

Prophylactic cholecystectomy in benign gallbladder disease as a preventive measure for gallbladder cancer: Is there any impact?

Colecistectomía profiláctica en la enfermedad benigna de la vesícula biliar como medida preventiva para el cáncer de vesícula biliar: ¿Existe algún impacto?

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Abstract

Benign gallbladder disease (BGD), namely cholelithiasis and chronic cholecystitis, pose a significant public healthcare problem given their impact on morbimortality and healthcare costs. Furthermore, cholelithiasis and chronic cholecystitis are the most frequent risk factors for developing gallbladder cancer (GBC), a condition that is often incurable at diagnosis due to delayed symptomatology; thus further contributing to the burden of morbidity and mortality. In light of this panorama, some healthcare systems began to adopt prophylactic cholecystectomy (PCH) as a preventive measure in patients diagnosed with BGD, aiming to reduce the potential development of GBC, as well as the need for recurrent consultation to the emergency room due to complications. Indeed, implementing a preventive surgical strategy, particularly in regions with higher incidence of GBC, has become a topic for

active discussion and continuous exploration. Evidence regarding PCH and its related benefits is emerging globally, with varied results and perspectives depending on local epidemiology and healthcare resources. As expected, studies across different populations reveal disparities in GBC rates as well as disparities regarding PCH outcomes and benefits. The great heterogeneity within the available data sets the ground for debate on the efficacy and advisability of this preventive approach. This review aims to analyze the impact of PCH on cancer incidence and mortality, adjusting for different populations and making a contrast between the pros and cons of this measure.

Keywords: Benign gallbladder disease, cholelithiasis, chronic cholecystitis, gallbladder cancer, prophylactic cholecystectomy.

La enfermedad benigna de la vesícula biliar (EBVB), específicamente la colelitiasis y la colecistitis crónica, representa un problema significativo de salud pública debido a su impacto en la morbimortalidad y los costos de atención médica. Además, la colelitiasis y la colecistitis crónica son los factores de riesgo más frecuentes para el desarrollo de cáncer de vesícula biliar (CVB), una condición que a menudo es incurable en el momento del diagnóstico debido a la sintomatología tardía; lo cual contribuye aún más a la carga de morbilidad y mortalidad. En este contexto, algunos sistemas de salud han comenzado a adoptar la colecistectomía profiláctica (CP) como una medida preventiva en pacientes diagnosticados con EBVB, con el objetivo de reducir el posible desarrollo de CVB, así como la necesidad de consultas recurrentes en urgencias debido a complicaciones. De hecho, la implementación de una estrategia quirúrgica preventiva, especialmente en regiones con mayor incidencia de CVB, se ha convertido en un tema de discusión activa y exploración continua. La evidencia sobre la CP y sus beneficios asociados está emergiendo a nivel mundial, con resultados y perspectivas variadas que dependen de la epidemiología local y los recursos de atención sanitaria. Como era de esperar, estudios en diferentes poblaciones revelan disparidades en las tasas de CVB, así como disparidades en los resultados y beneficios de la CP. La gran heterogeneidad dentro de los datos disponibles sienta las bases para el debate sobre la eficacia y conveniencia de este enfoque preventivo. Esta revisión tiene como objetivo analizar el impacto de la CP en la incidencia y mortalidad del cáncer, ajustándose a diferentes poblaciones y contrastando los pros y los contras de esta medida.

Palabras clave: Enfermedad benigna de la vesícula biliar, colelitiasis, colecistitis crónica, cáncer de vesícula biliar, colecistectomía profiláctica.

Benign gallbladder disease (BGD), namely cholelithiasis and chronic cholecystitis, poses a significant public healthcare problem given its impact on morbimortality and healthcare costs. The prevalence of these conditions is estimated to affect nearly 15% of adults in developed countries, with subtle variations by region, age, and gender^{1,2}. Notably, incidence rates continue to rise while also contributing to a considerable amount of hospital admissions, especially in patients with symptomatic presentations and recurrent complications³. BGD not only demands numerous healthcare resources, but the associated costs of diagnostics, treatment, surgical management, and post-operative care also exert a gigantic economic burden⁴. Furthermore, cholelithiasis and chronic cholecystitis are the most frequent risk factors for developing gallbladder cancer (GBC), a condition that is often incurable at diagnosis due to delayed symptomatology; thus, creating a substantial burden of morbidity and mortality, accounting for almost 2% of all cancer-related mortality⁵.

In light of these burdens, some healthcare systems began to adopt prophylactic cholecystectomy (PCH) as a preventive measure in patients diagnosed with BGD, aiming to reduce the potential development of GBC as well as the need for recurrent consultation to the emergency room due to complications^{6,7}. This approach has been supported by the hypothesis that removing the gallbladder before malignancy arises could benefit high-risk individuals⁸. Although GBC remains relatively rare compared to other malignancies, its mortality remains quite high due to late-stage diagnosis. Therefore, implementing a preventive surgical strategy, particularly in regions with higher incidence of GBC, has become a topic for active discussion and continuous exploration⁹.

Evidence regarding PCH and its related benefits is emerging globally, with varied results and perspectives depending on local epidemiology and healthcare resources. As expected, studies across different populations reveal disparities in GBC rates as well as disparities regarding PCH outcomes and benefits¹⁰. The great heterogeneity within the available data sets the ground for debate on the efficacy and advisability of this preventive approach. This review aims to analyze the impact of PCH on cancer incidence and mortality, adjusting for different populations and making a contrast between the pros and cons of this measure.

PROPHYLACTIC CHOLECYSTECTOMY: WHO? WHERE? WHEN?

GBC is a relatively rare neoplasm that shows a particular epidemiologic behavior with high incidence rates in certain populations. The interplay of genetic susceptibility,

lifestyle factors, and BGD appear to be particularly important risk factors; yet available data remains unable to provide an insightful understanding of said divergence in incidence. For instance, South American countries, such as Chile and Ecuador, alongside regions of Northern India, have some of the world's highest GBC rates, whereas North America and Eastern Europe have some of the lowest rates¹¹. As a result, healthcare practitioners in high-incidence regions face the pressing need to develop preventive measures against GBC, whether through the management of risk factors or more invasive approaches such as PCH. Nevertheless, establishing proper policies regarding PCH requires deep analysis of risk profiles, local epidemiological data, and outcome analysis of prospective studies, which is not always possible¹².

Drawing the line between those at "high risk" and those at "low risk" of GBC remains difficult, even within the population with the highest intrinsic risk. The most well-known risk factors for GBC are a family history of GBC, personal history of BGD, older age, lifestyle, and environmental factors, such as unhealthy diet, low physical activity, and obesity, alongside certain chronic infections like *Salmonella typhi* and *Helicobacter pylori*¹³⁻¹⁵. Nevertheless, to date, there is no multifactorial risk prediction model for GBC in high-incidence populations that allows for better allocation of financial resources and improvement of surgical capacity.

Boekstegers et al.¹⁶ aimed to develop a risk prediction model in the Chilean population by adding other variables to the underlying inclusion criteria: presence of gallstones, sex, and age. After adjusting for body mass index (BMI), history of GBC, and number of children, it was possible to enhance the number of cholecystectomies needed to prevent one case of GBC, going from 115 to 80 after 2 model adjustments. However, given the low population and the lack of prospective information, validation remains uncertain. Notwithstanding, there is a need for further research on this topic to provide a more standardized model for risk prediction and the previously given approach by Boekstegers et al. provides a detailed methodology and solid theoretical foundations to replicate it in other populations.

Moreover, despite its proposed benefits, PCH is not without downsides, particularly when assessing low-risk patients. Like any surgical procedure, PCH carries inherent risks, such as complications from the procedure itself and the anesthesia, injury of nearby organs, and the overall panel of postoperative complications such as infection, hemorrhage, and others¹⁷. Furthermore, it is well established that gallbladder removal can lead to long-term digestive issues in some patients, including bile reflux, chronic diarrhea, chronic abdominal pain, and malabsorption syndrome^{18,19}. These risks, although relatively infrequent, bring forth the ethical question of whether low-risk patients would benefit from such a preventive measure, especially when their likelihood of get-

ting GBC remains statistically low. In light of the above, after weighing these potential drawbacks, it falls under the healthcare provider's responsibility to carefully assess which patients should undergo PCH and which patients should remain under observation.

Several countries have implemented PCH programs to address the burden of GBC. For instance, in 2006, the Chilean government launched a preventive protocol, called AUGE, guaranteeing access to gallbladder surgery for patients aged 35-49 years diagnosed with BGD. Along these lines, Gonzalez et al.²⁰ conducted an interrupted time series analysis of hospitalization and mortality data from 2002 to 2018 that are publicly available from the Chilean Department of Health Statistics and Information. It was reported that the cholecystectomy rate increased by 45 operations per 100,000 individuals per year after the introduction of the preventive program. Likewise, for each 1% increase in the proportion of patients without gallbladder, there was a 0.73% decrease in GBC mortality (95% CI 1.05% to 0.38%). However, the negative correlation was limited to women, the southern Chilean population, and those aged over 60 years. Notoriously, the authors reported that the validation of this negative correlation requires using individual-level longitudinal data provided that their methodology has significant bias potential.

Another research by Cid et al.²¹ compared different GBC-associated variables before and after the prevention protocol was implemented. However, considering that GBC mortality has been globally declining for some time, adjustments were made to avoid confusion during analysis. It was observed that, in contrast to what was expected, GBC mortality in Chile began to drop in July 2005, before the implementation of the AUGE program. However, the rates began to decline more rapidly in women aged 35-59 in 2007-2010, and the same trend was followed by men between 2011-2013, reflecting a slower uptake in men. This post-AUGE reduction suggests that prioritizing young individuals has the highest impact on GBC mortality in the long term. Despite analyzing over 30 years of data, the authors suggest that individual-level data could yield better insights regarding longer waiting times for surgery, given that prioritizing young individuals makes the wait time for older individuals significantly longer, making it at the least questionable when considering access to care.

On the other hand, there is a divided consensus regarding these preventive measures in different countries with similar incidence of GBC. For instance, a report from Indian surgeons indicates that the overall amount of cholecystectomy has increased since the advent of laparoscopic cholecystectomy. However, most surgeons agreed that they would not operate on patients without enough risk factors, which, again, are still poorly understood²². However, other authors have stated that prospective population-based data from low-risk and high-risk patients reveal that PCH reduces mortality from

GBC in northern Indian women. The morbidity and mortality of laparoscopic cholecystectomy in uncomplicated cholelithiasis is very low in India. As a result, Mohandas et al.²³ state that PCH should be offered to young healthy women from high-risk regions whenever they are diagnosed with asymptomatic gallstones. Although there is a lack of consensus regarding risk factors for GBC, most of the evidence coming from countries with high GBC incidence suggests that the presence of BGD should be enough criteria to propose PCH.

PCH as a preventive approach to reducing GBC mortality presents a compelling yet complex strategy, especially in regions with higher incidence. While studies in countries like Chile and India have demonstrated possible benefits, particularly in younger, high-risk populations, questions remain about the efficacy, cost-effectiveness, and risks of PCH, especially for low-risk individuals. Evidence suggests that prioritizing high-risk patients could potentially reduce mortality; however, there are still unclear criteria for labeling patients as high- or low-risk profiles given the significant heterogeneity of risk factors across and within populations. Furthermore, the universal application of PCH remains impractical due to regional healthcare disparities, difficult access to healthcare, and lack of cost-effectiveness analysis. Further longitudinal, individual-level studies are essential to validate existing findings and optimize the selection criteria for PCH, ultimately balancing preventive benefits with the risks and costs associated with gallbladder removal.

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