Relative Risk of Colonic Cancer Post Cholecystectomy in Najaf

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Abstract

Background: Many studies have investigated the relationship between cholecystectomy and colorectal cancer, and have reported moderately increased risk of colorectal cancer in patients with cholecystectomies. The alteration of bile flow is one possible explanation for this increased risk.

Objective: The aim of this study is to evaluate the possible correlation between cholecystectomy and colorectal carcinoma.

Patients and Methods: Seventy five patients with carcinoma of colon were included in this retrospective study and they include 23 women and 52 men and their ages range from 28 years to 71 years. Those 75 patients with carcinoma of colon were compared to 75 patients with carcinoma of lung, whose ages range from 30 years to 85 years and include 36men and 39women.

This entire patient had been selected from those patients admitted to oncology unit in Al-Sadr medical city from July 2010 to March 2012.

Results: The history of cholecystectomy at the time of diagnosis of the carcinoma was significantly higher in the carcinoma of colon group compared to the carcinoma of lung group.

No statistically significant difference was noted in this study between men and women with colorectal carcinoma concerning the history of cholecystectomy.

In our study there was no significant association between time from cholecystectomy to diagnosis carcinoma of colon.

Also in our study there was no significant association between age in cholecystectomised patient and development carcinoma of colon.

Conclusion: We observed a significantly increased occurrence of cholecystectomy among patients with colorectal carcinoma but not related to age, sex and time from cholecystectomy to diagnosis carcinoma of colon.

الخطر النسبي لسرطان القولون بعد عملية رفع المرارة

الخلاصة

الخلفية: تَحرّتْ العديد مِنْ الدِراساتِ العلاقةَ بين استئصال المرارة والسرطانِ القولوني المستقيمي، وذَكرتْ خطرَ تزايدَ السرطانِ القولوني المستقيمي في مرضى عمليات استئصال المرارة. إنّ تعديلَ تدفقِ الصفراءِ تفسيرُ محتملُ لهذا الخطرِ المتزايدِ.

الهدف: إنّ هدفَ هذه الدراسةِ هو تُقيّمَ الارتباط المحتملَ بين استئصال المرارة والسرطانِ القولوني المستقيمي.

المرضى والطرق: خمسة وسبعون مريض بسرطانِ القولونِ تُضمّنوا في هذه الدراسةِ وهم يَتضمّنونَ ٢٣ امرأة و٥٢ رجلَ وأعمارَهم تتراوح مِنْ ٢٨ سنةِ إلى ٧١ سنةِ. أولئك المرضى الـ٧٥ المصابون بسرطانِ القولونِ قُورنوا إلى ٧٥ مريضِ مصابون بسرطانِ الرئةِ، و الذي تَتراوحُ أعمارَهم مِنْ ٣٠ سنةِ إلى ٨٥ سنةِ وتُتضمّنْ ٣٦ رجلَ و ٣٩ امرأة.

كل المرضى قد اختيروا مِنْ أولئك المرضى الذين أدخلوا إلى وحدة الأورام في مدينةِ الصدر الطبية مِنْ تموزِ ٢٠١٠ إلى آذار ٢٠١٢.

النَتائِج: تأريخ استئصال المرارة السابق في وقت تشخيصَ السرطانِ كَانَ أعلى في مجموعة سرطانِ القولونِ إذا ما قورن بمجموعة سرطان الرئة.

في هذه الدراسةِ لا يوجد فرق إحصائي بين الرجالِ والنِساءِ (من ناحية الجنس) المصابون بالسرطانِ القولوني المستقيمي الذي لديهم إستئصالِ المرارة سابقا.

في هذه الدراسة لم تكن المدة الزمنية ذات أهمية أي مِنْ وقت إستئصالِ المرارة إلى وقت تشخيصِ سرطان القولونِ. وكذلك لا توجد علاقة بين عمر المريض الذي استؤصلت مرارته وبين إصابته بسرطان القولون.

الخاتمة: لقد لوحظ في هذه الدراسة إن هناك ارتفاع في نسبة الإصابة بسرطان القولون عند المرضى الذين أُجريت لهم عملية استئصال المرارة من دون أن تكون هناك علاقة لا لجنس المريض ولا لعمره أو طول وقصر الفترة الزمنية بعد عملية استئصال المرارة.

Introduction

Cancer of the large bowel is the second cause of cancer death in the United States after lung cancer [1]. Most of colorectal cancers, regardless of etiology, arise from adenomatous polyps [2]**.** Colorectal cancer is preventable and is highly curable if detected early [2].

By far the two most common and clinically significant neoplastic lesions that appear in the large intestine are adenomatous polyps and adenocarcinoma arising from epithelial cells of the colonic or rectal mucosa. However, the large bowel is also the site of other malignant diseases. Including anal carcinoma (squamous or transitional cell types), lymphoma, leiomyosarcoma, malignant carcinoid tumor, and Kaposi's sarcoma. Malignant diseases from adjacent sites such as the prostate, ovary, uterus, and stomach may also involve the colon and/or rectum by direct invasion[2].

The prognosis for individuals having colorectal cancer is related to the depth of tumor penetration into the bowel wall and the presence of both regional lymph node involvement and distant metastases. These variables are incorporated into the staging system introduced by Dukes and applied to a TNM classification method [1]**.**

Many studies have investigated the relationship between cholecystectomy and colorectal cancer[4-12]., and have reported a moderately increased risk of colorectal cancer in patients with Cholecystectomy[4-9,12]. The alteration of bile flow is one possible explanation for this increased risk[4,7,13,14].

Two meta-analyses studies showed a modest increase in the risk of developing cancer in the proximal colon after a cholecystectomy [4,7] ,Similarly, three prospective cohort studies also observed an increased risk of proximal cancers, particularly among women[5,8,15]**.**

The association between cholecystectomy and colorectal cancer was plausible due to two possible factors:

(a)- Cholecystectomy can lead to alteration in the bile acid metabolism, thus causing an alteration in the concentrations of bile acids that are delivered to the colon which may act as carcinogens; and/or (b)- Factors that lead to symptomatic cholelithiasis may be shared with colorectal cancer, and therefore cholecystectomy may act as a surrogate maker for other true contributory factors[36].

However, previous research had shown that the bile of cholelithiasis patients contains a higher amount of secondary bile acids, such as deoxycholic acids, than that of healthy controls[16-19]. Secondary bile acids are thought to be carcinogenic[20-24] and, thus, it is highly possible that

cholelithiasis patients are also at risk for colorectal adenomas.

Aim of Study

The aim of this study is to evaluate the possible correlation between cholecystectomy and colorectal carcinoma in al Najaf.

Patients and Methods

Seventy five patients with CA(carcinoma) of colon were evaluated in this retrospective study that includes 23 women and 52 men and their ages range from 28 years to 71 years, those 75 patient of CA colon were compared with 75 patients of CA lung, whose ages range from 30 years to 85 years and include 36men and 39 women.

All these patients had been selected from those patients admitted to oncology unit in Al-Sadr medical city from July 2010 to March 2012.

The diagnosis of CA colon was confirmed by histopathological examination of the sample that were taken from patient after surgery or colonoscopy or both, and examined by two expert histopathologists.

The data about age, sex, histopathology of tumor, staging, history of cholecystectomy, and time duration from cholecystectomy to diagnosis CA colon were collected from patient.

The patients in this study were divided into two groups: Those with history of cholecystectomy and those without history of cholecystectomy.

Then those patients with history of cholecystectomy subdivided in two subgroups regarding time from surgery to diagnosis of CA colon: more than 10 year and less than 10 year.

Also the patients in this study were divided in two groups: patient's age<60years and ≥60 years.

The following patients with CA colon were excluded from this study:

1. Patients who previously diagnosed to have inflammatory bowel disease.
2. Previous diagnosis of FAP(familial adenomatous polyps).
3. Family history of CA colon.

Statistical analysis

The chi-square used for categorical variable, p value < 0.05 was considered to indicate statistical significance.

Calculation's done by interactive chi-square software.

Results

During 20 months period of this study, patients 75 patients with CA colon (23 women ,52 men) ages range from 28 years to 71 years with the mean age of 48 years (SD ±15) had been compared with control group of 75 patients with CA lung (39 women,36 men) ages range from 30 years to 85 years with the mean age 53 years (SD ±13), From those patients with CA colon 17 patients had been cholecystectomised (8 women,9 men) while from patient of CA lung only 2 patients were cholecystectomised (2 men) , The elapsed time between cholecystectomy and diagnosis of malignancy was 13.5(SD±10)years for the CA colon group and 15(SD±5.7) years for the CA lung group, as seen in table (1).

The history of cholecystectomy at the time of diagnosis of the carcinoma was significantly higher in the CA colon group compared to the CA lung group (17/75, 23% vs. 2/75, 3%; p-value=0.00023), as seen in table (2).

No statistically significant difference was noted between men and women with colorectal carcinoma concerning the history of cholecystectomy (9/52, 17.3% vs. 8/23, 13%; p-value=0.0956) as seen in table (3).

In this study there was no significant association between time from cholecystectomy to diagnosis of CA colon (6/17, 35% vs. 11/17, 64%; p-value=0.37), as seen in table (4).

Also in this study there were no significant association between age in cholecystectomised patient and development of CA colon (p-value=0.149), as seen in table (5).

Table 1 Demographic characteristics and incidence of cholecystectomy in patients with colorectal carcinoma and lung carcinoma

Type of tumor / Condition	CA colon (n=75)	CA lung (n=75)
Gender (female: male)	**23 women ,52 men**	**39 women,36 men**
Mean age	**48 years (SD ±15)**	**53 years (SD ±13)**
History of cholecystectomy	**17 patient**	**2 patient**
Elapsed time from cholecystectomy	**13.5±10 year**	**15±5.7 year**

Table 2 the Association between CA colon and cholecystectomy as compare to CA lung (N=150)

cholecystectomy / Tumor type	yes	No	Total
CA colon	**17(89.47%)**	**58(44.27%)**	**75(50%)**
CA lung	**2(10.53%)**	**73(55.73%)**	**75(50%)**
Total	**19(100%)**	**131(100%)**	

P-value=0.00023

Table 3 Association between sex and CA colon (n=75)

cholecystectomy / CA colon	yes	No	Total
male	9(52.94%)	43(74.14%)	52(69.33%)
female	8(47.06%)	15(25.86%)	23(30.67%)
Total	17(100%)	58(100%)	75(100%)

P-value=0.096

Table 4 Association between time from cholecystectomy to diagnosis of CA colon (n=17)

Time from surgery / cholecystectomised patient with CA colon	< 10 year	≥ 10 year	Total
male	4(66.67%)	5(45.45%)	9(52.94%)
female	2(33.33%)	6(54.55%)	8(47.06%)
Total	6(100%)	11(100%)	17(100%)

P-value=0.37

Table 5 Association between age and cholecystectomised CA colon (n=17)

Age / cholecystectomised patient with CA colon	< 60 year	≥ 60 year	Total
male	5(41.6%)	4(80%)	9 (52.94%)
female	7(58.4%)	1(20%)	8 (47.06%)
Total	12(100%)	5 (100%)	17 (100%)

P-value=0.149

Discussion

Multiple clinical studies have demonstrated association between colorectal cancer and Cholecystectomy [5,15, 25,26].

In the current study, cholecystectomy had a statistically significant association with CA colon (p-value=0.00023). This is in agreement with Mannes et al[30] and P. Katsinelos[37] who showed persistent risk of colorectal cancer in patients who had undergone cholecystectomy, and this may be due there is constant flow of bile into the gut and hence, enhanced exposure of the colon to bile salts[36]. Cholecystectomy leads to an even more increased concentration of primary bile acids in the intestinal lumen, which are transformed through Intestinal bacteria to secondary bile salts[13]. The role of secondary bile acids as an endogenous colon carcinoma has been shown in a number of clinical and experimental studies[28,29]. Narisawa et al proved that secondary bile salts can promote colonic epithelial cell proliferation in animal models[20].

In the current study, the effect of sex on development of CA colon in the cholecystectomised and non cholecystectomised patient was statistically non-significant (p-value=0.0956). This is in agreement with Reid et al[7] and Ali A. Siddiqui[36] who found that the risk of colon cancer was statistically non-significant in both sexes who underwent a cholecystectomy and this may be due to that sex had no effect on bile flow in colon which regarded as cause for developing CA colon[7,36].

The effect of age in this study on the cholecystectomised patients with CA colon was a statistically non-significant (p-value=0.149) This is not in agreement with P. Katsinelos [37] and Mannes AG [30] who found that increased risk of CA colon only in patient aged 60-80 years, whereas the younger patient had no increased risk, and this may be due to increased risk of all tumors in old age[30]. In our study we failed to find this relation to age, and this because of limited number of cholecystectomised patients with CA colon that were included in this study.

In the current study, there is statistically non-significant (p-value=0.3733) association between time after cholecystectomy and risk of developing CA colon. This is not in agreement with P. Katsinelos [37] and Mannes AG[30], how found increase risk of developing CA colon after 10 year from cholecystectomy. And this may be due to increase exposure to secondary bile acid lead to increased risk of CA colon[30], also we failed to find this relation to time, and this may related to limited number of cholecystectomised patients with CA colon that were included in this study.

Conclusion and Recommendations

- We observed a significantly increased occurrence of cholecystectomy among patients with colorectal carcinoma but not related to age, sex and time from cholecystectomy to diagnosis of CA colon.
- Since the exact pathogenic association of these conditions has not been fully proved and explained, there is no need for increased surveillance of these patients.

References

1. Lieberman DA et al: Use of colonoscopy to screen asymptomatic adults for colorectal cancer. N Engl J Med 343:162, 2000 [PMID: 10900274],

Harrison's textbook of internal medicine. 17th edition. 2008; 573-577.
2. Guillou PJ, Quirke P, Thorpe H, Multicentre, randomised controlled trial. *Lancet* 2005; 365:1718-1726. Goldman. Cecil textbook of internal medicine, 23rd edition. 2007; 345-372.
3. Nicholas A. Boon, et al. Liver & biliary tract disease, Davidson's principles and practice of medicine. 20th edition. 2006; 977-980.
4. Giovannucci E, Colditz GA, Stampfer MJ. A meta-analysisof cholecystectomy and risk of colorectal Cancer. Gastroenterology 1993; 105: 130–41.
5. Goldbohm RA,Van Den Brandt PA, van 'tVeer P, et al. Cholecystectomy and colorectal Cancer: Evidence from a cohort study on diet and Cancer. Int J Cancer 1993; 53:735–9.
6. Johansen C, ChowWH, Jorgensen T, et al. Risk of colorectal cancer and other Cancers in patients with gall stones. Gut 1996;39:439–43.
7. Reid FD, Mercer PM, Harrison M, et al. Cholecystectomy as a risk factor for colorectal Cancer :Ameta-analysis. Scand J Gastroenterol 1996;31:160–9.
8. Lagergren J, Ye W, Ekbom A. Intestinal CAncer after cholecystectomy: Is bile involved in Carcinogenesis? Gastroenterology 2001;121:542–7.
9. Schernhammer ES, Leitzmann MF, Michaud DS, et al. Cholecystectomy and the risk for developing colorectal cancer and distal colorectal adenomas. Br J cancer 2003;88:79–83.
10. Altieri A, Pelucchi C, Talamini R, et al. Cholecystectomy and the risk of colorectal CAncer in Italy. Br J cancer 2004;90:1753–5.
11. Goldacre MJ, Abisgold JD, Seagroatt V, et al. cancer after cholecystectomy: Record-linkage cohort study. Br J cancer 2005;92:1307–9.
12. Shao T, Yang YX. Cholecystectomy and the risk of colorectal cancer. Am J Gastroenterol 2005;100:1813–20.
13. Malagelada JR, Go VL, Summerskill WH, et al. Bile acid secretion and biliary bile acid composition altered by cholecystectomy. Am J Dig Dis 1973;18:455–9.
14. ZucCAto E, Venturi M, Di Leo G, et al. Role of bile acids and metabolic activity of colonic bacteria in increased risk of colon CAncer after cholecystectomy. Digest Dis Sci 1993; 38:514– 9.
15. Ekbom A, Yuen J, Adami HO, et al. Cholecystectomy and colorectal cancer. *Gastroenterology* 1993;105:142–147.
16. McDougall RM, Walker K, Thurston OG. Bile acid alterations in patients with cholesterol gallstones. J Surg Res 1976;21:233–7.
17. Heuman R, Norrby S, Sjodahl R, et al. Altered gallbladder bile composition in gallstone disease. Relation to gallbladder wall permeability. Scand J Gastroenterol 1980;15:581–6.
18. Shoda J, He BF, Tanaka N, et al. Increase of deoxycholate in supersaturated bile of patients with cholesterol gallstone disease and its correlation with de novo syntheses of cholesterol and bile acids in liver, gallbladder emptying, and small intestinal transit. Hepatologym 1995;21:1291–1302.
19. Thomas LA, Veysey MJ, Bathgate T, et al. Mechanism for the transit-induced increase in colonic deoxycholic acid formation in cholesterol cholelithiasis. Gastroenterology 2000; 119: 806–15.
20. Narisawa T, Magadia NE, Weisburger JH, et al. Promoting effect of bile acids on colon CArcinogenesis after intrarectal instillation of N-methyl-

N9-nitro-N-nitrosguanidine in rats. J Natl CAncer Inst 1974;53:1093–7.
21. Bull AW, Marnett LJ, Dawe EJ, et al. Stimulation of deoxythymidine incorporation in the colon of rats treated intrarectally with bile acids and fats. Carcinogenesis 1983;4:207–10.
22. Watabe J, Bernstein H. The mutagenicity of bile acids using a fluctuation test. Mutat Res 1985;158:45–51.
23. Morvay K, Szentleleki K, Torok G, et al. Effect of change of feCAl bile acid excretion achieved by operative procedures on 1,2-dimethylhydrazine-induced colon cancer in rats. Dis Colon Rectum 1989;32:860–3.
24. Bayerdorffer E, Mannes GA, Richter WO, et al. Increased serum deoxycholic acid levels in men with colorectal adenomas. Gastroenterology 1993;104:145–51.
25. Neugut AI, Murray TI, Garbowski GC, et al. Cholecystectomy as a risk factor for colorectal adenomatous polyps and Carcinoma. *cancer* 1991; 68:1644 – 1647.
26. Weiss NS, Daling JR, Chow WH. Cholecystectomy and the incidence of CAncer of the large bowel. *CAncer* 1982;49:1713–1715.
27. Shao T, Yang YX. Cholecystectomy and the risk of colorectal cancer. *Am J Gastroenterol* 2005;100:1813–1820.
28. Castleden WM, Detchon P, Misso NL. Biliary bile acids in cholelithiasis and colon cancer. Gut 1989; 30:860.865.
29. Paul J, Gessner F, Weshcler JG, Kuhn K, Orth K, Ditschuneit H. Increased incidence of gallstones and prior cholecystectomy in patients with large bowel cancer. Am J Gastroenterol 1992; 87:1120.1124.
30. Mannes AG, Weinzierl M, Stellaard F, et al. Adenomas of the largevintestine after cholecystectomy. *Gut* 1984; 25: 863– 866.
31. Breuer NF, Katschiski B, Mortl E, Leder LD, Goebell H. Large bowel cancer risk in cholelithiasis and after cholecystectomy. Postmortem study. Digestion 1988; 40:219. 226.
32. Gafa M, Sarli L, Sansebastiano G, Lupi M, Longinotti E, Rigamonti PP, Paracchia A. Gallstones and risk of colonic cancer: a matched Case.control study. Int Surg 1987; 72:20.24.
33. Allende HD, Ona FV, Davis HT. Gallbladder disease: risk factor for colorectal CArcinoma? J Clin Gastroenterol 1984; 6:51.55.
34. Gudmundsson S, Moller TR, Olsson H. cancer incidence after cholecystectomy. a cohort study with 30 years follow 1989; 15:113.117.
35. Todoroki I, Friedman GD, Slattery ML, et al. Cholecystectomy and the risk of colon cancer. Am J Gastroenterol 1999; 94:41.46.
36. Ali A. Siddiqui, *MD, Ramalinga Kedika, MD, Amar Mahgoub, MD,* A Previous Cholecystectomy Increases the Risk of Developing Advanced Adenomas of the Colon. The Southern medical journal (2009), Volume: 102, Issue: 11, Pages: 1111-1115.
37. P. Katsinelos, B. Papaziogas. Colorectal cancer Risk in Cholelithiasis and after Cholecystectomy in Northern Greece Annals of Gastroenterology 2004, 17(2):181-184.