

## CLINICAL SCIENCE

## ARE HISTOLOGICAL ALTERATIONS OBSERVED IN THE GALLBLADDER PRECANCEROUS LESIONS?

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**INTRODUCTION:** Gallbladder cancer, which is characterized by rapid progression and a poor prognosis, is a complex disease to treat. Unfortunately, little is known currently about its etiology or pathogenesis. A better understanding of its carcinogenesis and determining risk factors that lead to its development could help improve the available treatment options.

**METHOD:** Based on this better understanding, the histological alterations (such as acute cholecystitis, adenomyomatosis, xanthogranulomatous cholecystitis, polyps, pyloric metaplasia, intestinal metaplasia, dysplasia, cancer and others) in gallbladders from 1,689 patients who underwent laparoscopic cholecystectomy for cholecystolithiasis were analyzed. The association of these gallbladder histological alterations with clinical data was studied.

**RESULTS:** Gender analysis revealed a greater incidence of inflammatory changes in males, while dysplasia and cancer were only found in women. The incidence of cholesterolosis was greater in the patients 60 years of age and under, and the incidence of adenomyomatosis and gangrene was greater in the elderly patients. A progressive increase in the average age was observed as alterations progressed through pyloric metaplasia, intestinal metaplasia, dysplasia and then cancer, suggesting that the metaplasia-dysplasia-carcinoma sequence may occur in gallbladder cancer. Gallbladder histological alterations were also observed in asymptomatic patients.

**CONCLUSION:** The results of this study suggest that there could be an association between some histological alterations of gallbladder and cancer, and they also suggest that the metaplasia-dysplasia-carcinoma sequence could in fact be true in the case of gallbladder cancer. Nevertheless, further studies directed towards a perfect understanding of gallbladder carcinogenesis are required.

**KEYWORDS:** Gallbladder neoplasms; Cholecystectomy; Laparoscopic; Metaplasia; Adenomyoma; Cholelithiasis.

## INTRODUCTION

Gallbladder cancer is the most common cancer of the biliary tree and the fifth most common cancer of the gastrointestinal tract.<sup>1-3</sup> It is a disease known for its rapid evolution and high mortality rate. Its main prognostic factor

is the pathological stage of the disease.<sup>1,4,5</sup>

Because no specific symptoms are produced during the early stages, gallbladder cancer is often only discovered during surgery or diagnosed at an advanced stage of the disease. The small group of patients with prolonged survival rates are those patients with tumors in early stages who were diagnosed by chance after a cholecystectomy for cholecystolithiasis.<sup>6,7</sup> Nevertheless, incidental gallbladder cancer is discovered in 0.3 to 2% of all cholecystectomies performed for benign conditions.<sup>2,7-10</sup>

In comparison with other gastrointestinal malignancies, little is known about the etiology and pathogenesis of gallbladder cancer. The main difficulty in studying the precursor lesions of this disease is the fact that it is impossible to perform follow-up because the diagnosis is established after the cholecystectomy. Therefore, the

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evidence relating these lesions to the cancer is determined indirectly.

Because there is unfortunately no efficient method to detect gallbladder cancer, a better understanding of the risk factors for gallbladder cancer development and pre-malignant lesions of the gallbladder could help select patients for prophylactic cholecystectomies, and, perhaps, reduce the mortality of this almost invariably fatal disease. There are two important carcinogenesis models known: the adenoma-carcinoma sequence and the metaplasia-dysplasia-carcinoma sequence. The observation that the gallbladder presents proper histological alterations raises the possibility of other carcinogenesis models in the gallbladder. Due to this observation, analysis of the behavior of the histological alterations observed in the gallbladder with cholelithiasis is an interesting topic of study.

## METHODS

A retrospective analysis was conducted using the medical records of 1,689 patients who underwent laparoscopic cholecystectomies between November 1999 and December 2006 in two hospitals: Clinics' Hospital of the University of São Paulo and Oswaldo Cruz German Hospital. The histopathological analysis - coordinated by a single pathologist - was performed in both hospitals.

An abdominal ultrasound examination was used to diagnose cholelithiasis in all patients. Gallbladder cancer was not confirmed in any of the patients during the preoperative stage.

Analyzed clinical data included gender, age and presence of symptoms before surgery. The patients were classified according to their ages: 40 years of age or younger, 41 to 60 years of age and over 60 years of age. Regarding the symptoms before surgery, patients were divided in two groups: asymptomatic and symptomatic.

In all patients, the surgeon conducted a macroscopic examination after removing the gallbladder from the abdomen; if there was any abnormality, the specimen was sent for a frozen section test.

The histopathological examination consisted of an initial macroscopic examination of the specimen, where specific microscopic analysis of suspicious areas was performed. After that, the specimen was sent to a routine microscopic examination, which included a random sample of the fundus, body and neck of the gallbladder. These samples were then embedded in paraffin, sectioned, stained with hematoxylin-eosin and examined under an optical microscope. All histological alterations described on the pathologists' reports were included in the study. Analyzed pathological data included the presence of

acute cholecystitis, gangrene, abscess, fibrosis, sclero-atrophic gallbladder, adenomyomatosis, cholesterolosis, xanthogranulomatous cholecystitis, hyperplasic polyps, cholesterol polyps, pyloric metaplasia, intestinal metaplasia, dysplasia and cancer.

The Pearson chi-square test ( $\chi^2$ ) and Fisher exact probability test were used to determine the correlation between the clinical and pathological data.

The Standard Statistical Software Package (version 13) was used, and a statistically significant difference was set as  $p \leq 0.05$ .

## RESULTS

In 1,091 patients, no histological alteration was found, and the pathologist reported only chronic calculous cholecystitis. In the remaining patients, acute inflammation was observed in 174 patients (10.3%), gangrene in 23 (1.4%), abscess in 8 (0.5%), cholesterolosis in 305 (18.1%), adenomyomatosis in 40 (2.4%), xanthogranulomatous cholecystitis in 29 (1.7%), fibrosis in 12 (0.7%), sclero-atrophic gallbladder in 20 (1.2%), hyperplasic polyps in 3 (0.2%), cholesterol polyps in 17 (1.0%), pyloric metaplasia in 72 (4.3%), intestinal metaplasia in 18 (1.1%), dysplasia in 4 (0.2%) and cancer in 2 (0.1%). Adenomatous polyps were not observed in any patients (Table 1). More than one histological alteration was found in some patients.

In relation to gender, 1,238 patients were female (73.3%), and 451 patients were male (26.7%), making the female/male ratio was 2.7. The analysis of each

**Table 1** - Frequency of the gallbladder histological alterations studied.

	Number of cases	Frequency
Cholesterolosis	305	18.1%
Acute cholecystitis	174	10.3%
Xanthogranulomatous cholecystitis	29	1.7%
Sclero-atrophic gallbladder	20	1.2%
Hyperplasic polyp	3	0.2%
Cholesterol polyp	17	1.0%
Adenomyomatosis	40	2.4%
Fibrosis	12	0.7%
Gangrene	23	1.4%
Abscess	8	0.5%
Pyloric metaplasia	72	4.3%
Intestinal metaplasia	18	1.1%
Dysplasia	4	0.2%
Cancer	2	0.1%

histological alteration studied and female or male gender, showed a significant statistical difference for acute cholecystitis, sclero-atrophic gallbladder, gangrene, abscess and cholesterol polyps, all of them more frequent among men (Table 2).

**Table 2** - Analysis of the gallbladder histological alterations according to gender.

	Male n (%)	Female n (%)	P
Cholesterolosis	76 (16.9%)	229 (18.5%)	0.437 (P)
Acute cholecystitis	80 (17.7%)	94 (7.6%)	0.001 (P) <sup>§</sup>
Xanthogranulomatous cholecystitis	5 (1.1%)	24(1.9%)	0.245 (P)
Sclero-atrophic gallbladder	13 (2.9%)	7 (0.6%)	0.001 (P) <sup>§</sup>
Hyperplasic polyp	0 (0%)	3 (0.2%)	0.569 (F)
Cholesterol polyp	12 (2.7%)	5 (0.4%)	0.001 (F) <sup>§</sup>
Adenomyomatosis	10 (2.2%)	30 (2.4%)	0.805 (P)
Fibrosis	6 (1.3%)	6 (0.5%)	0.096 (F)
Gangrene	14 (3.1%)	9 (0.7%)	0.001 (P) <sup>§</sup>
Abscess	5 (1.1%)	3 (0.2%)	0.036 (F) <sup>§</sup>
Pyloric metaplasia	15 (3.3%)	57(4.6%)	0.250 (P)
Intestinal metaplasia	3 (0.7%)	15(1.2%)	0.430 (F)
Dysplasia	0 (0.0%)	4 (0.3%)	0.579 (F)
Cancer	0 (0.0%)	2 (0.2%)	1.000 (F)
Number of patients	451	1,238	

(P) Pearson's test; (F) Fisher's test; <sup>§</sup> = statistically significant difference.

Patient ages varied from 11 to 90 years, with an average age of 50 years and median age of 51 years. Among the 1,689 patients, 495 (29.3%) were 40 years of age or younger, 737 (43.6%) were 41 to 60 years of age and 457 (27.1%) were over 60 years of age. The analysis of this three bands of age and each histological alteration studied demonstrated a significant statistical difference for acute cholecystitis, sclero-atrophic gallbladder, gangrene and adenomyomatosis. Sclero-atrophic gallbladders were observed more often in patients in the 41-60 age range, while all other gallbladder alterations with age-related significant statistical differences were observed more frequently in patients over 60 (Table 3).

The study of the average age of each gallbladder histological alteration demonstrated, interestingly, a progressive increase in age for the pyloric metaplasia ( $50.6 \pm 15$  years), intestinal metaplasia ( $53.9 \pm 14$  years), dysplasia ( $56.8 \pm 24$  years) and cancer ( $60.0 \pm 27$  years) sequence; however, no statistical difference was observed (Table 4).

Regarding the presence or absence of symptoms, 147 (8.7%) patients were asymptomatic, and 1,542 (91.2%) presented symptoms before surgery. The statistical analysis of each histological alteration studied and the presence or absence of symptoms revealed a significant statistical difference for acute cholecystitis, cholesterol polyps and dysplasia. Acute cholecystitis had a bigger incidence among symptomatic patients, while cholesterol polyps and dysplasia had a bigger incidence among asymptomatic patients (Table 6).

**Table 3** - Analysis of the gallbladder histological alterations according to age.

	≤ 40 n (%)	41-60 n (%)	> 60 n (%)	P
Cholesterolosis	96 (19.3%)	143 (19.4%)	66 (14.4%)	0.063
Acute cholecystitis	34 ( 6.8%)	85 (11.5%)	55 (12.0%)	0.011 <sup>§</sup>
Xanthogranulomatous cholecystitis	8 (1.6%)	10 (0.1%)	11 (2.4%)	0.390
Sclero-atrophic gallbladder	2 (0.4%)	15 (2.0%)	3 (2.6%)	0.016 <sup>§</sup>
Hyperplasic polyp	1 (0.2%)	0 (0.0%)	2 (0.4%)	0.215
Cholesterol polyp	4 (0.8%)	10 (0.1%)	3 (2.6%)	0.435
Adenomyomatosis	8 (1.6%)	12 (1.6%)	20 (4.3%)	0.004 <sup>§</sup>
Fibrosis	2 (0.4%)	6 (0.8%)	4 (0.8%)	0.623
Gangrene	2 (0.4%)	9 (1.2%)	12 (2.6%)	0.012 <sup>§</sup>
Abscess	0 (0.0%)	4 (0.5%)	4 (0.8%)	0.136
Pyloric metaplasia	19 (3.8%)	31 (4.2%)	22 (4.8%)	0.754
Intestinal metaplasia	5 (1.0%)	6 (0.8%)	7 (1.5%)	0.497
Dysplasia	1 (0.2%)	1 (0.1%)	2 (0.4%)	0.570
Cancer	0 (0.0%)	1 (0.1%)	1 (0.2%)	0.608
Number of patients	495	737	457	

<sup>§</sup> = statistically significant difference.

**Table 4** - Average age of occurrence of each gallbladder histological alteration studied<sup>+</sup>

	Average age with an alteration (yr)	Average age without an alteration (yr)	p
Cholesterolosis	48.5 ± 14	50.4 ± 15	0.050 <sup>#</sup>
Acute cholecystitis	53.7 ± 14	49.6 ± 15	0.001 <sup>#</sup>
Xanthogranulomatous cholecystitis	52.5 ± 17	50.0 ± 15	0.384
Sclero-atrophic gallbladder	53.7 ± 10	50.0 ± 15	0.117
Hyperplasic polyp	56.7 ± 25	50.0 ± 15	0.446
Cholesterol polyp	50.2 ± 13	50.0 ± 15	0.955
Adenomyomatosis	56.1 ± 15	49.9 ± 15	0.010 <sup>#</sup>
Fibrosis	51.9 ± 15	50.0 ± 15	0.664
Gangrene	60.9 ± 14	49.9 ± 15	0.001 <sup>#</sup>
Abscess	62.4 ± 12	50.0 ± 15	0.020 <sup>#</sup>
Pyloric metaplasia	50.6 ± 15	50.0 ± 15	0.744
Intestinal metaplasia	53.9 ± 14	50.0 ± 15	0.275
Dysplasia	56.8 ± 24	50.0 ± 15	0.618
Cancer	60.0 ± 27	50.0 ± 15	0.350

<sup>+</sup>Continuous variables are described as mean ± SEM (standard error of mean); the p value was derived using student's T-test; <sup>#</sup> = statistically significant difference.

**Table 5** - Analysis of gallbladder histological alterations and metaplastic alterations

	Pyloric metaplasia n / p	Intestinal metaplasia n / p
Cholesterolosis	12 / 0.754 (P)	0 / 0.580 (F)
Acute cholecystitis	2 / 0.320 (P)	5 / 0.310 (F)
Xanthogranulomatous cholecystitis	1 / 1.000 (F)	0 / 1.000 (F)
Sclero-atrophic gallbladder	1 / 0.584 (F)	0 / 0.641 (P)
Hyperplasic polyp	0 / 1.000 (F)	0 / 1.000 (F)
Cholesterol polyp	0 / 1.000 (F)	0 / 1.000 (F)
Adenomyomatosis	4 / 0.087 (F)	4 / 0.001 (F) <sup>§</sup>
Fibrosis	0 / 1.000 (F)	0 / 1.000 (F)
Gangrene	0 / 0.308 (P)	0 / 0.616 (P)
Abscess	0 / 1.000 (F)	0 / 1.000 (F)
Pyloric metaplasia	-----	9 / 0.000 (F) <sup>§</sup>
Dysplasia	2 / 0.010 (F) <sup>§</sup>	2 / 0.001 (F) <sup>§</sup>
Cancer	2 / 0.002 (F) <sup>§</sup>	2 / 0.000 (F) <sup>§</sup>

(P) indicates Pearson's test; (F) indicates Fisher's test; <sup>§</sup> = statistically significant difference

Metaplastic alterations, considered precancerous lesions, were analyzed separately from other histological alterations. The analysis of pyloric metaplasia and other gallbladder histological alterations studied showed a significant

**Table 6** - Analysis of the histological alterations according to the presence or absence of symptoms

	Asymptomatic patients n (%)	Symptomatic patients n (%)	p
Cholesterolosis	34 (23.1%)	271 (17.6%)	0.094 (P)
Acute cholecystitis	4 (2.7%)	170 (11.0%)	0.002 (P) <sup>§</sup>
Xanthogranulomatous cholecystitis	3 (2.0%)	26 (1.7%)	0.735 (F)
Sclero-atrophic gallbladder	2 (1.4%)	18 (1.2%)	0.691 (F)
Hyperplasic polyp	1 (0.7%)	2 (0.1%)	0.239 (F)
Cholesterol polyp	4 (2.7%)	13 (0.8%)	0.054 (F) <sup>§</sup>
Adenomyomatosis	3 (2.0%)	37 (2.4%)	1.000 (F)
Fibrosis	2 (1.4%)	10 (0.6%)	0.281 (F)
Gangrene	1 (0.7%)	22 (1.4%)	0.715 (F)
Abscess	0 (0.0%)	8 (0.5%)	1.000 (F)
Pyloric metaplasia	7 (4.8%)	65 (4.2%)	0.754 (P)
Intestinal metaplasia	1 (0.7%)	17 (1.1%)	1.000 (F)
Dysplasia	2 (1.4%)	2 (0.1%)	0.040 (F) <sup>§</sup>
Cancer	0 (0.0%)	2 (0.1%)	1.000 (F)
Number of patients	147	1,542	

(P) indicates Pearson's test; (F) indicates Fisher's test; <sup>§</sup> = statistically significant difference.

statistical difference for adenomyomatosis, dysplasia, and cancer. In addition, the analysis of intestinal metaplasia and other gallbladder histological alterations studied also showed a significant statistical difference for pyloric metaplasia, adenomyomatosis, dysplasia and cancer (Table 5).

The only two patients with cancer were women, and they were diagnosed during the post-operative period by routine pathological examination. One patient was 41 years old and presented carcinoma *in situ*, with areas of pyloric metaplasia, intestinal metaplasia and dysplasia. The patient underwent a follow-up for five years and remained disease-free during this period. The other patient, who was 79 year olds, presented with a papilliferous adenocarcinoma with invasion to the muscular layer and the presence of areas of pyloric metaplasia, intestinal metaplasia, dysplasia and adenomyomatosis. This patient was observed for one year and remained disease-free during the period.

## DISCUSSION

In this study, there were low incidences of all studied histological alterations. All the gallbladders were submitted to a routine histopathological examination with only three histological segments (the fundus, body, neck) and any observed macroscopic alterations. According to Albores-

Saavedra and Henson (1986), the incidence of histological alterations in chronic cholecystitis is generally a reflection of the number of histological segments analyzed and the technique used. They report that when multiple sections of the gallbladder are examined, dysplasia and carcinoma *in situ* are observed in 13.5% and 3.5% of patients, respectively.<sup>11</sup> In the study of Jukemura and associates with completed sampled gallbladders, the analysis of 475 gallbladder specimens from cholecystectomies demonstrated a cancer incidence of 1.68%.<sup>12</sup>

Additionally, a larger population sample would probably also affect the results of this study. Flum and associates, who used 1500,000 patients who underwent laparoscopic cholecystectomy to study the effect of intraoperative cholangiography *per se* in preventing common bile duct injury during cholecystectomy, argue that infrequent events can only be detected in large samples of population.<sup>13</sup>

The association between cholelithiasis and gallbladder cancer is well known, as cholelithiasis occurs in over 80% of all gallbladder cancer cases.<sup>2,4,5,8,14</sup> Associations between cholelithiasis and other gallbladder alterations such as xanthogranulomatous cholecystitis, adenomyomatosis and pyloric and intestinal metaplasia have also been reported.<sup>15,16</sup>

In this study, cancer and dysplasia were only found in women, agreeing with the observations of other studies that gallbladder cancer occurs more often in women.<sup>1,17,18</sup> Similarly, a greater incidence of metaplastic alterations would also be expected in women. This finding, reported by Duarte and associates,<sup>19</sup> was also seen in this study, although no significant statistical difference was found.

The increased risk of gallbladder cancer in women is partially explained by the higher incidence of cholelithiasis in women when compared to men. Female hormones may play a role in the etiology of the disease. Higher and prolonged exposure to female sex hormones (such as estrogen and progesterone) may be a predisposing factor. Therefore, younger age at menarche, early age at first pregnancy, multiple pregnancies and a prolonged reproductive period may increase the risk of biliary tract cancer.<sup>41</sup>

For males, a greater association with inflammatory gallbladder alterations, such as acute cholecystitis, gangrene and sclero-atrophic gallbladder, was seen, which has also been demonstrated in other trials.<sup>20-22</sup> Acute cholecystitis has also been associated with cancer;<sup>2,23</sup> however, in this study, the association between metaplastic lesions, dysplasia or cancer and inflammatory gallbladder alterations such as acute cholecystitis, sclero-atrophic gallbladder or fibrosis was not seen.

The prevalence of cholelithiasis and gallbladder

cancer increased with the age of the studied population. An estimated 1% of the patients over the age of 65 with cholelithiasis will develop gallbladder cancer, and the increased cancer risk among the elderly may be related to the duration of gallstone disease rather than the absolute age of the patient.<sup>24</sup>

Adenomyomatosis, a non-inflammatory gallbladder alteration, occurs in middle age patients, and the incidence increases with age. Originally depicted as a benign finding, it is currently identified as a precancerous lesion, and cancer cases associated with areas of adenomyomatosis have been reported.<sup>17,25,26,43</sup> As in other trials, this study revealed a higher incidence of adenomyomatosis within elderly patients.<sup>43</sup>

Xanthogranulomatous cholecystitis is an uncommon inflammatory and destructive gallbladder process that can spread to adjacent structures and be confused with cancer.<sup>27</sup> This histological alteration occurs in approximately 2% of all cholecystectomies, affects men and women equally and is frequently associated with gallstones.<sup>42</sup> The occurrence of cancer in gallbladders with xanthogranulomatous cholecystitis has been reported and has been observed in 9% to 12% of these cases.<sup>27,28</sup> Similar to adenomyomatosis, xanthogranulomatous cholecystitis presented a higher incidence within elderly individuals in this study and, interestingly, occurred more often among women.

Metaplastic alterations (pyloric and/or intestinal metaplasia) are also associated with gallbladder cancer and are observed in the tumor area, although they are more frequently seen in the area surrounding the tumor. Dysplasia is also usually seen in the area surrounding the tumor, and this histological alteration may be a stage of progression from metaplasia to cancer.<sup>29-31</sup> In this study, the association of intestinal metaplasia and adenomyomatosis was also confirmed.

Assuming that the metaplastic alterations and dysplasia are precancerous lesions, their incidence should also increase with age, a fact confirmed in this study. Yamagiwa and Tomiyama<sup>16</sup> analyzed 1,000 resected gallbladders and observed that the number of cases of dysplasia and cancer increased with age, with the greatest incidence among patients over 60 years of age. In this same age group, they observed a greater number of cases of intestinal and pyloric metaplasia. Duarte and associates and Fernandes and associates also observed a bigger incidence of pyloric and intestinal metaplasia within patients over 50 years of age.<sup>19,32</sup>

Supporting the idea of the metaplasia-dysplasia-carcinoma sequence, we observed an association between pyloric metaplasia and dysplasia, pyloric metaplasia and cancer and an association between intestinal metaplasia and pyloric metaplasia, dysplasia and cancer.



Interestingly, the average age when the metaplastic alterations, dysplasia and cancer occur in this sequence demonstrated increases at three year intervals. The average age of patients with pyloric metaplasia was 10 years smaller than the average age of those with cancer. Roa and associates<sup>30</sup> observed that the average age of patients with dysplasia and carcinoma *in situ* is 15 and 5 years younger, respectively, than patients with invasive cancer. This observation provides indirect evidence of the progression of these gallbladder lesions, as observed in other organs, such as the uterus and colon.

Adenomatous polyps were not observed in this study. The occurrence of polyps in the gallbladder is uncommon, estimated at approximately 1% of the cholecystectomies performed for cholecystolithiasis. Among all types of polyps, only adenomatous polyps are associated with the occurrence of cancer. The malignant transformation of an adenoma is an uncommon event, and as in other organs, its evolution is related to the size of the adenoma. Therefore, even though the adenoma-carcinoma sequence could exist in the gallbladder, it is probably less important than in other gastrointestinal tract tumors, such as colorectal cancer.<sup>30,33</sup>

Strangely enough, adenomyomatosis, pyloric metaplasia, intestinal metaplasia and dysplasia were observed in asymptomatic patients, which demonstrates that potentially serious lesions could be present in patients with few or no symptoms.

Ransohoff and Gracie<sup>34</sup> performed follow-up on 123 patients with asymptomatic cholecystolithiasis for seven years with no occurrence of cancer in any of them.

However, the GREPCO Group<sup>35</sup> in Italy performed follow-up on 118 patients with asymptomatic gallstones for 10 years, with one occurrence of cancer (0.8%) in a patient who died as a result of this disease at the age of 64.

Maringhini and associates<sup>36</sup> performed follow-up on 2,583 patients for 13 years. During this period, five patients (0.2%) developed cancer.

Despite the low incidence of gallbladder cancer in these trials, the fact that this disease progresses slowly must be taken into consideration. Therefore, a longer follow-up period may be required for the studied population to attain incidence rates similar to the general population. Additionally, it is very possible that cancer was not identified among those patients with early stage lesions, which are often diagnosed by chance after a cholecystectomy.

In Chile, where the mortality for gallbladder cancer is the

leading cause of cancer deaths in the female population (15.6 death per 100,000 female habitants), the cholecystectomy is considered a crucial intervention for lowering the gallbladder cancer mortality rate. Chianale and associates<sup>37</sup> and Andia and associates<sup>38</sup> have correlated a reduced number of cholecystectomies with an increased gallbladder cancer mortality rate. In the USA, a country considered to have a moderate incidence of gallbladder cancer, Bartlett<sup>1</sup> observed a reduction in gallbladder cancer mortality rates between 1965 and 1989, which coincides with an increased number of cholecystectomies.

Kapoor<sup>39</sup> in India recommends prophylactic cholecystectomies for young patients with a long life expectancy who have asymptomatic gallstones; patients whose abdominal ultrasound examination shows a thickened gallbladder wall (greater than 3 mm) because 50% have xanthogranulomatous cholecystitis and the risk of cancer in these patients is higher; patients with large gallstones (greater than 3 cm); and patients with other conditions associated with gallbladder cancer, such as porcelain gallbladder, sessile polyps (greater than 1 cm), anomalous pancreaticobiliary junction, race and/or habitants of geographical locations with high incidence rates of gallbladder cancer.

Nevertheless, even though there are indications that performing prophylactic cholecystectomies in patients with asymptomatic gallstones may reduce the mortality rate of gallbladder cancer, this issue is still controversial. A systematic review published by Cochrane Library in 2007<sup>40</sup> compared the simple observation with the accomplishment of prophylactic cholecystectomy in patients with asymptomatic gallstones. Among 323 analyzed references, none congregated conditions for this revision. The authors (Gurusamy and Samraj) concluded that there is no evidence in literature to recommend cholecystectomy in patients with asymptomatic gallstones, and more studies are necessary.

The results of this study suggest that there could be an association between some gallbladder histological alterations and cancer. They also suggest that the metaplasia-dysplasia-carcinoma sequence could occur in the case of gallbladder cancer. Nonetheless, further studies directed toward a perfect understanding of gallbladder carcinogenesis are required. This understanding is crucial to establish surgical treatments for the various pathological gallbladder conditions, such as symptomatic or asymptomatic calculous cholecystopathy.

## REFERENCES

1. Bartlett DL. Gallbladder cancer. *Semin Surg Oncol*. 2000;19:145-55.
2. Lam CM, Yuen AW, Wai AC, Leung RM, Lee AY, Ng KK, et al. Gallbladder cancer presenting with acute cholecystitis. A population-based study. *Surg Endosc*. 2005;19:697-701.
3. Shih SP, Schulick RD, Cameron JL, Lillemoe KD, Pitt HA, Choti MA, et al. Gallbladder cancer: the role of laparoscopy and radical resection. *Ann Surg*. 2007;245:893-901.
4. Donohue JH, Stewart AK, Menck HR. The National Cancer Data Base report on carcinoma of the gallbladder, 1989-1995. *Cancer*. 1998;83:2618-28.
5. Lazcano-Ponce EC, Miquel JF, Munoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin*. 2001;51:349-64.
6. Akyürek N, Irkörtücü O, Salman B, Erdem O, Sare M, Tatlicioglu E. Unexpected gallbladder cancer during laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Surg*. 2004;11:357-61.
7. Misra S, Chaturvedi A, Misra NC. Gallbladder cancer. *Curr Treat Options Gastroenterologist*. 2006; 9:95-106.
8. Ziliotto Jr A, Kunzle JE, Sgarbi EC. Carcinoma primário de vesícula biliar. *Rev Bras Cancerol*. 1985;31:103-6.
9. Weinstein D, Herbert M, Bendet N, Sandbank J, Halevy A. Incidental finding of gallbladder carcinoma. *Isr Med Assoc J*. 2002;4:334-6.
10. Sun CD, Zhang BY, Wu LQ, Lee WJ. Laparoscopic cholecystectomy for treatment of unexpected early-stage gallbladder cancer. *J Surg Oncol*. 2005; 91:253-7.
11. Albores-Saavedra J, Henson DE. Tumors of the gallbladder and extrahepatic ducts. In: Atlas of tumor pathology, 2<sup>nd</sup> series, fascicle 22. Washington DC: Armed Forces Institute of Pathology, 1986.
12. Jukemura J, Leite KRM, Machado MCC, Montagnini AL, Penteadó S, Abdo EE, et al. Frequency of incidental gallbladder carcinoma in Brazil. *ABCD Arq Bras Cir Dig*. 1997;12:10-3.
13. Flum DR, Dellinger EP, Cheadle A, Chan L, Koepsell T. Intraoperative Cholangiography and Risk of Common Bile Duct Injury During Cholecystectomy. *JAMA*. 2003;289:1639-44.
14. Kapoor VK. Gallbladder cancer: a global perspective. *J Surg Oncol*. 2006; 93:607-9.
15. Martínez-Guzmán G, de la Rosa-Bayón J. Neoplasms and dysplasias of the gallbladder and their relationship with lithiasis. A case-control clinicopathological study. *Rev Gastroenterol Mex*. 1998;63:82-8.
16. Yamagiwa H, Tomiyama H. Intestinal metaplasia-dysplasia-carcinoma sequence of the gallbladder. *Acta Pathol Jpn*. 1986;36:989-97.
17. Tazuma S, Kajiyama G. Carcinogenesis of malignant lesions of the gallbladder. The impact of chronic inflammation and gallstones. *Lagenbecks Arch Surg*. 2001;386:224-9.
18. Kayhara M, Nagakawa T. Recent trends of gallbladder cancer in Japan: an analysis of 4770 patients. *Cancer*. 2007;110:572-80.
19. Duarte I, Llanos O, Domke H, Harz C, Valdivieso V. Metaplasia and precursor lesions of gallbladder carcinoma. *Cancer*. 1993;72:1878-84.
20. Botaitis S, Polychronidis A, Pitiakoudis M, Perente S, Simopoulos C. Does gender affect laparoscopic cholecystectomy? *Surg Laparosc Endosc Percutan Tech*. 2008;18:157-61.
21. Kanaan SA, Murayama KM, Merriam LT, Dawes LG, Prystowsky JB, Rege RV, et al. Risk factors for conversion of laparoscopic to open cholecystectomy. *J Surg Res*. 2002;106:20-4.
22. Merriam LT, Kanaan SA, Dawes LG, Angelos P, Prystowsky JB, Rege RV, et al. Gangrenous cholecystitis: analysis of risk factors and experience with laparoscopic cholecystectomy. *Surgery*. 1999;126:680-5; discussion 685-6.
23. Chao TC, Jeng LB, Jan YY, Hwang TL, Wang CS, Chen MF. Concurrent primary carcinoma of the gallbladder and acute cholecystitis. *Hepatogastroenterology*. 1998;45:921-6.
24. Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. *Am J Gastroenterol*. 2000; 95:1402-10.
25. Sermon A, Himpens J, Leman G. Symptomatic adenomyomatosis of the gallbladder-report of a case. *Acta Chir Belg*. 2003;103:225-9.
26. Aldridge MC, Gruffaz F, Bismuth H. Adenomyomatosis of the gallbladder: a premalignant lesion? *Surgery*. 1991;109:107-10.
27. Spinelli A, Schumacher A, Pascher A, Lopez-Hanninen E, Al-abadi H, Benckert C, et al. Extended surgical resection for xanthogranulomatous cholecystitis mimicking advanced gallbladder carcinoma: a case report and review of literature. *World J Gastroenterol*. 2006;12:2293-6.
28. Kwon A, Sakaida N. Simultaneous presence of xanthogranulomatous cholecystitis and gallbladder cancer. *J Gastroenterol*. 2007;42:703-4.
29. Kijima H, Watanabe H, Iwafuchi M, Ishihara N. Histogenesis of gallbladder carcinoma from investigation of early carcinoma and microcarcinoma. *Acta Pathologica Japonica*. 1989;39:235-44.
30. Roa I, de Aretxabala X, Araya JC, Roa J. Preneoplastic lesions in gallbladder cancer. *J Surg Oncol*. 2006;93:615-23.
31. Black WC. The morphogenesis of gallbladder carcinoma. In: Fenoglio CM, Wolff M, editors. *Progress in surgical pathology*. New York: Masson; 1984, p. 207-33.
32. Fernandes JE, Franco MI, Suzuki RK, Tavares NM, Bromberg SH. Intestinal metaplasia in gallbladders: prevalence study. *Sao Paulo Med J*. 2008;126:220-2.
33. Roa I, de Aretxabala U, Morgan F<sup>a</sup> R, Molina U<sup>a</sup> R, Araya JC, Roa J, et al. Pólipos e adenomas de la vesícula biliar: consideraciones clínicopatológicas. *Rev Med Chil*. 2004;132:673-9.
34. Ransohoff DF, Gracie WA. The natural history of silent gallstones: the innocent gallstone is not a myth. *N Engl J Med*. 1982;307:798-800.
35. Attili AF, De Santis A, Capri R, Repice AM, Maselli S. The natural history of gallstones: the GREPCO experience. *The GREPCO Group. Hepatology*. 1995; 21:655-60.
36. Maringhini A, Moreau JA, Melton J, Hench VS, Zinsmeister AR, DiMaggio EP. Gallstones, gallbladder cancer and other gastrointestinal malignancies. *Ann Intern Med*. 1987;107:30-5.

37. Chianale J, Valdivia G, Del Pino G, Nervi F. Mortalidad por cáncer vesicular en Chile y su relación con las tasas de colecistectomía. Análisis de la última década. *Rev Méd Chile*. 1990;118:1284-8.
38. Andia KM, Gederlini GA, Ferreccio RC. Gallbladder cancer: trend and risk distribution in Chile. *Rev Med Chil*. 2006;134:565-74.
39. Kapoor VK. Cholecystectomy in patients with asymptomatic gallstone to prevent gallbladder cancer - the case against. *Indian J Gastroenterol*. 2006;25:152-4.
40. Gurusamy KS, Samraj K. Colecistectomía versus no colecistectomía em pacientes com cálculos biliares asintomáticos. Systematic review in: *La Biblioteca Cochrane Plus*. 2007; Number 2.
41. Shukla V K, Chauhan V S, Mishra R N, Basu S. Lifestyle, reproductive factors and risk of gallbladder cancer. *Singapore Med J*. 2008;49:912-5.
42. Uchiyama K, Ozawa S, Ueno M, Hayami S, Hirono S, Ina S, et al. Xanthogranulomatous cholecystitis: the use of preoperative CT findings to differentiate it from gallbladder carcinoma. *J Hepatobiliary Pancreat Surg*. 2009;16:333-8.
43. Nabatame N, Shirai Y, Nishimura A, Yokoyama N, Wakai T, Hatakeyama K. High risk of gallbladder carcinoma in elderly patients with segmental adenomyomatosis of the gallbladder. *J Exp Clin Cancer Res*. 2004;23:593-8.