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Review

Cholelithiasis in gallbladder cancer: Coincidence, cofactor, or cause!

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Abstract

Background: While gallstones are associated with cancers of the gallbladder, the actual nature of their relationship needs to be clarified. This would aid the recommendations on the need for prophylactic cholecystectomy.
Methods: A systematic search of the scientific literature was carried out using the Medline, the Embase, and the Cochrane Central Register of Controlled Trials for the years 1891–2009 to obtain access to all publications involving gallstones in gallbladder cancer.
Results: While some epidemiological evidence supports a causal relationship for gallstones in gallbladder cancer, other studies have demonstrated a relatively low incidence of gallbladder cancer in countries reporting a high incidence of gallstones as a whole. In those studies where gallstones appear to have a causative role for cancer, the risk increases with increasing size, volume and weight, and number of the stones. The impact of duration of the stone or its composition is not clear. Experimental evidence from studies examining the impact of artificially introducing gallstones in the gallbladder has failed to lead to carcinogenesis.
Conclusions: The evidence at the current time indicates that gallstones are a cofactor in the causation of gallbladder cancer. Absolute proof of their role as a cause for gallbladder cancer is lacking. The recommendation for prophylactic cholecystectomy in countries reporting a high incidence of gallbladder cancer and associated gallstones needs to be tailored to the epidemiological profile of the place.

Keywords: Gallstones; Cancer; Randomised; Gallbladder cancer

Introduction

While the presence of gallstones with gallbladder cancer has been appreciated since the 19th century,[1,2] the cause–effect relationship is a matter of debate. Do we consider the gallstone to be an innocent bystander, a contributory factor, or a cause for gallbladder cancer?!

The apparent urgency to answer the question on the association of gallstones and gallbladder cancer stems from the fact that gallbladder cancer is a disease with a poor outcome and should we able to demonstrate the causal relationship of gallstones to gallbladder cancer, we would place ourselves in a position to offer cholecystectomy for gallstones as a preventative measure against the cancer.

Reviewing the literature to answer the question on the nature of the association of gallstones and gallbladder cancer is not easy. This is because there are numerous points that need to be addressed on gallstones which include the following:

1) What is the strength of the epidemiological association between gallstones and gallbladder cancer?
2) Does the duration for which the patient has the gallstone play a role in the pathogenesis of cancer?
3) Do the size, weight and volume of the gallstone affect its ability to influence cancer development?
4) Does the number or type of gallstone play a role in cancer causation?

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Methods

In an attempt to answer these questions, a systematic search of the scientific literature was carried out using the Medline, the Embase, and the Cochrane Central Register of Controlled Trials for the years 1891–2009 to obtain access to all publications involving gallstones in gallbladder cancer.

The search strategy was that described by Dickersin and colleagues[3] with the appropriate specific search terms 'gallstones', 'cholelithiasis', 'and gallbladder cancer' looking for studies linking gallstones to gallbladder cancer. Confounding factors such as the presence of Mirizzi's syndrome and its association with gallstones and gallbladder cancer have not been included in this review. Similarly, gallstones in women has been addressed only wherever indicated but no attempt has been to specifically derive any conclusions on the female sex being at an increased risk for gallbladder cancer as a recently published review by one of the authors (SGB)[4] has quite conclusively indicated that the current data does not support such an argument.

Results

The adopted search strategy revealed 1570 articles of which 1526 were excluded for lack of clear data relating to gallstones and gallbladder cancer. Of the remaining 44 articles included in the study, 26 articles which provided clear epidemiological evidence of the relationship of gallstones to gallbladder cancer were then specifically analysed.

Gallstones and gallbladder cancer – the epidemiology

Evarts Graham[5] in the early 1930s was disgruntled with the lack of interest in preventative work on gallbladder cancer by national and international cancer control societies and went on to demonstrate for the first time the hitherto noted, but underappreciated, association of gallstones with gallbladder cancer. His observations based on the literature available at the time, as well as his own experience at the Barnes Hospital, were that gallstones were present in 69–100% of cases of gallbladder cancer and in turn gallbladder cancer was found in 4.5–14% of patients with gallstones.[1,2,5,6] This led him to suggest the role of cholecystectomy for patients diagnosed with gallstones on cholecystography as a method of prevention of gallbladder cancer. The basis for linking gallstones to the development of gallbladder cancer was the repeated trauma caused by its presence to the gallbladder mucosa leading to a state of chronic inflammation. The repeated inflammation along with superadded infection by chronic organisms such as salmonella typhi was believed to be able to lead to dysplastic and eventually malignant changes in the gallbladder mucosa.[7] Other similar reports then followed linking gallstones with cancer.[8,9]

In 2001, Lazcano-Ponce et al.[10] summarised the large epidemiological studies available linking gallstones and gallbladder cancer. Besides the mere presence of gallstones as a risk factor, studies have looked at other factors related to gallstones. Table 1and Refs. [11–36] represent a compilation of studies looking at gallstones, as well as, these various other factors including duration of presence of the stone in the gallbladder, its size, weight and volume and even the number and type of stones.

Duration of gallstones

The rationale behind the long duration of gallstones as a cause for gallbladder cancer is that it provides time for chronic trauma to the mucosa,[37] coupled with an increase in enteric bacteria as the person ages[31] which eventually initiate a sequence of pathologic changes that can result in cancer. While gallstones present for more than 20 years have been shown to be associated with an increased risk for gallbladder cancer,[20,29,30] other authors[22] have found that the duration of presence of the stone did not alter the risk of gallbladder cancer already associated with gallstones.

Number, weight and volume of gallstones

More stones, as well as, larger and heavier stones have been shown to be associated with an increased risk for cancer causation. A greater risk of trauma caused by such stones to the gallbladder mucosa has been linked to the causation of dysplasia and progression to carcinoma. Warren et al.[38] had noted a larger mean stone diameter (20.3 mm) in patients with cancer as compared to 11.9 mm in controls in 902 patients analysed retrospectively. Evidence in support of gallstone >3 cm in size as a causative factor for gallbladder cancer have been listed in Table 1.

Infection

Csendes et al.[31] found that patients with gallbladder cancer tended to have more organisms in their bile than controls of which *Salmonella typhi* was present in 4% cases. Further, it is believed that the presence of infection in the bile is a risk for stone formation and hence the attendant risk of cancer.

Type of stone

The presence of cholesterol in the gallstone as a cause for gallbladder cancer has also been analysed.

Srivastava et al.[39] recently demonstrated differences in cholesterol, calcium and magnesium composition in gallstones in patients with gallbladder cancer and chronic cholecystitis using proton nuclear magnetic resonance spectroscopy. Whether such changes in the inorganic