 1.4; 95% CI: 1.2–1.7), and cancer mortality (multivariate-adjusted HR = 1.3; 95% CI: 0.98–1.8). Individuals with gallstones had a similar increase in risk of death as those with cholecystectomy (multivariate-adjusted HR = 1.1; 95% CI: 0.92–1.4). **CONCLUSIONS: In the US population, persons with gallstone disease have increased mortality overall and mortalities from cardiovascular disease and cancer. This relationship was found for both ultrasound-diagnosed gallstones and cholecystectomy.**

Keywords: Gallstone Disease; Epidemiology; Gallbladder; Cholelithiasis.

Gallstones are common and greatly contribute to health care costs and patient morbidity, yet death directly from complications of gallstones is rare today. Whether gallstone disease is associated with increased mortality is unclear. One study of American Pima Indians found increased overall mortality and cancer mortality among persons with gallstone disease.[1] In this population-based survey with 20 years of follow-up, participants with gallstones, measured by oral cholecystography or previous cholecystectomy, had almost twice the risk of death as those with no gallstone disease. The risk of death from malignancy was >6.5 times as high with gallstone disease. However, the increased risk of overall mortality was not entirely explained by the higher cancer death rate with gallstone disease. Gallstones are considered to be the main risk factor for gallbladder cancer, however, this condition is rare.[2] Gallstone disease has also been associated with extrabiliary malignancies.[3,4]

An association of gallstones with cardiovascular disease has been suggested.[5–8] Gallstone disease and cardiovascular disease are both common conditions and share a number of risk factors, particularly age, obesity, diabetes, and components of the metabolic syndrome. Cholesterol is the main component of the majority of gallstones in the United States as well as of atheroma. Whether the 2 conditions are found together more frequently than would be expected of 2 common conditions and, if so, whether this is the result of a common underlying cause or of a causal relationship between them is uncertain. Few studies have investigated the relationship of mortality with gallstone disease and, to our knowledge, none have done so in the general US population.

Using death certificate data from the third National Health and Nutrition Examination Study (NHANES III), a prospective, population-based sample, we examined whether gallstone disease (gallstones or cholecystectomy) was associated with increased mortality overall and from specific causes. If an association was found, a second objective was to determine whether the relationship was similar for gallstones and cholecystectomy. The multi-

Abbreviations used in this paper: CI, confidence ratio; GGT, γ-glutamyltransferase; HR, hazard ratio; ICD, *International Classification of Diseases*; NHANES, National Health and Nutrition Examination Survey.

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tude of other variables collected in NHANES III allowed evaluation of potential confounders for mortality.

Methods

NHANES III was conducted in the United States from 1988 through 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention.[9] It consisted of a cross-sectional interview, examination, and laboratory data collected from a complex multistage, stratified, clustered probability sample representative of the civilian, noninstitutionalized population with oversampling of persons aged 60 years and older, African Americans, and Hispanics. The survey was approved by the Centers for Disease Control and Prevention Institutional Review Board, and all participants provided written informed consent to participate.

Of 18,738 sampled persons aged 20 to 74 years, 14,645 (78%) were examined. We excluded participants who did not undergo a gallbladder ultrasound (n = 351) or whose gallbladder lumen could not be adequately visualized on ultrasound (n = 56) and those for whom mortality status was unknown (n = 10). The analysis sample, therefore, consisted of 14,228 participants. Measures of insulin resistance have been shown to be related to gallstone disease,[10] but were only available for a subgroup of participants who fasted before the examination. Therefore, a secondary analysis of 6258 participants randomly assigned to be examined in the morning after an overnight fast excluded 840 who missed the morning examination or who fasted <8 or >24 hours.

Gallstone disease was defined as ultrasound-documented gallstones or evidence of a cholecystectomy (a right upper quadrant or epigastric scar and the absence of a gallbladder) by standard criteria.[11] Based on videotaped recordings of ultrasound examinations, there was excellent agreement on gallbladder disease diagnosis between the ultrasonographer and reviewing radiologist (agreement of 99% with a κ-statistic of 0.97).

Data were collected at baseline, as described previously, on factors known or thought to be related to gallstone disease or mortality and included as covariates in multivariate analyses: age (years), sex, ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), education (<12, 12, >12 years), cigarette smoking (never, former, <1 pack/day, ≥1 pack/day), alcohol drinking (never, former, <1 drink/day, 1–2 drinks/day, or >2 drinks/day), doctor-diagnosed diabetes, physical activity intensity, caffeinated beverage consumption (mg of caffeine/day), body mass index (calculated as weight [kg]/height [m2]), waist and hip circumferences (cm), systolic and diastolic blood pressure (mm Hg), hemoglobin A_{1C} (%), serum total and high-density lipoprotein cholesterol concentrations (mg/dL), and C-reactive protein (mg/dL; 0–0.3, >0.3).[10,12–18] γ-Glutamyltransferase (GGT) was added to the protocol after data collection began (n = 10,442) and categorized as normal or elevated (>51 IU/L in men or >33 IU/L in women). Among a subgroup of participants who attended a morning examination after an overnight fast, concentrations of serum triglycerides (mg/dL), plasma glucose (mg/dL), and serum insulin (pmol/L) were measured; and an insulin resistance index using the homeostasis model assessment was determined.[19]

Participants were passively followed for mortality through December 31, 2006, using a probabilistic match that linked NHANES III participants with National Death Index records to ascertain vital status and cause of death. This matching methodology is well established and has been described in detail.[20] The accuracy of the NHANES III-National Death Index matching methodology was high in a validation study that applied it to the NHANES I Epidemiologic Follow-Up Study (96.1% of decedents and 99.4% of living participants were classified correctly).[21] Persons not matched to a death record were considered to be alive through the end of follow-up. Mortality outcomes were based on death certificate underlying cause of death coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) for deaths occurring between 1988 and 1998, and according to the *International Classification of Diseases, Tenth Revision* (ICD-10) for deaths occurring between 1999 and 2006.[20] Outcomes consisted of all-cause mortality and the following cause-specific mortality: complications of gallbladder disease, excluding gallbladder cancer (ICD-9 codes 574-576; ICD-10 codes K80.0-K80.8 and K81-K83), cardiovascular disease (ICD-9 codes 390-459; ICD-10 codes I00-I99), malignancy (ICD-9 codes 140-239; ICD-10 codes C00-D48), digestive disease (excluding dental, malignant, and infectious) (ICD-9 codes 530-537, 550-571 and 572.1-579; ICD-10 codes K20-K31, K40-K74.6, and K75.1-K93.8), diabetes mellitus (ICD-9 code 250; ICD-10 codes E10-E14), infectious disease (ICD-9 codes 001-139.8, 320-326, 460-466.1, 480-487.8, 540-543, 572.0, 590, 599.0, and 680-686; ICD-10 codes A00-B99, G00-G09, J00-J06, J20-J21, J09-J18, K35-K38, K75.0, N39.0, and L00-L08), and all other mortality.

Statistical Analysis

Baseline characteristics were compared by gallstone disease status using a *t* test for continuous variables or a χ^2 test for categorical variables. Age-adjusted baseline characteristics were compared using linear regression analysis (SUDAAN, PROC REGRESS, SUDAAN User's Manual, Release 10.0, 2008; Research Triangle Institute, Research Triangle Park, NC) to calculate adjusted (least squares) mean estimates. Cumulative mortality during follow-up among persons with and without gallstone disease was calculated using Kaplan-Meier analysis. Hazard rate ratio (HR) estimates (relative risk) for mortality outcomes were calculated by Cox proportional hazard regression analysis (SUDAAN, PROC SURVIVAL, SUDAAN User's Manual, Release 10.0, 2008; Research