

Correlation between Cholelithiasis and Gallbladder Carcinoma in Surgical and Autopsy Specimens

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ABSTRACT

Gallbladder (GB) cancer is the most common malignant lesion of the biliary tract. The decision for a cholecystectomy in asymptomatic cholelithiasis as a measure of the secondary prevention of gallbladder cancer is based on the data of incidence and selected predictive factors for a specific population. A consecutive series of 3351 cholecystectomies in five year period was reviewed. That data was compared with the data from 2395 consecutive autopsies from the same period. Possible risk factors for gallbladder cancer were analysed. In surgical specimens, the incidence of gallbladder carcinoma was 0.62%. Of those, 24% were in patients younger than 60 years and 95.24% were associated with cholelithiasis. In autopsy material, in cases in which cholelithiasis was present, the incidence of gallbladder carcinoma was 3.4%. All cases were in patients older than 60 years and all were associated with cholelithiasis. Correlation between cholelithiasis and gallbladder carcinoma was most significant for women in the surgical group while it was not as strong for men or in the autopsy group. The results vary whether we analyse surgical or autopsy material, but in both cases female gender and the duration of cholelithiasis were significant risk factors. In our population GB cancer is not uncommon in elderly women with gall stones and is diagnosed in advanced stage if one waits for symptoms.

Key words: gallbladder neoplasms, cholelithiasis, cholecystectomy

Introduction

Primary gallbladder carcinoma is a relatively rare but fatal disease that was first described in 1777. A particular feature of gallbladder carcinoma is its unusual local demographic variability when compared to other malignant diseases. It is known for its high variability in incidence in different areas, with the highest rates reported in Chile, Poland, India, Japan and Israel. It is relatively rare in other parts of the world. The highest incidence in Europe is in Poland, the Czech Republic and the Slovak Republic¹.

Prevention of cholelithiasis has not proven to be highly effective so far². Broad diagnostic use of ultrasound has led to an increased number of diagnosed cases of clinically silent cholelithiasis, which has resulted in a growing interest in the optimal treatment of such silent cholelithiasis³. While cholecystectomy is undoubtedly the gold standard for the treatment of symptomatic cholelithiasis, the natural course of silent, asymptomatic cholelithiasis is not known well enough to suggest a de-

finite strategy for the treatment of such patients. Therapeutic options range from observation only, selective cholecystectomy in high risk patients to elective cholecystectomy in all patients. Each of these options has a large number of supporters, and none can be discounted. Since most cases of gallbladder carcinoma are associated with cholelithiasis, the reasons for performing a prophylactic cholecystectomy are: life expectancy of more than twenty years and stones of more than 3 cm in diameter, especially in people coming from areas with high prevalence of gallbladder carcinoma. Because of considerable variability in incidence of gallbladder carcinoma in various areas, and due to its variable relationship with cholelithiasis, it is necessary to be familiar with these data for each individual area in order to be able to make appropriate decisions about the choice of the treatment of asymptomatic cholelithiasis.

The topic of this paper is the examination of the correlation between cholelithiasis and gallbladder carcino-

ma in clinical and autopsy material analysed at the Clinical Centre »Sestre milosrdnice«, Zagreb over a five year period with the objective of determining the incidence of gallbladder carcinoma and its relation to cholelithiasis in our region.

Patients and Methods

This paper introduces a series of 3351 patients with cholelithiasis, chronic calculous cholecystitis, acalculous cholecystitis, hydrops of gallbladder, acalculous cholesterolosis, calculous cholesterolosis and gallbladder carcinoma who were surgically treated at the Clinical hospital »Sestre milosrdnice« Zagreb over a five year period.

In addition, results from 2395 autopsies performed in the same period were evaluated, including analyses of cholelithiasis, chronic calculous cholecystitis and gallbladder carcinoma. We have calculated the incidence of gallbladder carcinoma and cholelithiasis by gender and age group. These results were compared with results obtained from surgically treated patients.

Based on the analysis of data obtained from surgically treated patients, the data was statistically adjusted to a normal population, and theoretical frequencies were calculated. The correlation between the surgically treated patients and autopsy cases regarding the incidence of gallbladder carcinoma was statistically analysed.

Results

In the reporting period, a total of 3351 cholecystectomies were performed (Figure 1), of which 2475 (73.58%) were in women and 876 (26.15%) were in men. The patients ranged between 11 and 100 years of age. The highest number of operated patients was in the age group 51-60 years (26.04%) with the ratio of women to men being 73.12% to 26.88%. The second largest age group (24.44%) was the 41-50 age category, with the ratio of women to men 74.11% to 25.89%. In younger age groups,

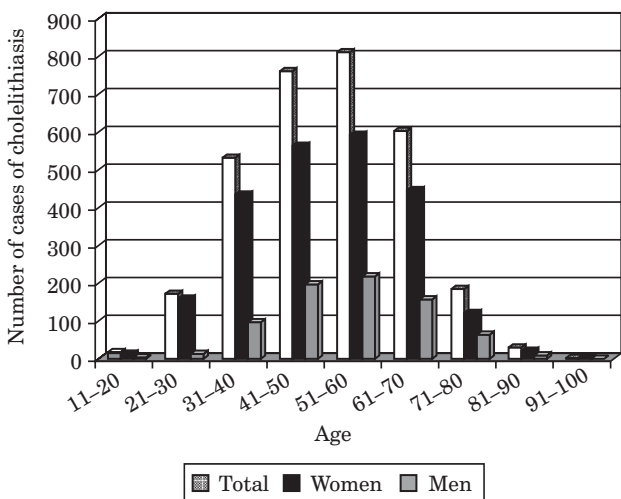


Fig. 1. Cholelithiasis in surgical group by gender and age.

the ratio was higher for women (94.44% in the age group 21-30, and 81.77% in the age group 31-40). Cholelithiasis itself was an indication for cholecystectomy in 23.49% of cases, whereas chronic calculous cholecystitis was an indication for surgical treatment in 69.44% of cases.

Gallbladder carcinoma was diagnosed in 21 (0.62%) patients (Figure 2), 17 women (0.69% of all operated women) and 4 men (0.46% of all operated men). The highest number of gallbladder carcinoma cases (42.86%) was diagnosed in the age group 71-80 years, with 77.78% of these occurring in women. The second predominant age group was the 61-70 age category (28.57%) with a 100% of these occurring in women. The third largest age group was the 51-60 age category (23.81%) with a 60% of these occurring in women. Gallbladder adenocarcinoma was pathohistologically confirmed in all patients. Among all patients with gallbladder carcinoma, only one did not have a gallbladder stone, which means that 95.24% of patients with gallbladder carcinoma also had cholelithiasis.

Pre-operative gallbladder ultrasound examination was performed in all patients with gallbladder carcinoma and there was no suspicion of gallbladder carcinoma in any of these evaluations. ERCP was carried out in two cases and, as a result, the suspicion of a malignant process was raised in both cases. CT scanning of the gallbladder was performed in 10 patients, by which gallbladder carcinoma was diagnosed in 7 patients, and the suspicion of gallbladder carcinoma was raised in the three remaining patients. All diagnosed tumours were in an advanced stage of the disease.

In the reporting period, a total of 2395 autopsies were performed (Figure 3). As a result, cholelithiasis and chronic calculous cholecystitis were diagnosed in 558 (23.29%) of all autopsy cases with an age range of 21-100 years and 67.72% of these occurring in women. In 335 autopsy cases (60.04%), cholelithiasis was accompanied by inflammation. The highest incidence of cholelithiasis and chronic calculous cholecystitis (37.46%) was in the age group 71-80 years with 61.72% of these occurring in women. The second highest incidence was in the age group of 81-90 years (28.49%) with 66.04% of these occurring in women.

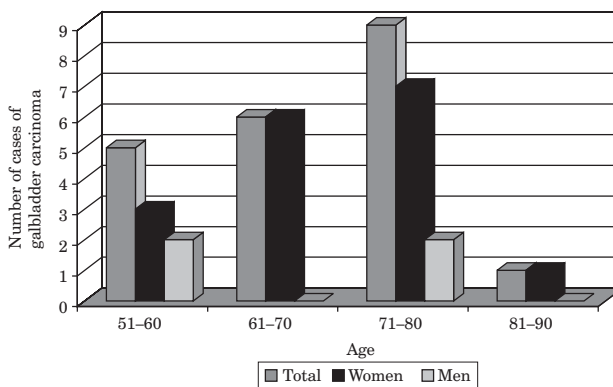


Fig. 2. Gallbladder carcinoma in surgical group by gender and age.

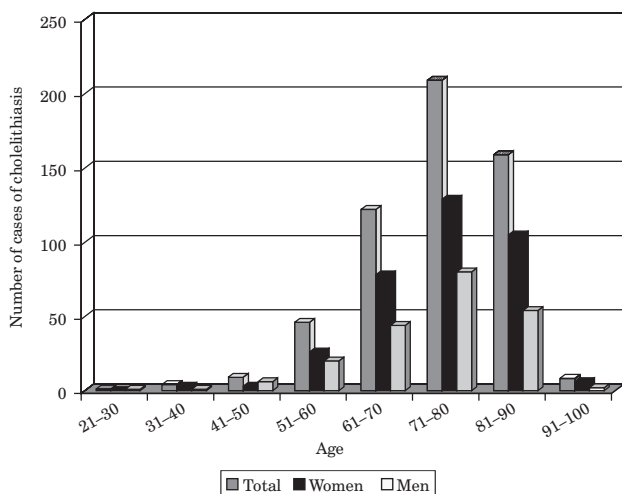


Fig. 3. Cholelithiasis in autopsy group by gender and age.

Gallbladder carcinoma (Figure 4) was found in 19 autopsy cases (3.4% of all cases of cholelithiasis) with 84.21% of these occurring in women. The highest number (47.37%) was found in the age group 71–80 years with a 88.89% predominance in women. The incidence rates in the age groups 61–70 and 81–90 years were identical (26.32%) with an 80% predominance in women. Pathohistologically, all cases of gallbladder carcinoma were adenocarcinoma and all were connected with calculosis, which represents a 100% correlation. In the autopsy group, there were no patients younger than 60 years with gallbladder carcinoma, while in the surgical group 24% of gallbladder carcinomas were younger than 60 years (Figure 5).

Correlation coefficient between cholelithiasis and gallbladder carcinoma was most evident in surgical findings in women ($r=0.118$), whereas it was considerably lower in men and in autopsy material ($r=0.018-0.037$).

Discussion

Gallbladder carcinoma was first described in 1777. Today, more than 200 years after its discovery, late diagnosis and lack of effective treatment are still typical for

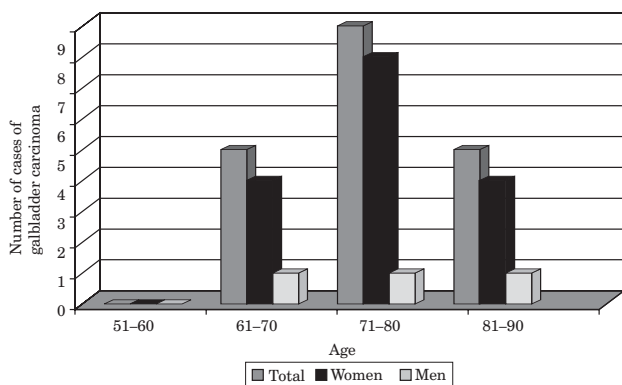


Fig. 4. Gallbladder carcinoma in autopsy group by gender and age.

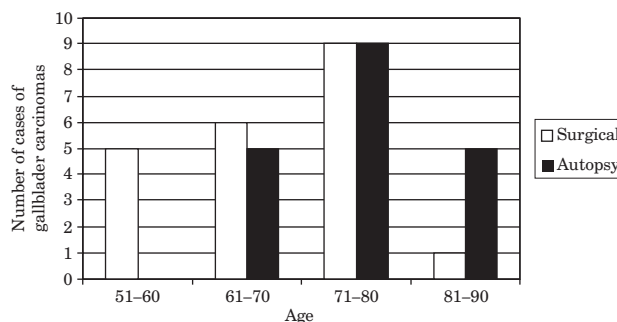


Fig. 5. The number of gallbladder carcinoma in surgical and autopsy group by age.

this illness. Prognosis is still poor with a five-year survival rate ranging from approximately 30% in case of disease limited to the gallbladder mucosa to less than 10% in advanced disease⁴.

The ratio of women to men with regard to gallbladder carcinoma is about 2:1. The highest incidence is in women more than 65 years old, but there exists significant regional and ethnic variability in the occurrence of the disease. The highest incidence rates are reported in Chilean Mapuche Indians and Hispanic Americans, Bolivians, North American Indians and Mexicans in the United States of America. The incidence is considerably lower in Europe and India. The highest incidence in Europe is reported in Eastern European Countries (Poland, the Czech Republic and the Slovak Republic). The incidence of gallbladder carcinoma in Croatia is relatively low: 1/100,000 in men and 2.4/100,000 in women; it is similar to the incidence reported in Switzerland (1.0/2.5) and is about half of the incidence in Poland (3.7/6.5) and the Czech Republic (3.0/5.7).

The development of gallbladder carcinoma is associated with a number of risk factors that have been described in various countries of the world, but there have been no controlled trials that could prove the role of any of them in tumour development. The most frequently mentioned ones are chronic inflammatory diseases and infections⁵, especially *Salmonella typhi*, obesity, female gender⁶, older age, ethnic origin, the effects of some chemical carcinogens (especially of smoking), benign gallbladder tumours, workplace exposure, nutritional risk factors^{7,8} and ionise radiation exposure.

The incidence of gallbladder carcinoma rises with age, and it is theorized that gallbladder carcinoma is a disease of older people whose gallbladder has been exposed to long-lasting irritation by chronic calculous cholecystitis. Stasis of the bile, chronic inflammation and mechanical irritation^{9,10} of the gallbladder are associated with an increased risk of developing gallbladder carcinoma¹¹. Initial studies indicated a strong correlation between the size of gallstones and the incidence of gallbladder carcinoma, but more recent research has not confirmed such a relation^{12–15}. Therefore, the question remains whether long-lasting irritation by gallstones is the etiological factor for developing gallbladder carcinoma, i.e. whether

gallbladder carcinoma can be regarded as a complication of cholelithiasis. The reason for the inconsistent results in the literature is probably related to the facts that various populations have been evaluated, which are characterized by varying rates of cholelithiasis and gallbladder carcinoma. The main limiting factors in epidemiological studies of gallbladder carcinoma are the small number of patients and specific problems of determining exposure to the assumed risk factors.

According to our analysis of the surgical material, cholelithiasis occurred in ages ranging from 11 to 100 years. The highest number of patients was in the 51–60 age range (26.04%), and the second largest group was patients aged between 41–50 years (24.44%). Out of 3114 patients with cholelithiasis, 2327 patients (74.37%) also had chronic calculous cholecystitis, which leads to the conclusion that the occurrence of gallstones is associated with an inflammatory process in the majority of patients (2.96 times more likely).

Epidemiologically, the predominance of cholelithiasis in women in Croatia is 2.4:1, which is similar to the predominance in women in Switzerland (2.5), and is slightly higher than that in Poland (1.75) and the Czech Republic (1.9). In our study, the predominance of cholelithiasis in women was 3.1 in the surgical group and 1.7 in the autopsy group, which might indicate that cholelithiasis is diagnosed and operated in women in a higher percentage than in men. It is worthwhile to note in the age group 21–30 years, that stone formation was 10.3 times higher in women than in men.

In addition to thyroid carcinoma, gallbladder carcinoma is the only malignant disease that does not depend on sex hormones but is more common in women with an incidence 3–4 times higher than in men. Early menarche, late menopause, higher number of pregnancies and late age at last childbirth are factors related to the development of gallbladder carcinoma. According to our findings, the incidence of gallbladder carcinoma in the surgical group was 0.67%, whereas it was as high as 3.4% in the autopsy group. It is interesting to note that there was a significant difference in the ratio of cholelithiasis to carcinoma between women and men in both the surgical and autopsy groups. While the analysis of the surgical group resulted in a ratio of 1.36 (0.72% of all cases of cholelithiasis in women against 0.53% in men), this ratio was considerably higher in the autopsy group: 3.2 in favour of women (4.5% in women and 1.4% in men).

According to data from the literature, cholelithiasis is found in almost all cases of gallbladder carcinoma (78–85%), which was confirmed by our findings (95.4% in surgical and 100% in autopsy specimens). The connection between cholelithiasis and gallbladder carcinoma has been known since 1861 and has been confirmed by numerous studies on autopsy and surgical material in various areas. This connection has been found in clinically symptomatic disease lasting longer than 20 years. Chronic trauma and inflammatory response to irritation of gallbladder by stones and by recurrent infection are the most probable causes of gallbladder carcinoma. This is illus-

trated by an increased risk for gallbladder carcinoma with stones of more than 3 cm in diameter¹⁶.

Little is known about the natural course of gallbladder carcinoma, but the majority of studies indicate the general existence of dysplastic changes and carcinoma in situ 5–15 years before the occurrence of invasive carcinoma. Although the incidence of dysplastic lesions in the pathohistological findings in patients who had a cholecystectomy for cholelithiasis is, according to data from the literature, up to 13.5%, and the incidence of carcinoma in situ up to 3.5%, we did not detect such lesions. We did, however, detect a significant difference in age between the patients with cholelithiasis in the surgical group in whom gallbladder carcinoma was or was not found (the highest incidence of cholelithiasis without carcinoma was in the age range of 51–60 years, and the highest incidence of gallbladder carcinoma was in the age range of 71–80 years). Such difference was not found in the autopsy group, in which the highest incidence of both cholelithiasis and carcinoma was in the age range of 71–80 years.

Literature data indicates that gallbladder carcinoma is found in less than 1% of all cases of cholelithiasis, with an increased incidence in high risk areas. In our study, this percentage is, in the surgical group, consistent with the data from the literature for low risk areas (0.62%), but the incidence in the autopsy group was surprisingly high (3.4% of all cases of cholelithiasis). This difference could be explained by the advanced age in the second group. This explanation is supported by the fact that in the autopsy group, no patient younger than 60 years was found to have gallbladder carcinoma, whereas in the surgical group 24% of gallbladder carcinomas were detected in the age group 51–60 years.

While the therapeutic choice for symptomatic cholelithiasis is clear, and elective cholecystectomy has a significant effect in the secondary prevention of gallbladder carcinoma, the issue of appropriate management of asymptomatic cholelithiasis is still under discussion. According to research, in areas with a high incidence of gallbladder carcinoma it is necessary to consider elective cholecystectomy in cases of asymptomatic cholelithiasis. In areas with a low risk of gallbladder carcinoma, the benefit of elective cholecystectomy has not been confirmed.

Conclusion

In order to be able to make an appropriate decision about a procedure in the case of asymptomatic cholelithiasis, it is necessary to be familiar with the data about the prevalence of gallbladder carcinoma in a given population. When studying the incidence of gallbladder carcinoma and its relation to cholelithiasis, it is important to specify the research methodology because the data from the analysis of surgical specimens after elective cholecystectomy differ significantly from the results obtained by analysis of autopsy specimens in the same population.

According to our knowledge, this is the first such analysis of the correlation between surgical and autopsy

findings of gallbladder carcinoma in our area. Our results indicate that there exist significant differences in results that can be drawn from the analysis of surgical and autopsy specimens. We find the significant difference in the ratio between the number of cases of cholelithiasis and gallbladder carcinoma to be especially important, because it indicates that the risk of developing gallbladder carcinoma significantly increases with the duration of cholelithiasis and with age, especially in women.

Standard diagnostic procedures (ultrasound scanning of gallbladder) included in our study demonstrated low sensitivity (0%) for detecting gallbladder carcinoma. More sophisticated and more sensitive techniques (ERCP 100%,

CT 100%) are not applied as the standard for cholelithiasis examination, and the tumours discovered by those techniques were diagnosed at an advanced stage with poor prognosis. After considering these facts in the light of the recently published results for elective laparoscopic cholecystectomy covering our region¹⁷, by means of which tumours were detected at a much earlier stage with proven better outcomes¹⁸, our opinion is that elective cholecystectomy should be considered more frequently for treatment of asymptomatic cholelithiasis in our population because the gallbladder carcinoma is not uncommon in elderly women with gall stones, and is diagnosed in an advanced stage if one waits for symptoms.

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KORELACIJA IZMEĐU KOLELITIJAZE I KARCINOMA ŽUČNJAKA U KIRURŠKOM I OBDUKCIJSKOM MATERIJALU

SAŽETAK

Karcinom žučnjaka je najčešći malignitet žučnog trakta. Odluka o indiciranju kolecistektomije kod asimptomatske kolelitijaze kao mjere sekundarne prevencije karcinoma žučnjaka ovisi o podacima o incidenciji karcinoma žučnjaka i specifičnim prediktivnim čimbenicima u pojedinoj populaciji. U našem radu smo obradili uzastopnu seriju od 3351 kolecistektomija tijekom 5 godina. Te podatke smo usporedili s podacima od 2395 uzastopnih obdukcija u istom periodu. Analizirali smo moguće čimbenike rizika nastanka karcinoma žučnjaka. U kirurškoj skupini incidencija karcinoma žučnjaka bila je 0,62%. Od njih, kod 24% bolesnika se radilo o osobama mlađim od 60 godina i u 95,24% slučajeva je karcinom žučnjaka bio povezan s nalazom kolelitijaze. U obdukcijском materijalu, karcinom žučnjaka je nađen kod 3,4% uzorka s prisutnom kolelitijazom. Korelacija kolelitijaze i karcinoma žučnjaka bila je najizraženija kod žena u kirurškoj skupini, dok nije bila toliko izražena kod muškaraca i u obdukcijском uzorku. Rezultati se razlikuju u ovisnosti o tomu analiziramo li kirurški ili obdukcijски materijal, ali u oba slučaja ženski spol i trajanje kolelitijaze bili su značajni čimbenici rizika. U našoj populaciji karcinom žučnjaka nije rijedak kod žena starije životne dobi s kolelitijazom, a dijagnosticira se u uznapredovalom stadiju ukoliko se čeka na pojavu simptoma.