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# Incidence and clinicopathological features of incidental gallbladder cancer

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## ABSTRACT

**INTRODUCTION.** Annually, more than 9,000 cholecystectomies are performed in Denmark. All gallbladders are submitted for histological examination to rule out preoperatively undetected gallbladder cancer. The histological examination at the Department of Pathology is costly. Therefore, it is relevant to investigate whether adopting a selective approach in which only selected gallbladders are submitted for histological examination is reasonable.

**METHODS.** All cholecystectomies submitted for histological examination at the Department of Pathology at Herlev Hospital from 1 January 2014 to 31 December 2023 were included in the study. In cases of gallbladder cancer, the results of the preoperative diagnostic imaging, intraoperative findings and the macroscopic examination at the Department of Pathology were systematically reviewed.

**RESULTS.** In total, 9,698 gallbladders were included in the study. Across all patients, the incidence of gallbladder cancer was 0.29%, with a total of 28 cases being identified. In patients ≤ 60 years, the incidence of gallbladder cancer was 0.08%, whereas the incidence of gallbladder cancer was 0.67% in patients > 60 years. Among the 28 cases of gallbladder cancer, the surgeon noted macroscopic changes in 27 cases, while such changes were observed in all cases during the macroscopic examination at the Department of Pathology.

**CONCLUSION.** The study supports implementing a selective approach to histopathological examination of the gallbladder after cholecystectomy but also emphasises the need for a thorough macroscopic examination.

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**TRIAL REGISTRATION.** Not relevant.

Annually, more than 9,000 routine cholecystectomies are performed in Denmark, primarily due to gallstones and related complications, including cholecystitis [1]. In Denmark, all gallbladders are routinely submitted for histological examination. This examination is performed to rule out preoperatively undetected gallbladder cancer; incidental gallbladder cancer. The histological examination at the Department of Pathology is time-consuming and costly regarding materials and chemicals. Therefore, it is relevant to investigate whether it is reasonable to omit routine histopathological examination of all gallbladders removed for benign indications and adopt a selective approach, where only selected gallbladders are examined histologically [2].

The incidence of gallbladder cancer is low in Denmark [3] and other Western countries [4] but varies across populations, being significantly higher in Asia and Latin America [4]. A recent meta-analysis reported the incidence of incidental gallbladder cancer as 0.32% in low-incidence countries and 0.83% in high-incidence countries [5]. The incidence of incidental gallbladder cancer increases with age. In a Dutch cohort of 22,025

gallbladders, the reported mean age for patients with gallbladder cancer was 71.3 years, whereas the mean age for patients without gallbladder cancer was 52.4 years [6]. Therefore, it has been suggested that age should be included as a predictive marker when deciding whether a gallbladder should be sent for histopathological examination. Additionally, acute cholecystitis is associated with an increased risk of incidental gallbladder cancer [7, 8].

In a recently published clinical guideline, the Surgical Advisory Board for the Capital Region of Denmark recommends implementing selective histopathological examination of gallbladders. However, the most recent data on incidental gallbladder cancer in the Danish population is from 2001 [9]. The current study aimed to examine the incidence and macroscopic features of incidental gallbladder cancer in a non-selected Danish population of patients who had cholecystectomy performed for benign disease.

## Methods

All cholecystectomies sent for histopathological examination at the Department of Pathology at Herlev and Gentofte Hospital in the ten years from 1 January 2014 to 31 December 2023 were included in the study. Cases were identified from the Danish Pathology Register based on the SNOMED topography code for gallbladder (T57000) combined with the SNOMED procedure code for ectomy specimen (P306X0) or resection specimen (P30620).

In cases of gallbladder or associated tissue (e.g., lymph nodes and soft tissue) malignancy, the results of the preoperative diagnostic imaging, intraoperative findings and macroscopic examination at the pathology department were systematically reviewed.

The expenses for histopathological examination were estimated by calculating the average price points used for the benign gallbladders included in the study from 1 January 2023 to 31 December 2023. The price points estimate the personnel time used for the histopathological examination and are based on extensive time studies conducted at several Danish pathology departments [10].

Continuous data are presented as mean and standard deviation (SD). Categorical variables are presented as numbers and percentages. The two-tailed unpaired T-test was used to compare mean age between patients with and without gallbladder cancer, and the chi-squared test was used to compare the incidence of gallbladder cancer in patients younger and older than 60 years. A $p < 0.05$ was considered significant. Data analysis and visualisation were performed using Excel and Python. The collection of clinical data was approved by Team Journal Data at “Center for Sundhed”, Region H, in accordance with the Danish Health Care Act Section 46, Subsection 5. Registration number R-24053200.

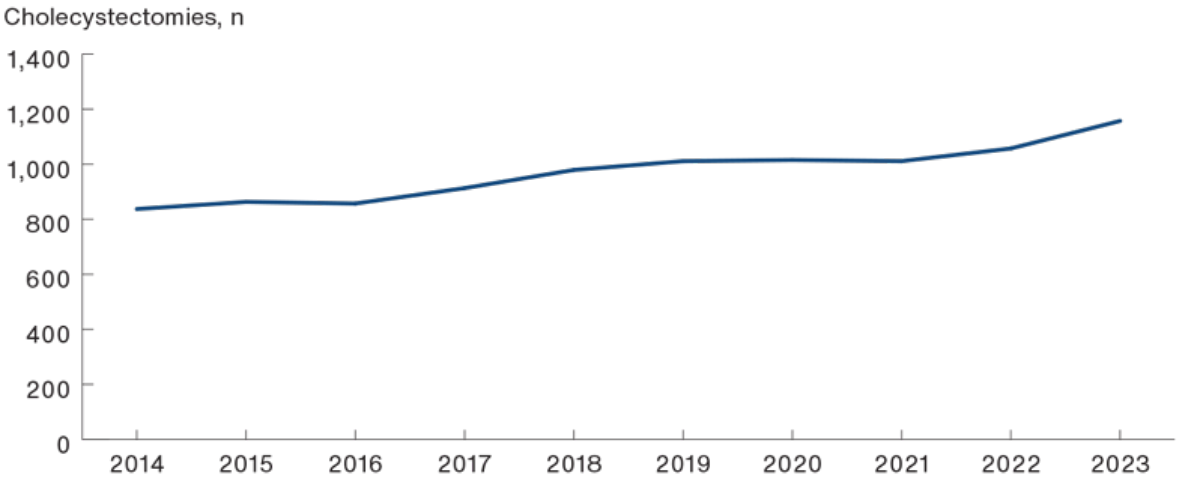
*Trial registration:* not relevant.

## Results

The study included 9,698 gallbladders. Over the ten-year period, the annual number of gallbladders submitted for histopathological examination steadily increased, with 38% more gallbladders being submitted in 2023 than in 2014 (**Figure 1**).

**FIGURE 1** Annual number of gallbladders examined at the Department of Pathology at Herlev Hospital in 2014-2023. From 2014 to 2023, a steady increase was observed in the number of gallbladders submitted for histopathological examination at the Department of Pathology at Herlev Hospital with 38% more gallbladders being examined in 2023 than in 2014.



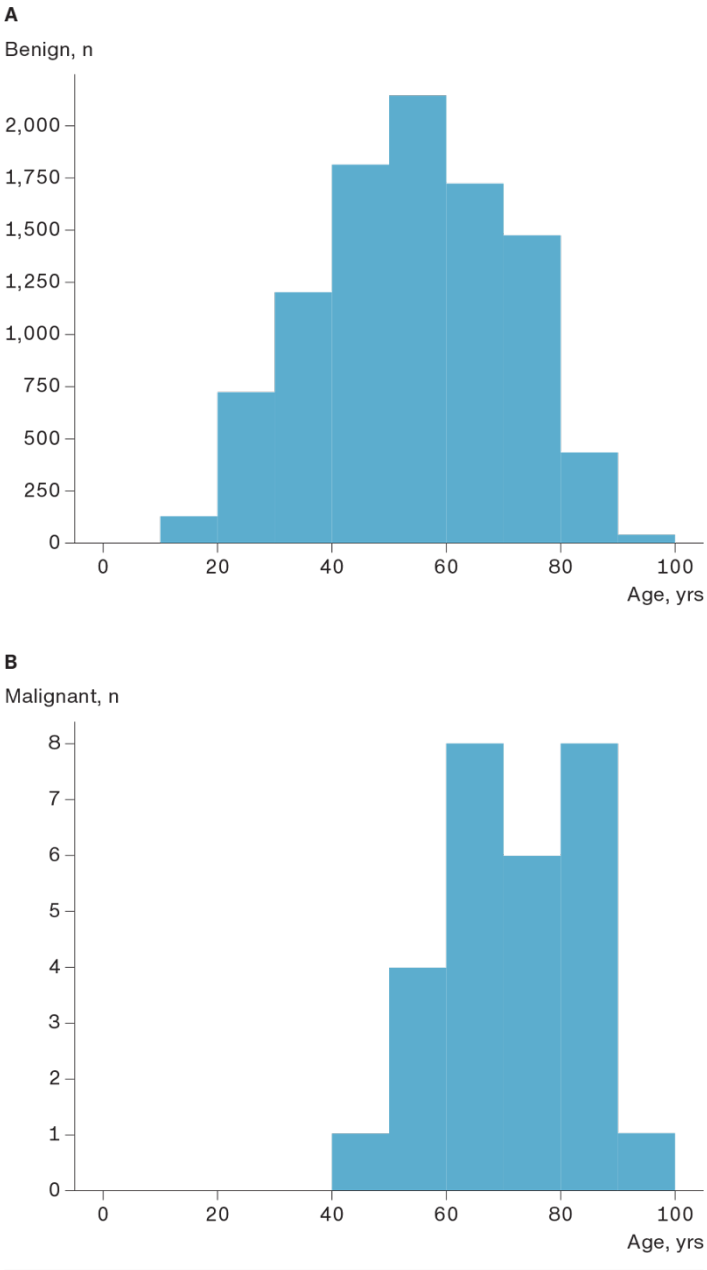

Across all patients, the incidence of incidental gallbladder cancer was 0.29%, with a total of 28 cases being identified (**Table 1**). In patients ≤ 60 years, the incidence of incidental gallbladder cancer was 0.08%, whereas the incidence of incidental gallbladder cancer was 0.67% in patients > 60 years, $p < 0.4 \times 10^{-6}$. The mean age of the patients with benign histopathological examination was 54 years (SD: ± 16), whereas the mean age of patients with malignancy was 71 years (SD: ± 12), $p < 0.5 \times 10^{-7}$ (**Figure 2**).

**TABLE 1** Clinical and histopathological characteristics of incidental gallbladder cancer (N = 28).

| | |
|---|---|
| Age, mean (± SD), yrs | 71 (± 12) |
| *Sex, n (%)* | |
| Female | 20 (71) |
| Male | 8 (29) |
| *Preoperative imaging findings, n (%)* | |
| Polyp/tumour suspicion | 4 (14) |
| Gallbladder wall thickening + inflammation | 17 (61) |
| Stones | 7 (25) |
| *Intraoperative findings, n (%)* | |
| Polyp/tumour suspicion | 5 (18) |
| Gallbladder wall thickening ± inflammation | 20 (71) |
| Normal/stones | 1 (4) |
| Perforation (%) | 2 (7) |
| *Macroscopic examination at the Pathology Department, n (%)* | |
| Polyp/tumour suspicion | 7 (25) |
| Gallbladder wall thickening | 17 (61) |
| Acute inflammation | 4 (14) |
| *Histopathological characteristics, n (%)* | |
| Adenocarcinoma | 20 (71) |
| Adenosquamous carcinoma | 3 (11) |
| Poorly differentiated adenocarcinoma | 4 (14) |
| Carcinoma | 1 (4) |
| *Stage of gallbladder cancer, n (%)* | |
| pT1a | 1 (4) |
| pT1b | 1 (4) |
| pT2 | 17 (61) |
| pT3 | 5 (18) |
| Not specified | 4 (14) |

SD = standard deviation.

**FIGURE 2** Age distribution of benign (**A**) and malignant (**B**) gallbladders. The mean age of patients with gallbladder cancer was significantly higher (71 years) than that of patients with benign histopathological examination (54 years), $p < 0.5 \times 10^{-7}$.




Most incidental gallbladder cancer cases were categorised as adenocarcinoma, and most of the cases were staged as pT2.

The results from the preoperative imaging originate from CT, MR imaging (MRI), ultrasound and MR cholangiopancreatography (MRCP) and are not subcategorised. Most cases were described with signs of cholecystitis and stones and, as expected in a cohort of patients with routine cholecystectomies performed on benign indication, only a few patients had preoperative polyps or tumour suspicion.

At our hospital, the surgeon routinely opens and examines the gallbladder in the operating room. Among the 28 cases of incidental gallbladder cancer, macroscopic changes were noted by the surgeon in 27 gallbladders. The

majority had gallbladder wall thickening, while only a minority presented with a polyp or tumour suspicion. One gallbladder was noted as normal except for stones. At the macroscopic examination at the Department of Pathology, all cases of gallbladder cancer had macroscopic changes. Most cases presented with wall thickening or tumour/polypoid changes and a minority with signs of acute inflammation.

The average labour cost for histopathological examination of a benign gallbladder was estimated at 1,340 DKK, distributed across the personnel groups, with 804 DKK for the physician, 365 DKK for the laboratory technician and 171 DKK for the secretary salary. This figure does not include materials, reagents, equipment expenses, etc.

## Discussion

### Key findings

In this single-centre study of 9,698 gallbladders removed on benign indication in 2013-2023, we found a low rate of incidental gallbladder cancer. We also found that incidental gallbladder cancer was more frequent in patients over 60 years than in younger patients, though the rate remained low. The mean age of patients with malignancy was higher than that of patients with a benign histopathological examination. All gallbladders with gallbladder cancer had macroscopic changes when examined at the Department of Pathology and, except for one, when examined intraoperatively by the surgeon.

### Discussion of the primary outcome

In the present study, we found a low incidence of incidental gallbladder carcinoma of 0.29% in all patients, with an incidence of 0.08% in patients below 60 years and 0.67% in patients above 60 years. These results align with extensive studies in low-incidence countries showing similar incidences and age correlations [4].

For the macroscopic changes of the gallbladders, our study found that wall thickening was the most common macroscopic change associated with gallbladder cancer. This finding demonstrates that incidental gallbladder cancer is not necessarily associated with tumours or polypoid processes and that changes may be subtle. A total of 27 of the 28 identified cases of malignancy had macroscopic changes described by the surgeon and during the macroscopic examination at the Department of Pathology. While the trend is clear, exceptions may occur, such as in the 28th case, where the gallbladder was described as normal except for stones by the surgeon but was found to have diffuse wall thickening at the Department of Pathology. The case was stage pT1b, which will likely have fewer macroscopic changes. This highlights the need for surgeons to be thorough in their examination of the specimens. Still, the case also illustrates that with proper training and well-defined criteria, surgeons should be able to identify the proper specimens to select for histopathology examination. Therefore, it is important to define what can be considered a normal or low-risk gallbladder and to unify these criteria across surgical protocols. For example, gallbladders with diffuse wall thickening or signs of inflammation should not be considered normal and should be submitted for histopathological examination [2].

These findings align with previous studies systematically reviewing the macroscopic changes associated with incidental gallbladder cancer. The vast majority of incidental gallbladder cancer cases present with macroscopically recognisable changes, including diffuse wall thickening, tumours, polypoid changes and inflammation [5, 7, 11, 12]. However, in the literature, there are still a few cases where incidental gallbladder cancer appears in a macroscopically normal gallbladder. In the majority of these cases, the cancer is in an early stage (pT1a) [12] and would be radically treated by cholecystectomy [13].

### Discussion of secondary outcomes

The labour cost of histopathological examination of a gallbladder was estimated at 1,340 DKK. This figure does

not include other expenses, and the actual cost is higher. With approximately 9,000 cholecystectomies performed annually in Denmark, introducing selective histopathological examination may have considerable economic and operational benefits.

Since the macroscopic changes in benign gallbladders were not systematically reviewed in the present study, it cannot be determined how many gallbladders could potentially be omitted from the histological examination if selective histopathological examination is implemented in Denmark. Although a proportion of the benign gallbladders is expected to appear macroscopically normal, it should also be anticipated that a considerable number will present with macroscopic changes, including inflammation and wall thickening.

In 2016, the Netherlands introduced a selective approach to histopathological examination of the gallbladder, where the surgeon opens the gallbladder in the operating room and assesses whether there is an indication for histopathological examination. After introducing selective histopathological examination, a large prospective clinical study from the Netherlands investigated surgeons' ability to detect cancer by examining the gallbladder in the operating room. The study included a total of 10,041 gallbladders and 22 cases of gallbladder carcinoma. The authors reported that selective histopathological examination would have yielded a 78.1% reduction in submitted samples [14].

### Strengths and limitations

Our data are from a single centre but are in accordance with more extensive international studies in low-incidental areas of gallbladder cancer with a rate of 0.29%. The data also show the link between age and incidence of incidental gallbladder cancer, which is in accordance with previously published studies showing that age is associated with an increased risk of incidental gallbladder cancer [4].

### Perspectives

Gallbladder cancer is a rare disease, and although Denmark is a low-incidence country, it has been customary for all gallbladders to undergo routine histopathological examination to rule out incidental gallbladder carcinoma. Based on our findings and considering the cost of histopathological examination of gallbladders undertaken every year in Denmark, this paper supports that routine histopathological examination of the gallbladder after cholecystectomy on benign indication may be replaced by a selective approach, where the surgeon decides if the gallbladder should be submitted for histopathological examination. The study shows that the incidence of gallbladder carcinoma is extremely low in patients under 60 years of age, which means that the selective approach is even safer in patients in this age group.

This study did not include patients with primary sclerosing cholangitis and fibrocystic liver diseases, both of which carry an increased risk of developing cholangiocarcinomas at a younger age. In such cases, if a cholecystectomy is performed, the gallbladder should be sent for histopathological examination irrespective of the patient’s age or the findings from intraoperative macroscopic assessment. In the present study, all cases of gallbladder carcinoma were associated with macroscopic changes, although in most cases, the carcinoma did not present with a tumour but with wall thickening. There is only limited international literature describing how surgeons should perform the macroscopic examination of the gallbladder, including objective criteria for when it should be sent for histopathological examination [8, 15]. However, it is important that not only gallbladders with polyps and tumours but also gallbladders with wall thickening are submitted for histopathological examination.

Although the omission of histopathological examination may potentially lead to missed cases of incidental gallbladder cancer, our data show that the risk is extremely low in Denmark.

## Conclusion

The present retrospective single-centre study found a low incidence of incidental gallbladder carcinoma of 0.08% in patients ≤ 60 years and an incidence of 0.67% in patients > 60 years. A total of 28 cases of malignancy were identified. Macroscopic changes were noted in 27 of the 28 cases by the surgeon and in all cases at the macroscopic examination at the Department of Pathology. The most common macroscopic feature was wall thickening, followed by polypoid changes.

The present study supports the implementation of a selective approach to histopathological examination of the gallbladder after cholecystectomy but also emphasises the need for thorough macroscopic examination by the surgeon in the operating room.

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