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Review Article

Revisiting the Association Between Gallstones and Gallbladder Cancer: Is Reverse Causation an Under-explored Explanation?

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Abstract

Background: Gallstones have long been considered a major risk factor for gallbladder cancer (GBC), based primarily on observational and epidemiological studies. However, most available evidence assumes a unidirectional causal relationship, without adequately considering the possibility of reverse causation.

Objective: This article aims to critically analyze existing epidemiological evidence linking gallstones and gallbladder cancer and to propose an alternative hypothesis: that early gallbladder malignancy or pre-malignant pathology may impair gallbladder function, leading to secondary gallstone formation.

Methods: A narrative review of epidemiological studies, case-control analyses, and meta-analyses examining the gallstone-GBC association was conducted, with a focus on study design, temporality, and potential biases.

Results: While multiple studies report an increased relative risk of gallbladder cancer in patients with gallstones, most lack detailed information regarding the duration, size, and chronology of gallstone development. This raises uncertainty about the direction of causality.

Conclusion: The relationship between gallstones and gallbladder cancer may be more complex than traditionally believed. Reverse causation-where early cancer-related gallbladder dysfunction leads to stone formation-cannot be excluded. Future prospective studies with precise temporal documentation are needed.

Keywords: Gallstones, Gall bladder, Gall Badder Carcinoma (GBC).

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Introduction

Gallbladder carcinoma (GBC) is an aggressive malignancy of the biliary tract with a poor prognosis due to its late clinical presentation and rapid progression. It is more prevalent in certain geographic regions, particularly North India, where gallstone disease is also highly common. Despite advances in diagnostic modalities, early detection of gallbladder carcinoma remains difficult, emphasizing the need to better understand its etiopathogenesis.

Gallstones are widely recognized as the most important risk factor for gallbladder carcinoma, with studies reporting their presence in a majority of affected patients. The conventional explanation describes a sequence in which long-standing gallstones cause chronic mechanical irritation and inflammation of the gallbladder mucosa, leading to epithelial dysplasia and eventual malignant transformation. Chronic inflammation, repeated mucosal injury, and subsequent cellular changes play a central role in this process. However, this traditional unidirectional model does not fully explain all clinical observations. Gallstones are common in the general population, yet only a small proportion of individuals develop gallbladder carcinoma. Furthermore, gallstones detected at the time of cancer diagnosis may not always precede malignant transformation. These observations suggest that gallstone formation and gallbladder carcinoma may share a more complex relationship.

Early gallbladder pathology, including premalignant changes and early-stage carcinoma, can impair gallbladder motility by affecting the muscular layer and neural control of contraction. Impaired gallbladder emptying leads to bile stasis and cholesterol supersaturation, which are key factors in gallstone formation. Thus, in some cases, gallstones may develop secondary to early

gallbladder pathology rather than acting solely as the initiating cause.

Additionally, bile stasis and gallbladder dysmotility further promote chronic inflammation, creating a self-perpetuating cycle that may accelerate disease progression. This overlap between stone-related inflammation and malignancy-associated functional changes can make it difficult to determine the temporal sequence between gallstone formation and gallbladder carcinoma.

Therefore, a bidirectional relationship between gallstones and gallbladder carcinoma is proposed, in which gallstones may contribute to chronic inflammation and carcinogenesis, while early gallbladder carcinoma may also predispose to gallstone formation through impaired motility and bile stasis. This concept highlights the importance of careful evaluation of gallstone disease, particularly in high-risk populations, for the possibility of underlying early gallbladder malignancy. Epidemiological studies have consistently demonstrated a strong association between gallstones and gallbladder cancer, particularly in high-risk regions such as North India [1-6].

This study aims to critically analyze existing epidemiological evidence linking gallstones and gallbladder cancer and to propose an alternative hypothesis: that early gallbladder malignancy or pre-malignant pathology may impair gallbladder function, leading to secondary gallstone formation.

Methods

A narrative review of epidemiological studies, case-control analyses, and meta-analyses examining the gallstone-GBC association was conducted, with a focus on study design, temporality, and potential biases. The proposed conceptual framework illustrating the bidirectional relationship between gallbladder pathology, gallstone formation, and gallbladder carcinoma is summarized in Figure 1.

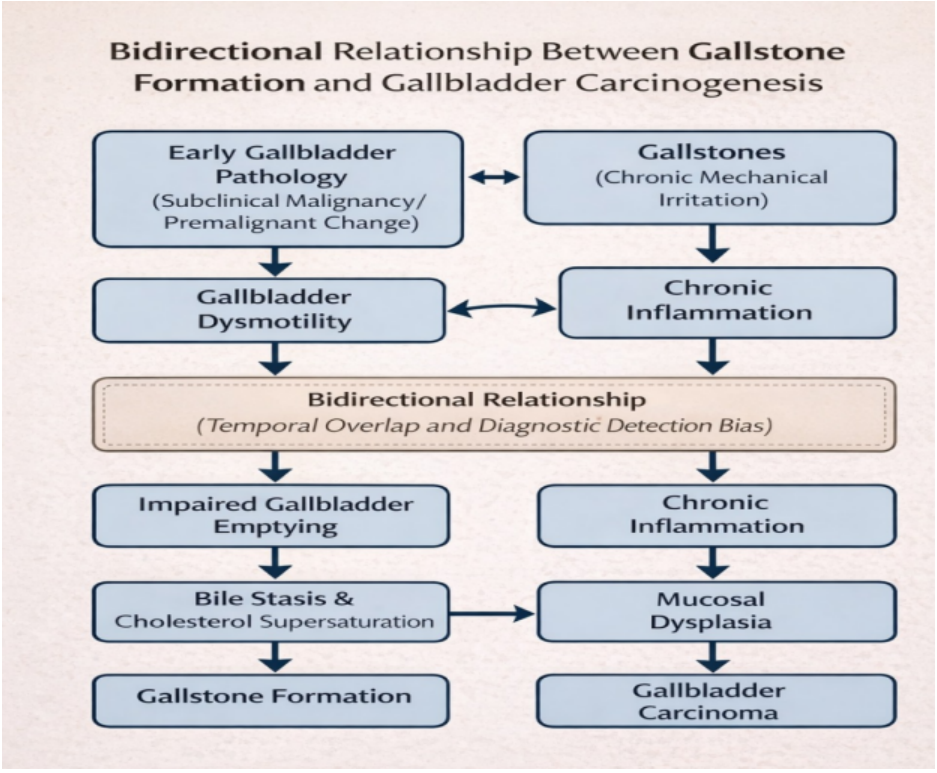

Figure 1: Bidirectional Relationship between Gallstones and Gallbladder Carcinoma

Proposed bidirectional relationship between gallbladder pathology and gallstone formation, illustrating how early gallbladder carcinoma or premalignant changes may lead to dysmotility and bile stasis resulting in gallstone formation, while chronic gallstones may promote inflammation and carcinogenesis.

Results

Several epidemiological and clinicopathological studies have demonstrated a strong association between gallstones and gallbladder carcinoma, particularly in high-incidence regions such as North India [1-6]. Chronic mechanical irritation of the gallbladder mucosa by gallstones is believed to induce persistent inflammation, epithelial injury, and subsequent dysplastic changes that may progress to malignancy. However, this conventional causative explanation does not fully

account for all observed clinical patterns. Notably, gallbladder cancer has been detected in patients with relatively short durations of gallstone disease, while many individuals with long-standing gallstones never develop malignancy [7].

This raises the possibility that gallstones may, in some cases, represent a secondary phenomenon rather than the initiating event. Emerging evidence suggests that early gallbladder pathology, including premalignant mucosal alterations and early-stage carcinoma, may impair gallbladder motility through involvement of the muscular layer and neural regulation [8,9].

Impaired gallbladder emptying leads to bile stasis and cholesterol supersaturation, which are key mechanisms underlying gallstone formation. This bidirectional relationship creates a self-perpetuating cycle in which gallstones promote chronic inflammation and carcinogenesis, while early malignant or premalignant changes predispose to gallstone formation through dysmotility and bile stasis [10].

Several observational and clinicopathological studies have explored the causal and temporal relationship between gallstones and gallbladder cancer, though reverse causation remains under-investigated [7-10].

Conclusions

Gallstones and gallbladder cancer share a well-established epidemiological association; however, the direction of causality remains incompletely understood. While chronic gallstone disease has traditionally been considered a major risk factor for gallbladder carcinogenesis through sustained inflammation and mucosal injury, emerging evidence suggests that early gallbladder pathology may itself contribute to gallstone formation by inducing dysmotility and bile stasis.

The frequent detection of gallstones at or near the time of gallbladder cancer diagnosis, coupled with limited documentation of stone duration in retrospective studies, raises the possibility of reverse causation or a bidirectional relationship.

This highlights an important evidence gap in distinguishing long-standing causal gallstones from stones that may develop secondary to early malignant or premalignant gallbladder changes.

Future prospective, longitudinal studies with precise temporal assessment of gallstone development, gallbladder function, and histopathological progression are essential to clarify this relationship. A clearer understanding of the causal pathway may improve risk stratification, guide surveillance strategies in high-risk populations, and facilitate earlier detection of gallbladder malignancy.

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