Gall bladder cancer (GBC) is a leading cause of cancer-related mortality in the northern parts of the Indian subcontinent. A majority of patients with GBC are middle-aged women, who normally would have substantial family responsibilities. Most patients are diagnosed with advanced cancer and are suitable for palliative care only. There is a strong association between long-standing gallstone disease and the development of GBC. Although randomized trials are lacking, prospective population-based data from low-risk and high-risk regions reveal that cholecystectomy reduces the mortality from GBC. Prophylactic cholecystectomy is recommended in populations with high incidence of GBC. The morbidity and mortality of laparoscopic cholecystectomy in uncomplicated gallstone disease is very low in India. Because of these reasons we argue that prophylactic cholecystectomy should be offered to young healthy women from high-risk regions of India whenever they are diagnosed to have asymptomatic gallstones. Simultaneously, population-based observational studies could be undertaken to generate more evidence. [Indian J Gastroenterol 2006;25:147-151]

"Mind all logic is like a knife all blade. It bleeds the hand that uses it."
— Rabindranath Tagore, Stray Birds

The population incidence rates of gall bladder cancer (GBC) vary widely among various races and different geographic regions (Table 1).<sup>1</sup> Although the age-adjusted incidence peaks after 65 years, there is a characteristic earlier peak in high-incidence regions.<sup>2,3,4</sup> The incidence of GBC has been rising steeply in northern India in the past two decades (Fig 1).<sup>4,5</sup> GBC is one of the commonest causes of cancer-related mortality in women in the northern and north-eastern states of India.<sup>6</sup> This disease is also very common in Karachi, Pakistan.<sup>7</sup> The age-specific incidence of GBC in Delhi women varies from 8/100,000 to 48/100,000 (Fig 2).<sup>4</sup> The highest recorded truncated incidence rate (35-75 years) for GBC in the world is seen in Delhi.<sup>4</sup>

Treatment options for GBC after the onset of symptoms are unsatisfactory and cure rates are dis-

<table>
<thead>
<tr>
<th>Place of registry</th>
<th>Year</th>
<th>Incidence rates/1,000,000*</th>
</tr>
</thead>
<tbody>
<tr>
<td>India, Delhi</td>
<td>1993-1996</td>
<td>21.5 7.1</td>
</tr>
<tr>
<td>Pakistan, Karachi</td>
<td>1995-1997</td>
<td>13.8 2.6</td>
</tr>
<tr>
<td>Korea, Seoul</td>
<td>1993-1997</td>
<td>6.7 5.31</td>
</tr>
<tr>
<td>Japan, Osaka Prefecture</td>
<td>1993-1997</td>
<td>5.85 4.4</td>
</tr>
<tr>
<td>China, Shanghai</td>
<td>1993-1997</td>
<td>5.47 2.22</td>
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<tr>
<td>India, Mumbai</td>
<td>1993-1997</td>
<td>5.1 2.4</td>
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<tr>
<td>Colombia, Cali</td>
<td>1992-1996</td>
<td>9.5 1.57</td>
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<td>Uruguay, Montevideo</td>
<td>1993-1995</td>
<td>6.22 3.81</td>
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<td>1993-1997</td>
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<td>USA, SEER</td>
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<td>1.78 1.03</td>
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<tr>
<td>Poland, Warsaw city</td>
<td>1993-1997</td>
<td>8.42 3.97</td>
</tr>
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<td>Russia, St Petersburg</td>
<td>1994-1997</td>
<td>3.49 1.78</td>
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<td>Italy, Varese Province</td>
<td>1993-1997</td>
<td>3.85 1.81</td>
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<td>UK, Scotland</td>
<td>1993-1997</td>
<td>1.41 0.6</td>
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<tr>
<td>UK, England</td>
<td>1993-1997</td>
<td>1.11 0.48</td>
</tr>
</tbody>
</table>

All incidence rates are truncated for 35-75 years and age standardized for world population.

Source: Reference 1

Fig 1: Trends in incidence of gall bladder cancer in Mumbai population registry.
More recent incidence data suggest that the trun-
cation of gallstones in patients developing GBC, which is typical of high-incidence regions. 
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More recent incidence data suggest that the tru-
cated rates in Delhi are the highest in the world. These prove beyond doubt that, like Chile, the northern Indian subcontinent is a high-incidence region that extends from Karachi to Kolkata. High incidence rates of GBC in Indian immigrants to Singapore and the United Kingdom support this viewpoint.

Over 80% of GBC in India are diagnosed in an advanced stage, leading to little chance of cure. Female illiteracy, gender bias and poor public health services contribute to late diagnosis. A large proportion of Indian patients have jaundice when diagnosed. In a study from New York, the median disease-specific survival in patients with GBC presenting with jaundice was 6 months, which was significantly lower compared with 16 months in patients without jaundice. In the group presenting with jaundice, there were no disease-free survivors at 2 years, compared with 21% in the group without jaundice. With no effective treatment options for symptomatic patients, the only way to reduce mortality from GBC is by prophylactic cholecystectomy.

Present knowledge of the risk factors for GBC and epidemiological transition in northern India suggest that the incidence rate for GBC will remain at the present high levels or may continue to rise for several decades. There are no population-based studies from India to estimate the population-attributable proportion to various risk factors (e.g., early pregnancy, multiple pregnancy, etc.) and the likelihood of interventions for primary prevention of GBC is unlikely. The balance of risk factors for GBC is changing in northern India. With increasing life expectancy of northern Indian women, more of them will survive beyond 65 years and this will increase the burden of GBC-related deaths. The slow but steady decline in early marriage and multiple pregnancies among northern Indian women will reduce the incidence of gallstone formation or delay the age at which they start to appear.

Primary prevention of GBC is unlikely given the fact that no population-based study has been started for prevention of GBC. Medical prevention and dissolution of cholesterol gallstones have ceased to interest researchers in the era of laparoscopic cholecystectomy (LC). Therefore, creating adequate high-quality facilities for prompt laparoscopic surgery for gallstone disease is the only effective way for prevention of GBC. More importantly, recent data show that early LC reduces the hospitalizations and mortality and costs from acute illnesses caused by gallstones, such as cholecystitis, pancreatitis and cholangitis.

Some may argue that there are no randomized clinical trials to provide high-level evidence for prophylactic cholecystectomy in northern Indian women. The rising rates of GBC and its dismal prognosis in northern India have been highlighted repeatedly during the last two decades. Unfortunately, to date we are unaware of any study being undertaken that will provide a better level of evidence for this problem. We hope that at least a population-based registry for all cholecystectomy as part of the National Cancer Registry Program of Indian Council of Medical Research and a prospective study of prophylactic cholecystectomy in one or more high-risk districts in northern Indian states will be undertaken so that we have better evidence to deal with the problem.

**Cholecystectomy for prevention of gall bladder cancer**

The traditional recommendation for asymptomatic gallstones has been expectant observation. The consensus statements however make an exception to this in high-risk population groups. The risk of LC is low when performed in young adults as an elective surgery when the gall bladder is not inflamed or complicated. A recent cost-effectiveness analysis of screening and treating Chilean women under 40 years old with asymptomatic cholelithiasis showed that prophylactic LC can significantly benefit the population at a very low incremental cost.

Cholecystectomy is the most frequent of all intra-abdominal operations worldwide. The incidence of GBC has diminished considerably and inversely correlates with the increase in cholecystectomies. While patients with gallstone disease are at increased risk of dying from GBC in the absence of cholecystectomy, a Swedish cohort study found significant lowering of GBC deaths following cholecystectomy on long-term follow up of patients. Age-standardized mortality rates from GBC have been declining over a 16-year period from 1980 to 1995 in twelve North American and European countries, correlating with increasing cholecystectomy rates during the same period. On the other hand, in Chile there has been a marked increase in GBC during the period from 1982 to 1991 attributed to declining cholecystectomy rates.

**Anticipated problems**

It could be argued that the magnitude of the exercise to treat all patients with asymptomatic gallstones may be impossible in India. This should not prevent us from offering LC to those who have incidentally detected gallstones. Large experience from India shows
that the morbidity and mortality associated with LC is very low. The fear of increased risk of colorectal cancer (CRC) and other cancers after LC is not proven. The baseline prevalence of CRC is low in India.

Our patients must be explained and educated about the benefits of LC and risks of a wait-and-watch policy for asymptomatic gallstones. The proven benefits of prophylactic cholecystectomy in reducing morbidity, mortality and expenses from acute benign diseases like cholecystitis, pancreatitis and cholangitis, etc. must be considered in the decision making. What to recommend when patients choose not to go for LC is a challenge. There is no evidence to suggest that regular screening with ultrasound or tumor markers is useful in reducing mortality from GBC. We have seen numerous northern Indian patients who had been advised observation for asymptomatic gallstone and were then diagnosed with advanced GBC (personal observation).

Conclusions
Harboring gallstones for several decades from early life increases the lifetime risk of developing GBC. Adoption of LC has reduced the incidence of GBC in men and women in many developed countries. Laparoscopy has proven to be very safe in Indian hospitals. In high-incidence regions, the risk of keeping young healthy women with asymptomatic gallstones under observation for development of symptoms out-weighs the risks of LC. Therefore, prophylactic cholecystectomy should be offered to young health women from high-incidence regions of northern India, when they are diagnosed to have asymptomatic gallstones.

References
Prophylactic cholecystectomy to reduce gall bladder cancer mortality


29. Serra IC. Has gallbladder cancer mortality decreased in Chile? Rev Méd Chile 2001;129:1079-84.


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News and Notices

The 4th S R Naik Memorial Workshop on "Biomedical Research: Methods, Tools and Future" will be organized by the Department of Gastroenterology, SGPGI, Lucknow, September 23 and 24, 2006. For details contact: Dr Uday C Ghoshal. E-mail: ghoshal@sgpgi.ac.in

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