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Does appendectomy increase the risk of colorectal adenocarcinoma?

Research Article

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Abstract: Colorectal cancer ranks third as the most common malignancy in the United States and represents the second leading cause of cancer-related mortality. The appendix is thought to have a productive effect against colorectal carcinoma by the immune function based on its association with substantial lymphatic tissue. But, an appendectomy is still the most commonly performed emergency surgical procedure. It is aimed to assess the association between colorectal cancer and appendicectomy. The medical records of 455 patients who received medical and/or surgical treatment with the diagnosis of colorectal carcinoma in two medical centers in a-five-year period were reviewed. The patients were divided into subgroups according to the colonic localization of the tumor, appendectomy status and their body mass indexes (BMI). In order to define independent predictors of colon adeno-cancer, multiple logistic regression analysis was used. Statistically significant variables according to the univariate statistics were selected as candidate variables for multiple logistic regression analysis. A p-value<0.05 was considered statistically significant. Out of 455 colorectal adenocarcinoma patients, 122 (26.81%) were in right colon adenocarcinoma (CA) group, 267 (56.68%) were in left CA group and 66 (14.5%) were in the rectum adenocarcinoma group. Appendectomy was found as the second highest risk factor in rectum and right colon adenocarcinoma. Being appendectomized increases the risk of rectum adenocarcinoma 3.232 times (95%CI: 1.670-6.254), left CA 2.537 times (95%CI: 1.544-4.168) and right CA 3.607 times (95%CI: 2.056-6.330). In the light of our findings, we suggest that being appendectomized might increase the risk of colorectal adenocarcinoma in sporadic cases.

Keywords: *Adenocarcinoma • Appendectomy • Colorectal carcinoma • Rectum*

1. Introduction

Colorectal cancer ranks third (behind prostate and lung cancer in men and behind breast and lung cancer in women) as the most common malignancy in the United States and represents the second leading cause of cancer-related mortality. Approximately 147,000 patients are diagnosed with colorectal cancer each year, and 57,000 deaths are attributed to this disease [1].

Appendectomy is the most commonly performed emergency surgical procedure and accounts for 1-2% of all surgical operations [2]. The appendix is thought to have some immune function based on its association with substantial lymphatic tissue [3]. The main function of appendix is not clearly described, yet. It seems like a guardian of colon [4]. In this study, it is aimed to assess the association between colorectal cancer and appendicectomy.

2. Material and Methods

We reviewed the medical records of 455 patients who received medical and/or surgical treatment with the diagnosis of colorectal carcinoma in two medical centers in a-five-year period. Also, we reviewed the records of 166 patients (as control group) at the same period.

Our criteria of accepting a patient to the control group are: 1) Having a negative colonoscopy (for tumor, inflammatory bowel disease or polyp), 2) No history

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of drug usage, 3) having a negative family history for any malignant diseases, 4) Having a negative thorax and abdominal tomography for any kind of tumors. The patients of control group were selected from the ones in the check-up procedure.

The patients were divided into subgroups according to the localization of the tumor (as right colon, left colon and rectum), appendectomy status (appendectomized and non-appendectomized) and their body mass indexes (BMI) (as over 35 kg/m^2 and under 35 kg/m^2). Also, the control group was divided into subgroups according to appendectomy status and BMI.

The patients, who had appendectomy more than three years before diagnosed, were named appendectomized (AP). The ones, who had appendectomy less than three years before diagnosed and who were not appendectomized, were named as non-appendectomized. The patients, who have a history of appendectomy due to mucocele or other malign causes, were excluded. Also, the patients, who had family history of colorectal carcinoma or hereditary non-polyposis colon cancer or familial adenomatous polyposis, were excluded. Nevertheless, the ones who had a history of inflammatory bowel disease, colorectal carcinoma, hereditary non-polyposis colon cancer or familial adenomatous polyposis, were excluded, too. Only, pathologically approved adeno-carcinoma cases were included. Other types of colorectal cancer patients were excluded due to the low number of individuals in the subgroups.

2.1. Statistical Analysis

Data analysis was performed by using SPSS for Windows, version 11.5. Univariate data analyses were evaluated by Chi-square or Fisher's Exact test, where appropriate. In order to define independent predictors of outcome variable (colon cancer) multiple logistic regression analysis was used. Statistically significant variables according to the univariate statistics were selected as candidate variables for multiple logistic regression analysis. Odds Ratio and 95%CIs for each independent variable were calculated. A *p*-value less than 0.05 was considered statistically significant.

3. Results

Out of 455 colorectal adenocarcinoma (CRA) patients, 122 (26.81%) were in right colon adenocarcinoma (CA) group (G1), 267 (56.68%) were in left CA group (G2) and 66 (14.5%) were in rectum adenocarcinoma group (G3).

325 (71.4%) of 455 CRA patients were male. Although, 85 (51.2%) of 166 patients of control group were male (p<0.05). 80 (65.6%) of G1, 201 (75.3%) of G2 and 44 (66.7%) of G3 were male. There was a statistically significant difference between the control group and the other groups individually (p<0.05).

While 116 (69.9%) of 166 control groups patients were over 50-years of age, 327 (71.9%) of CRA patients were over 50-years of age (p=0.628). 77 (63.1%) of G1, 195 (73%) of G2, 55 (83.3%) of G3 were over 50-years of age. G1 and G2 did not have a statistically significant difference to the control group (p>0.05). On the contrary, group-3 (rectum) had a statistically significant one (p<0.05).

67 (40.4%) of control group patients, and 330 (72.5%) of CRA patients had BMI>35kg/m^2 (p<0.05). 90 (73.8%) of G1, 193 (72.3%) of G2 and 47 (71.2%) of G3 had BMI>35kg/m^2. There was a statistically significant difference between the control group and the other groups individually (p<0.05).

Out of 166 control group patients, 36 (21.7%) were appendectomized. Although, 169 (37.1%) of CRA patients were appendectomized (p<0.05). 53 (43.4%) of G1, 91 (34.1%) of G2 and 25 (37.9%) of G3 were appendectomized. There was a statistically significant difference between the control group and the other groups individually (p<0.05).

According to the Wald statistics; BMI>35kg/m^2 was most efficient variable which increased the risk of colorectal adenocarcinoma at any location. Male gender came the second and being appendectomized was the third. Fifty years old and older was the worst efficient variable in our cohort. It has only a borderline significance in rectum adenocarcinoma (p=0.062) (Table 1).

In right colon and rectal adenocarcinomas; while BMI>35kg/m^2 was the most efficient variable, being appendectomized and of the male gender were second and third, respectively (Table 1).

In left colon adenocarcinoma; again BMI>35kg/m^2 was the most efficient variable, with an odds ratio of 4.916 (95% confidence interval 3.132-7.716). Male gender and being appendectomized came second (OR: 3.296 [95% CI: 2.119-5.127]) and third (OR: 2.537 [95% CI: 1.544-4.168]), respectively (Table 1).

According to our analyses; being appendectomized increases the risk of rectum adenocarcinoma 3.232 times (95% CI: 1.670-6.254), left colon adenocarcinoma 2.537 times (95% CI: 1.544-4.168) and right colon carcinoma 3.607 times (95% CI: 2.056-6.330).

Table 1. Statistical analysis of the variables according to the site.

Variables according to the site	Wald statistics	p-value	Odds ratio	95% Confidence interval
Right Colon				
BMI>35kg/m^2	41.299	0.000	6.377	3.624-11.220
App(+)*	19.989	0.000	3.607	2.056-6.330
Male gender	8.429	0.004	2.153	1.283-3.612
Age>50 years	2.631	0.105	0.633	0.364-1.100
Left Colon				
BMI>35kg/m^2	47.947	0.000	4.916	3.132-7.716
Male gender	27.996	0.000	3.296	2.119-5.127
App(+)*	13.492	0.000	2.537	1.544-4.168
Age>50 years	0.002	0.967	0.990	0.613-1.598
Rectum				
BMI>35kg/m^2	16.803	0.000	3.906	2.036-7.493
App(+)*	12.135	0.000	3.232	1.670-6.254
Male gender	5.853	0.016	2.141	1.156-3.967
Age>50 years	3.488	0.062	2.092	0.964-4.538

**Being appendectomized*

4. Discussion

The probability of colorectal cancer developing during a life time is approximately 6%; the highest rates of colorectal carcinoma predominate in the more industrialized countries [5]. The development of colorectal malignancy involves interplay between genetic and environmental influences. The most easily identified risk factors include being 50 years of age or older, a personal or family history of colorectal cancer or adenoma, and a personal history of long-standing inflammatory bowel disease. Colorectal cancers that develop in individuals without hereditary links are referred to as "sporadic" and account for 75% of all such cancers. A potential genetic influence is identified in the remaining 25% of patients, including family history (15-20%), hereditary non-polyposis colon cancer (5%), and familial adenomatous polyposis (1%)[6].

There is no doubt that environmental factors play a critical role in the development of colorectal cancer. However, the association between dietary and lifestyle factors and development of colorectal neoplasms is extraordinarily complex. Obesity, smoking and red meat are probable, alcohol, processed or heavily cooked meat and iron are the possible factors which increase the risk of colorectal carcinomas [7]. Polycyclic aromatic hydrocarbons are the potential carcinogenetic substances which were advocated as a factor that increase the risk of colorectal neoplasms.

We hypothesized that appendix may particularly protect the colon from orally taken carcinogens. Thus, we only divided the patients into subgroups according to their BMI. Also, we did not have enough information about dietary status and daily physical activity of our patients. We know that they have nearly same socioeconomical parameters but we could not test it, because of limited records and patients' personal resistances to give the information.

BMI>35kg/m^2 was the most efficient risk factor for colorectal carcinoma in our cohort. The relation between colorectal cancer and obesity may occur via adiponectin. Adiponectin, an adipocyte-secreted hormone that plays an important role in diabetes and cardiovascular disease, may also be of importance in the development and progression of several malignancies. Circulating adiponectin concentrations, which are determined mainly by genetic factors, nutrition, and adiposity, are lower in patients with breast, endometrial, prostate, and colon cancer. It has thus been proposed that adiponectin may be a biological link between obesity (especially central obesity) and increased cancer risk. Adiponectin may influence cancer risk through its well-recognized effects on insulin resistance, but it is also plausible that adiponectin acts on tumor cells directly. Several cancer cell types express adiponectin receptors that may mediate the effects of adiponectin on cellular proliferation [8].

No relationship was found by Al-Saleh *et al.* between urinary cotinine as a marker of tobacco smoke and 1-hydroxypyrene as an indicator of an individual's internal dose of polycyclic aromatic hydrocarbons and DNA adducts [9]. In a logistic regression model, they found only adducts in cancerous tissue were associated

with the subsequent risk of colon cancer, with an odds ratio of 3.587 (95% confidence interval 0.833-15.448) after adjustment for age and the duration of living in the current region, but of a borderline significance (p=0.086)[9]. Montgomery suggested that smoking itself is a cofactor which increases the risk of being acute appendicitis, in the light of the unadjusted odds ratio which he found for appendicectomy associated with cigarette smoking is 2.34 (%95 CI 1.52-3.59)[10]. On the contrary, we found in our case control study that smoking might not only decrease the risk of acute appendicitis but that it might also be protecting against it [11]. But we still have limited information about how the cigarettes smoke exactly affecting the gut. Thus, this study is not including the active or passive smoking history of the patients. Also, we did not have full information about patients' history with the subject.

A detailed study of the morphological and histological changes in the appendix and the caecum of different mammals with varying dietary habits revealed a distinctly well-defined vermiform appendix in rabbit only. However, the apical part of caecum among the carnivorous animals like cat and dog showed a clear histological picture with heavy infiltration of lymphoid tissue in the mucous and sub-mucous coats as seen in rabbit or human being [3]. Based on a recently acquired understanding of immune-mediated biofilm formation by commensal bacteria in the mammalian gut, biofilm distribution in the large bowel, the association of lymphoid tissue with the appendix, the potential for biofilms to protect and support colonization by commensal bacteria, and on the architecture of the human bowel, Randal Bollinger *et al* proposed that the human appendix is well suited as a "safe house" for commensal bacteria, providing support for bacterial growth and potentially facilitating re-inoculation of the colon in the event that the contents of the intestinal tract are purged following exposure to a pathogen [12].

Also, M-cells have an important role in the immune response of the bowel. They are specialized cells found in the follicle-associated epithelium of intestinal Peyer's patches of gut-associated lymphoid tissue and in isolated lymphoid follicles, appendix and in mucosal-associated lymphoid tissue sites outside the gastrointestinal tract. In the gastrointestinal tract, M-cells play an important role in transport of antigen from the lumen of the small intestine to mucosal lymphoid tissues, where processing and initiation of immune responses occur. Thus, M-cells act as gateways to the mucosal immune system and this function has been exploited by many invading pathogens [13]. But, M-cells are not specifically localized at the appendix. Thus, appendectomy does not affect the M-cell function at bowel.

Fan and Zhang found in their large cohort that 7.07% of colorectal carcinoma group and 3.5% of control group were appendectomized ($p<0.05$)[14]. But they did not give a risk ratio. In our cohort, 36 (21.7%) of control group patients were appendectomized. Although, 169 (37.1%) of CRA patients were appendectomized ($p<0.05$). 53 (43.4%) of G1, 91 (34.1%) of G2 and 25 (37.9%) of G3 were appendectomized. There was a statistically significant difference between the control group and the other groups individually ($p<0.05$).

Experimental research on appendicectomized rats confirmed that the incidence of clinically induced tumors is no greater than that observed in control animals [15]. We think that experimental studies can not be a model of colonic carcinogenesis due to orally taken carcinogenetic substances. Thus, they can not show the effect of appendicectomy on colonic carcinogenesis properly.

5. Conclusion

As a summary, we still have limited information about the function of appendix. In the light of our findings, we can suggest that being appendectomized might increase the risk of colorectal adenocarcinoma in sporadic cases, but prospective studies are still needed.

References

[1] Cancer statistics 2004. In cancer facts and figures. Atlanta, American Cancer Society, 2004, p.11
[2] Ergul E. Heredity and familial tendency of acute appendicitis. Scand J Surg 2007; 96: 290–292
[3] Malla BK. A study on 'Vermiform Appendix'--a caecal appendage in common laboratory mammals. Kathmandu Univ Med J (KUMJ). 2003; 1:272-275
[4] Grobost O, Boutron MC, Arveux P, Bedenne L, Chatrenet P, Faivre J. Appendectomy, cholecystectomy, Cholelithiasis and colorectal cancer. A retrospective case control study at the Cote-d'Or. Gastroenterol Clin Biol 1991; 15: 594-599
[5] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108
[6] Sandler RS. Epidemiology and risk factors for colorectal cancer. Gastroenterol Clin North Am 1996; 25: 717-735
[7] Fuchs CS. Dietary and lifestyle influences on

colorectal carcinogenesis. In Saltz LB (ed.): Colorectal Cancer: Multimodality Management. Totowa, NJ, Humana Pres, 2002, pp 47-64

[8] Barb D, Williams CJ, Neuwirth AK, Mantzoros CS. Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. Am J Clin Nutr 2007; 86: 858-866

[9] Al-Saleh I, Arif J, El-Doush I, Al-Sanea N, Jabbar AA, Billedo G, Shinwari N, Mashhour A, Mohamed G. Carcinogen DNA adducts and the risk of colon cancer: case-control study. Biomarkers. 2008;13: 201-216

[10] Montgomery SM. Smoking in adults and passive smoking in children are associated with acute appendicitis. Lancet 1999; 353:379

[11] Ergul E, Kusdemir A. Smoking and acute appendicitis. The Internet Journal of Surgery. 2008; 14(1)

[12] Randal Bollinger R, Barbas AS, Bush EL, Lin SS, Parker W. Biofilms in the large bowel suggest an apparent function of the human vermiform appendix. J Theor Biol. 2007; 249: 826-831

[13] Corr SC, Gahan CC, Hill C. M-cells: origin, morphology and role in mucosal immunity and microbial pathogenesis. FEMS Immunol Med Microbiol. 2008; 52: 2-12

[14] Fan YK, Zhang CC. Appendectomy and cancer- an epidemiological evaluation. Zhonghua Zhong Liu Za Zhi 1986; 8: 121-214

[15] Abeatici S, Raso AM, Locatelli L. Appendectomy and colo-rectal carcinoma. Clinico- statistical and experimental studies. Minerva Chir 1977; 32: 333-340