ASYMPTOMATIC CHOLELITHIASIS AND THE INCIDENCE OF GALLSTONE DISEASE

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SYNOPSIS

We determined the prevalence of cholelithiasis, by ultrasound in 728 Asian subjects and calculated the annual incidence of disease amongst the gallstone carriers. The prevalence of asymptomatic cholelithiasis in the age group > 29 years, was 11.8% (95% confidence interval: 7.2—16.4%) in males and 13.7% (8.4—19.0%) in females. The median diameter of the stones — 10mm (range 4—17) did not differ from that of symptomatic stones — 12.5mm (3-21). The odds of having cholelithiasis increased by 5% each year of life ($p < 0.001$), whilst the relative risk of gallstones in females was 62% greater than the risk in males (p 0.001). There was no relationship between cholelithiasis and ethnic group. Despite the common occurrence of gallstones, the annual incidence of asymptomatic carriers (> 29 years) developing symptoms leading to a hospital-based investigation was estimated as only 1/1000, whilst the annual cholecystectomy rate was 6/100,000. The chance of a carrier having a cholecystectomy in Malaysia was approximately 5 times less than the chance in the United Kingdom. We conclude that asymptomatic gallstones are common in Malaysians, but the risk of disease is low. The low cholecystectomy rate may be the result of a conservative approach to cholelithiasis due to limited surgical resources.

INTRODUCTION

The detection of asymptomatic gallstone carriers will become increasingly common with the widespread availability of diagnostic abdominal ultrasound. Should these stones be removed or left alone? Review of 40, text book articles on the treatment of asymptomatic gallstones, published since 1980, revealed that 48% of authors recommended removal, 30% suggested that the stones be left alone, while 22% could not give an answer either way. In third world countries, prophylactic operations would be a serious burden on often limited surgical facilities, unless such a policy was of proven value.

We decided to determined the prevalence of asymptomatic carriers in our population in order to estimate the incidence rate of disease in individuals with cholelithiasis.

METHODS

Cases of cholelithiasis and controls were obtained from 2 sources. Firstly, from a serial sample of 266 patients (age > 14 years), collected over 20 months and investigated by ultrasound for symptoms thought to be due to gallstones, for example, abdominal pain and jaundice. Secondly, from a random sample of 462 patients and volunteers (age 14 years), who were asymptomatic as regards biliary tract disease and who were not known to have been suffering from a disease predisposing to cholelithiasis, eg liver cirrhosis or haemolytic anaemia. Real time ultrasonography of the liver and biliary tree was performed after an overnight fast using 2.5mHz probes and either linear or sector scanning (aloka, Japan). Details recorded were; (i) the presence of stones or sludge, (ii) the maximum diameter and number of any stones, and (iii) the occurrence of abdominal pain, jaundice or dietary fat intolerance over the preceeding year in 260 subjects from the asymptomatic group.

The influence of the risk factors age, sex and ethnic group on the presence or absence of cholelithiasis was ascertained by fitting a retrospective logistic regression model to the data (1). Using this model the probability p of an individual being a case of cholelithiasis in this study was shown by:

$$\sum p(x_1 = 1(d, x_2, \ldots, x_5) = 1/\ 1 + \exp[-(b_0 + b_1 d + \sum_{i=2}^{5} b_i x_i)]$$

Where x_1 was the presence ($x_1 = 1$) or absence ($x_1 = 0$) of cholelithiasis, d indicated symptoms (d = 1) or no symptoms (d = 0), x_2 was age in years, x_3 was sex (female, $x_3 = 1$, male, $x_3 = 0$), x_4 and x_5 were indicator variables for ethnic group (Malay, $x_4 = 1$, others, $x_4 = 0$; Chinese, $x_5 = 1$, others, $x_5 = 0$). The intercept of the line was represented by b_0 and $b_1, \ldots, b_5$ were the logistic parameters of each variable. X^2 values for each estimated regression coefficient were derived from the likelihood ratio test (1).

The incidence of symptoms in gallstone carriers was determined firstly, by calculating the estimated incidence in the total population, obtained by recording the number of patients found to have cholelithiasis by radiological or ultrasound examination and the number of cholecystectomies performed, at hospitals within the state of Kelantan during the same 20 month period. Secondly, by estimating the relative risk of symptomatic disease from parameter b_1 above (1). Bayes's theorem was used for prediction of the posterior probability of cholecystectomy.

RESULTS

There were 44 asymptomatic subjects with gallstones and 4 with sludge. Amongst the symptomatic sample, 49 had gallstones and 10 sludge. No asymptomatic gallstones were detected in the age group 15—29. The prevalence of asymptomatic cholelithiasis in the age group > 29 years, was 11.8% (95% confidence interval: 7.2—16.4%) in males and 13.7% (8.4—19.0%) in females.

The asymptomatic sample was comparable with the symptomatic sample regarding sex and age, the sex distribution was not significantly different ($X^2 = 2.9$, $p > 0.05$), whilst the mean age of the symptomatic sample — 44 years was only slightly less than the asymptomatic sample — 47 years ($t = 2.2$, $p < 0.05$). The maximum likelihood estimates of the logistic parameters are listed in table 1. The logistic model 1 provided a good fit for the data ($X^2 = 3$, degrees of freedom = 3, $p > 0.05$). The occurrence of cholelithiasis was most significantly related to age ($X^2 = 599$, $p < 0.001$) (figure 1 and 2). The odds of having choleli-

TABLE 1
MAXIMUM LIKELIHOOD ESTIMATES OF LOGISTIC PARAMETERS RELATING AGE, SEX AND ETHNIC GROUPING TO THE RISK OF CHOLELITHIASIS

VARIABLE	PARAMETER	ESTIMATED MODEL 1	2
x_0 intercept	b_0	−4.995	−4.989
x_1 symptoms	b_1	1.166	1.170
x_2 age	b_2	0.049	0.049
x_3 sex	b_3	0.484	0.484
x_4 ethnic group	b_4		0.058
x_5 ethnic group	b_5		0.058
Log likelihood ratio		257.7	258.2

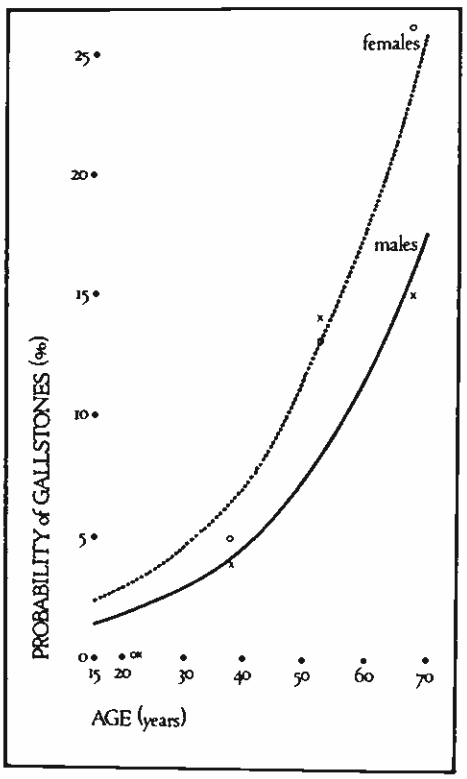

Figure 1: Probability of cholelithiasis in asymptomatic males and females according to age. The unadjusted mid point prevalences for four age groups is indicated by a cross (males) and a circle (females)

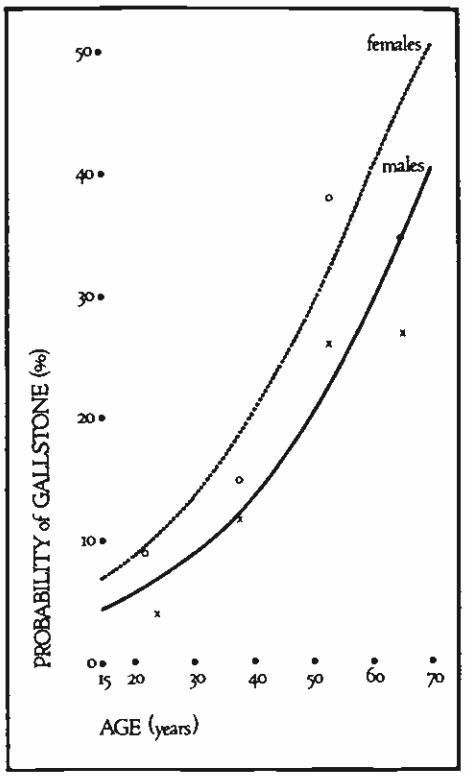

Figure 2: Probability of cholelithiasis in symptomatic males and females according to age. The unadjusted mid point prevalences for four age grous is indicated by a cross (males) and a circle (females)

thiasis increased by 5% for every year of life and were 62% greater in females compared to males (X^2 = 76, $p < 0.001$) (figure 1 and 2, table 2). Fitting a separate model for each sample did not show any significant difference between the samples for the coefficients of sex and age. Eighty two percent of the subjects were Malay, 15% Chinese and 3% Indian, however, there was no difference between the three ethnic groups regarding the occurrence of cholelithiasis (logistic model 2 table 1, table 2). The relative risk of gallstone disease-like symptoms in individuals with cholelithiasis was three fold higher than the risk in individuals without cholelithiasis.

TABLE 2
ADJUSTED ODDS RATIOS ESTIMATED FROM THE LOGISTIC MODEL FOR THE RISK FACTORS AGE, SEX AND ETHIC GROUP

Risk Factor	Odds	X^2	Significance
Age	1.05 (1.04-1.07)	599	P < 0.001
Sex	1.62 (1.04-2.54)	76	P < 0.001
Malay	0.94 (0.71-1.25)	1	P > 0.05
Chinese	1.06 (0.80-1.40)		

The 95% confidence interval is shown in parenthesis

The median size of asymptomatic stones — 10mm (range 4—17) was similar to that of symptomatic stones, 12.5mm (3—21). There was more than one stone in 44% of asymptomatic stone carriers and in 52% of symptomatic carriers. The prevalence of gallstone disease-like symptoms elicited on direct questioning of the asymptomatic sample was uninfluenced by the presence of absence of cholelithiasis (table 3).

TABLE 3
PREVALENCE OF GALLSTONE DISEASE-LIKE SYMPTOMS IN SUBJECTS WITHOUT KNOWN BILIARY TRACT DISEASE

	Asymptomatic Cholelithiasis	No Cholelithiasis
	n = 29	n = 231
Abdominal Pain	9 (31)	63 (26)
Jaundice	0	11 (5)
Fat Intolerance	4 (14)	13 (6)

Figures in parenthesis represent percentage

Ther was a mean of 3.2 consultant surgeons caring for the Kelantan population of 893,753 during the study period. Cholelithiasis was demonstrated in 31% of 325 patients investigated for possible gallstone-related disease and there were 48 cholecystectomies. Pigment stones, defined by naked eye examination, constituted < 10% of the stones removed. The annual incidence of an asymptomatic gallstone carrier (> 29 years) developing symptoms leading to hospital-based investigation of the biliary tree was 1/1000. The annual incidence of cholecystectomy was 6/100,000 (age-standardised to a European population). The probability of cholecystectomy in gallstone carrier was approximately 5 fold less in our population compared to a European population (table 4).

TABLE 4
ANNUAL PROBABILITY (EXPRESSED AS A PERCENTAGE) OF CHOLECYSTECTOMY IN A GALLSTONE CARRIER (AGE > 29 YEARS)

	Malaysia	United Kingdom
Prior probability of cholecystectomy	0.01	0.07
Probability of stones given no cholecystectomy	13.4	17.1*
Probability of stones given cholecystectomy	100	100
Probability of cholecystectomy given stones	0.08	0.41

*Necropsy prevalence

DISCUSSION

The occurrence of gallstones in the tropics is stated to be much less frequent than their occurrence in Western countries (2). However, most of the reports refer to surveys of symptomatic gallstone disease rather than asymptomatic cholelithiasis. Necropsy prevalences are available, but may be unrepresentative due to the low necropsy rate in many tropical countries (3). We, too found that the incidence of symptomatic stones, as reflected by the cholecystectomy incidence, was much less than in European and North American countries. For example, our annual incidence of cholecystectomy was 6/100,000, compared

to 70/100,000 in the United kingdom and 240/100,000 in Canada (4). These rates do not purely reflect differences in gallstone prevalence, as the prevalence in our subjects was similar to that found in European subjects of comparable age and sex (5,6,7). Furthermore, the probability of a gallstone carrier having a cholecystectomy was approximately 5 times less likely in Malaysia than in the United Kingdom.

In fact, the cholecystectomy rate in an area has been shown to correlate not only with the prevalence of cholelithiasis, but also with the number of surgeons and the number of hospital beds available (8). In our state, access to modern medicine treatmet is freely available, but the shortage of surgeons restricts non-essential surgery. This may account for the low cholecystectomy rate. Other hypotheses are that (i) the stones in our Asian population grow more slowly, the stone diameter was 10mm or less in two thirds of asymptomatic subjects, (ii) the asymptomatic stones may be pigment stones and possibly are less likely to cause symptoms due to the smaller size of such gallstones, compared to cholesterol stones, (iii) patients with mild symptoms of cholelithiasis my seek non-operative, traditional medicine treatment such as massage. It is unlikely that many of these individuals die from their gallstones, as death due to untreated cholelithiasis is uncommon (4,6,9) and in Malaysia, cholelithiasis does not figure amongst the top 50 causes of medically certified death (10).

Justification for prophylactic cholecystectomy is usually based on the studies of Wenckert and Robertson (11) who noted that 6.3% of untreated, mildly, symptomatic gallstone carriers developed symptoms each year of follow up. Fitzpatrick et al (12) used this pessimistic data in a computer simulation program to determine the value of surgery and found that prophylactic operation for gallstones prolonged life by only 7 to 16 days.

In our study, age was the major risk factor for cholelithiasis, sex a lesser factor, whilst ethnic status was not a significant factor. Other risk factors for cholelithiasis, like body weight or parity in females are not so definite (5), for example, in one study these factors were associated with asymptomatic gallstones, but not with symptomatic stones, treated by cholecystectomy (13). The occurrence of symptoms in gallstone carriers was related to neither sex, age, stone size nor number. This would support the hypotnesis that the development of symptoms e.g. due to the passage of the stones into the common duct, is mainly a random event (14). Although the logistic model provided a good fit for the data, study of the unadjusted odds of cholelithiasis in figures 1 and 2 might suggest that the odds of occurrence diminish after the sixth decade in males, perhaps due to a propensity to early death in gallstone bearing males. This speculation is supported by data from the Framingham study, where cholesterol gallstones were found to be positively associated with coronary heart disease in men, but not in women (15).

In conclusion, cholelithiasis is common amongst Malaysians, but has a low morbidity. Longitudinal follow up of gallstone carriers by sonography is required before the true natural history of cholelithiasis can be understood.

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