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Predictors of colonic pathologies in active acromegaly: single tertiary center experience

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Summary
Background Regarding the incidence of colorectal malignancy and polyps in patients with acromegaly, studies reported different results in different populations. For this reason, the aim of this study was to determine the frequency of possible colonic pathologies, such as diverticula, polyps, and malignancies in Turkish patients with active acromegaly and factors affecting them.
Methods A total of 134 patients with acromegaly and 134 patients with irritable bowel syndrome/dyspeptic symptoms as a control group were included in the study. None of these patients had a previous or family history of colonic neoplasms. Colonoscopies of patients with acromegaly were performed before definitive surgery in a single center by experienced endoscopists.
Results The acromegaly and control groups were similar in terms of age and sex. The incidence of all colonic polyps was significantly higher in the acromegaly group ($p=0.012$). The frequency of hyperplastic polyps was also increased in the acromegaly group ($p=0.004$); however, the frequencies of adenomatous polyps and colonic diverticula were similar in both groups. In the comparison of patients with acromegaly for the presence of polyps, those with polyps were older, had higher levels of insulin-like growth factor (IGF-1), were of male sex, and skin tags were more common ($p=0.016$, $p=0.034$, $p=0.006$ and $p=0.001$, respectively). There were no colorectal malignancies in the patients with active acromegaly.
Conclusion The frequency of hyperplastic polyps was increased, whereas colonic malignancy was not observed in Turkish patients with active acromegaly.

Keywords Insulin-like growth factor-1 · Colonic polyp · Colonic diverticula · Colorectal neoplasia · Colonoscopy

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Introduction

Acromegaly is a rare multisystemic disease caused by hypersecretion of growth hormone (GH), which causes multiple comorbidities [1]. There is increased mortality due to diabetes, hypertension, and cardiovascular, cerebrovascular, respiratory system diseases associated with acromegaly [2]; however, data about the increased malignancy rate and mortality in acromegaly are controversial [3–9]. An increased frequency of breast, prostate, thyroid, and colorectal malignancies has been reported in these patients [1, 2, 6, 9, 10]. Acromegaly also has well known side effects on the bones and joints [11]. Both GH and insulin-like growth factor-1 (IGF-1) are thought to play a major role in oncogenesis [12]. In particular, IGF-1 has mitogenic and antiapoptotic effects in colorectal epithelial cells. Thus, it has been shown to cause increased cellular proliferation and colorectal cancers [13, 14]. Colorectal polyps or adenomas are the most common benign tumors in acromegaly [15–20]. Furthermore, colonic diverticula are more frequent

in patients with acromegaly [21]. Increased GH and IGF-1 levels play a major role in the development of these colonic lesions, and also factors such as hyperglycemia, hyperinsulinemia, and social nutritional habits may also have an effect.

The frequency of colonic pathologies may differ according to ethnicity which is very important [15, 22–24]. The aim of this study was to determine the frequency of colonic polyps, diverticula, malignancies, and related factors in Turkish patients with active acromegaly.

Material and method

The study was a retrospective cross-sectional study. A total of 134 patients with acromegaly who had been diagnosed in the university hospital's pituitary outpatient clinic. Colonoscopies were performed in the laboratory for gastroenterological endoscopy. The diagnosis of acromegaly was made according to the presence of typical clinical signs, symptoms, pituitary magnetic resonance imaging findings, high IGF-1 levels and nonsuppressible GH levels with an oral glucose tolerance test in accordance with the current guideline [1]. The colonoscopies were performed prior to surgery or medical treatment of acromegaly during active disease. The control group consisted of 134 patients who had clinically diagnosed irritable bowel syndrome (IBS) according to the Rome IV criteria and during the follow-up had colonoscopy for differential diagnosis of continuing abdominal pain and diarrhea despite symptomatic treatment. The prevalence of polyps, diverticula and malignancies in the control group were recorded. Colonoscopies were performed in a single center by experienced endoscopists. Informed consent was obtained from all patients and the same protocol was used in the colon preparation of the patients (polyethylene glycol-electrolyte oral solution). During the procedure, the presence and localization of polyps were recorded and all possible polyps were removed or biopsied for histologic evaluation. Colonic polyps were evaluated by a single pathologist specialized in the gastrointestinal system. The presence of diverticula was also recorded. The levels of IGF-1 and GH, fasting plasma glucose (FPG) levels, hemoglobin A1C (HbA1c), insulin levels, homeostasis model assessment of insulin resistance (HOMA-IR), maximum pituitary tumor diameter and presence of skin tags in patients were compared according to the presence of polyps. The GH and IGF-1 levels were measured using a two-site chemiluminescent immunometric assay (IMMULITE 2000, Siemens Medical Solutions Diagnostics, Germany). The sensitivity of the assay was 0.01 ng/ml for GH levels. The IGF-1 (xULN- upper limit of normal) was defined as multiples of IGF-1 according to age-appropriate cut-off. Insulin and glucose levels were measured in fasting blood samples using a Roche Diagnostics Modular Autoanalyzer System (Roche Diagnostics, Mannheim, Germany). The HOMA-IR was calculated by using the following formula: (fasting insulin [μU/ml] × FPG [mmol/l]) / 22.5 [25] and HbA1c was analyzed using a turbidimetric inhibition immunoassay (Roche Diagnostics, Mannheim, Germany).

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 22.0 for Windows (IBM SPSS Statistics Data Editor) was used for the statistical analysis of data. Descriptive data are given as the number of participants and frequency. Categorical variables are expressed as the number of cases and percentage value. The comparison of categorical variables was performed using χ^2-testand Fisher's exact test. Continuous variables are given as mean and standard deviation. The Shapiro-Wilk test was used to determine whether the continuous variables were normally distributed. For continuous variables, Student's t-test and the Mann-Whitney-U test were used according to the situation of variables (normally distributed or not). A p-value of <0.05 was considered statistically significant.

Results

There were no differences between the groups in terms of sex and age distribution. The frequency of colonic polyps was significantly higher in the acromegaly group (38%) than in the control group (23%; odds ratio, OR = 2.04, 95% confidence interval, CI:1.2–3.47; $p = 0.012$). While hyperplastic polyp frequency was increased in the acromegaly group (OR = 3.04, 95% CI: 1.4–6.6), ($p = 0.004$), adenomatous polyp frequency was similar in both groups. Polyp localization was similar between the groups, and rectosigmoid colon was the most common region for both groups. In our study, acromegaly and control groups had the same frequency of colonic diverticula. Colorectal malignancy was not detected in either group. The comparison of acromegaly and control groups is given in detail in Table 1.

When both groups were divided according to age (cut-off age 50 years), all types of polyps and hyperplastic polyps were more common in the acromegaly group than in the controls aged less than 50 years ($p = 0.006$ and $p = 0.007$, respectively); however, this difference disappeared after age 50 years, and the frequency of polyp was similar in both groups (Table 2).

In the comparison of acromegalic patients with and without polyps, patients with polyps were older, most were male, skin tags were more common, and had higher levels of IGF-1 ($p = 0.016$, $p = 0.001$, $p = 0.006$, and $p = 0.034$, respectively). Other parameters were similar between the groups. Detailed results of the comparison of patients with acromegaly according to the presence of polyps are given in Table 3.

Table 1 Comparison of acromegaly and control groups according to baseline characteristics

	Acromegaly group ($n=134$)	Control group ($n=134$)	p-value
Age (years) Mean ± SD	47 ± 12	47 ± 11	NS
Gender (M%/F%)	49/51	51/49	NS
Colonic polyp (n; %)	51 (38)	31 (23)	*0.012*
Hyperplastic polyp (n; %)	26 (20)	10 (8)	*0.004*
Adenomatous polyp (n; %)	25 (19)	23 (17)	NS
Colonic polyp distribution (RC/TC/DC/RSC)	24%/14%/10%/52%	7%/19%/13%/61%	NS
Colonic diverticula (n; %)	12 (9)	12 (9)	NS

RC right colon, *TC* transverse colon, *DC* descending colon, *RSC* rectosigmoid colon, *NS* not significant
$p<0.05$ statistically significant, significant p-values are shown in italics

Table 2 Comparison of colonoscopic findings of patients grouped by age limit of 50 years

Colonoscopic findings	<50 years old			≥50 years old		
	Acromegaly n (%)	Control n (%)	p-value	Acromegaly n (%)	Control n (%)	p-value
Colonic polyp (all type)	28 (35)	12 (15)	*0.006*	23 (43)	19 (34)	NS
Hyperplastic polyp	16 (21)	4 (5)	*0.007*	10 (18)	6 (11)	NS
Adenomatous polyp	10 (13)	9 (12)	NS	15 (28)	14 (25)	NS
Colonic diverticula	4 (5)	4 (5)	NS	8 (14)	8 (15)	NS

NS not significant
$p<0.05$ statistically significant, significant p-values are shown in italics

Table 3 Comparison of acromegalic patients with and without polyps according to baseline characteristics

	Patients with polyp ($n=51$)	Patients without polyp ($n=83$)	p-value
Age (years) Mean ± SD	48 ± 12	42 ± 13	*0.016*
Gender (M; %)	69	37	*0.001*
GH (ng/ml) Mean ± SD	16 ± 13	21 ± 20	NS
IGF-1(xULN) Mean ± SD	3.3 ± 1.1	2.7 ± 1.1	*0.034*
FPG (mg/dl) Mean ± SD	114 ± 37	116 ± 43	NS
HOMA-IR Mean ± SD	4.1 ± 2.1	4.4 ± 3.3	NS
HbA1c (%) Mean ± SD	6.6 ± 1.6	6.6 ± 1.9	NS
Presence of skin tag (%)	57	29	*0.006*
Pituitary tumor size (mm) Mean ± SD	17 ± 9	17 ± 11	NS
Estimated duration of acromegaly (years) Mean ± SD	7.1 ± 4.6	6.2 ± 4.7	NS

FPG fasting plasma glucose, *GH* growth hormone, *IGF-1* insulin-like growth factor-1, *HOMA-IR* homeostasis model assessment for insulin resistance, *HbA1c* hemoglobin A1c, *ULN* upper limit of normal, *NS* not significant
$p<0.05$ statistically significant, significant p-values are shown in italics

Acromegalic patients with adenomatous polyps were older ($p=0.03$) and male sex was more prominent ($p=0.013$) than patients without adenomatous polyps; however, other basal metabolic parameters did not differ in patients with and without adenomatous polyps.

Discussion

In the present study, it was demonstrated that the frequency of colonic polyps in Turkish patients with active acromegaly was increased in comparison with controls. A study with a small number of patients from Turkey [26], and several other studies conducted in different ethnicities also showed increased frequency of colonic polyps in patients with acromegaly [16–21, 27]. On the contrary, a study from India reported

that there was no increase in the frequency of colonic polyps in acromegaly [28]. The main causes of this difference may be dependent on the age, geographic and ethnic origin of the patients. In the latter study with no increased frequency of colonic polyps, the mean age of patients with acromegaly was 37 years. In contrast, in other studies with significantly higher frequency of polyps, the mean age of the study populations was higher (over 45 years), similar to this study [16–21, 27]. In the literature it is well known that colonic polyps increase with age, independent of the presence of acromegaly [29].

In the general population, the most common type of colonic polyps is benign hyperplastic polyp [30]. In this study, it was also similarly found that the patients with active acromegaly had a higher frequency of hyperplastic polyps. There are several studies supporting these results in acromegaly patients [18–20, 27]. On the contrary, there are also studies demonstrating a higher incidence of adenomatous polyps in acromegaly [21, 22, 26, 31]. Benign hyperplastic polyps are characterized by elongated and branched crypts with epithelial hyperplasia and increased colonic mucosal proliferation in patients with acromegaly is responsible in the formation of hyperplastic polyps [13, 14, 32]. Adenomatous polyps are lesions that require more careful monitoring due to the potential for malignancy [33]. The frequency of adenomatous polyps in acromegaly was similar to the controls, therefore, the distribution of precancerous lesions did not show a difference.

Generally colonic polyps are known to localize in the rectosigmoid region, and this has been supported in a study conducted in the Turkish population [29, 34]. In our study, it was also observed that polyps were frequently localized in the rectosigmoid colon, and acromegaly had no effect on the localization of colonic polyps; however, in one study polyps were predominantly localized on the left colon in acromegalic patients [35].

Many factors such as age, sex, body mass index, duration of disease, increased GH/IGF-1 levels, FPG, and insulin resistance and pituitary tumor size have been found to be related with the presence of polyps in acromegalic patients [19, 21, 22, 27]. The results of this study showed that the risk of polyps is higher in older patients, male gender and higher IGF-1 levels. In these patients with active acromegaly, circulating IGF-1 levels and probably local IGF-1 expression from colorectal cells may induce proliferation in the colonic epithelium with autocrine and paracrine activity as previously reported [14, 36]. Dutta et al. also demonstrated the relationship of elevated serum IGF-1 levels and proliferation in superficial crypt cells [15].

In the general population, skin tags (achrochordon) are very common benign lesions which are also associated with acromegaly. An association between skin tags and colonic polyps in acromegaly is also known [28, 37, 38]. In accordance with these studies, we found that skin tags were more common in acromegalic patients with polyps; however, there are also studies indicating no relationship between them [9, 39].

Although the frequency of colonic diverticula was similar in both groups in the present study, another study reported that the frequency of colonic diverticula was increased in patients with acromegaly compared to a control group (37% vs. %19; [21]). In that study the prevalence of diverticula even in the control group was higher than our control group (9%). This difference may be related to the age of the patients and different nutritional habits because the most important factors related to colonic diverticula are reported as aging and low fiber-based nutrition [40]. Supporting that fact, the mean age of patients in the study of Wassenaar et al. at the time of colonoscopy was 10 years older than our patient group, and the cuisine in Turkey is based on a richer fiber diet (Mediterranean diet; [21]).

No colonic malignancies were detected in both groups. As such, it was shown that the colonic polyp frequency was increased in our patients with active acromegaly, but the risk of colonic malignancy was not. Previously a meta-analysis of nine studies reported an increased frequency of colorectal adenomatous and hyperplastic polyps, as well as an increased risk of colorectal cancer in these patients [24]; however, studies conducted after this meta-analysis showed that the risk of colonic malignancy was not increased in acromegaly compared with controls [6–8, 21]. These results are compatible with the results of the present study. In another study important factors that play a role in colonic neoplasms are reported as ethnicity, socioeconomic status and nutritional habits [41]. Furthermore, having a diet rich in fiber and calcium reduces the frequency of colorectal neoplasms [42, 43]. The diet of the Turkish population is mainly based on nutrition which is rich in fiber and probably has an important effect on the prevalence of colonic polyps and malignancy.

Screening for colonic neoplasms is recommended for the general population at the age of 50 years and over [44]. In our analysis with this age cut-off, it was shown that the frequency of colonic polyps in patients with acromegaly younger than 50 years was higher than in the controls; however, the difference between the two groups disappeared after the age of 50 years with the increase in colonic polyps in the normal population. Therefore, the age limit of 50 years that is recommended for the general population may be late for screening in patients with acromegaly. Therefore, it seems appropriate to perform colonoscopy scans in patients with acromegaly at the time of diagnosis independent of age, as suggested by the Endocrine Society guidelines [1].

In conclusion, although the frequency of colonic polyps was increased in patients with active acrome-

galy, colonic malignancy was not detected in this Turkish population.

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Compliance with ethical guidelines

Conflict of interest R. Iliaz , S.C. Dogansen, S. Tanrikulu, G.Y. Yalin, B. Cavus, M. Gulluoglu, F. Akyuz and S. Yarman declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local ethics committee (Ethics Committee of Istanbul Medical Faculty, 2017-377).

References

1. Endocrine Society, Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51. https://doi.org/10.1210/jc.2014-2700.
2. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev. 2004;25(1):102–52.
3. Boguszewski CL, Ayuk J. Management of endocrine disease:acromegaly and cancer: an old debate revisited. Eur J Endocrinol. 2016;175(4):R147–R56. https://doi.org/10.1530/EJE-16-0178.
4. Renehan AG, Brennan BM. Acromegaly, growth hormone and cancer risk. Best Pract Res Clin Endocrinol Metab. 2008;22(4):639–57. https://doi.org/10.1016/j.beem.2008.08.011.
5. Loeper S, Ezzat S. Acromegaly: re-thinking the cancer risk. Rev Endocr Metab Disord. 2008;9(1):41–58.
6. Wolinski K, Stangierski A, Dyrda K, et al. Risk of malignant neoplasms in acromegaly: a case-control study. J Endocrinol Invest. 2017;40(3):319–22. https://doi.org/10.1007/s40618-016-0565-y.
7. Kauppinen-Mäkelin R, Sane T, Välimäki MJ, et al. Increased cancer incidence in acromegaly – a nationwide survey. Clin Endocrinol (Oxf). 2010;72(2):278–9. https://doi.org/10.1111/j.1365-2265.2009.03619.x.
8. Petroff D, Tönjes A, Grussendorf M, et al. The incidence of cancer among acromegaly patients: results from the German acromegaly registry. J Clin Endocrinol Metab. 2015;100(10):3894–902. https://doi.org/10.1210/jc.2015-2372.
9. Terzolo M, Reimondo G, Berchialla P, et al. Acromegalyis associated with increased cancer risk: a survey in Italy. Endocr Relat Cancer. 2017;24(9):495–504. https://doi.org/10.1530/ERC-16-0553.
10. Wright AD, Hill DM, Lowy C, Fraser TR. Mortality in acromegaly. Q J Med. 1970;34:1–16.
11. Claessen KM, Mazziotti G, Biermasz NR, Giustina A. Bone and joint disorders in acromegaly. Neuroendocrinology. 2016;103(1):86–95. https://doi.org/10.1159/000375450.
12. Cohen P, Clemmons DR, Rosenfeld RG. Does the GH–IGF axis play a role in cancer pathogenesis? Growth Horm Igf Res. 2000;10(6):297–305.
13. Lahm H, Amstad P, Wyniger J, et al. Blockade of the insulin-like growth-factor-I receptor inhibits growth of human colorectal cancer cells: evidence of a functional IGF-II-mediated autocrine loop. Int J Cancer. 1994;58(3):452–9.
14. Cats A, Dullaart RP, Kleibeuker JH, et al. Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res. 1996;56(3):523–6.
15. Dutta P, Bhansali A, Vaiphei K, et al. Colonic neoplasia in acromegaly: increased proliferation or deceased apoptosis? Pituitary. 2012;15(2):166–73. https://doi.org/10.1007/s11102-011-0300-9.
16. Krzentowska A, Gołkowski F, Bałdys-Waligo'rska A, Hubalewska-Dydejczyk A. Gastrointestinal tract polyps in acromegaly patients. Prz Lek. 2010;67:1266–9.
17. Tirosh A, Shimon I. Complications of acromegaly: thyroid and colon. Pituitary. 2017;20(1):70–5. https://doi.org/10.1007/s11102-016-0744-z.
18. Bogazzi F, Cosci C, Sardella C, et al. Identification of acromegalic patients at risk of developing colonic adenomas. J Clin Endocrinol Metab. 2006;91:1351–6.
19. Gonzalez B, Vargas G, Mendoza V, Nava M, Rojas M, Mercado M. The prevalence of colonıc polyps in patients withacromegaly: a case-control, nested in a cohort colonoscopıc study. Endocr Pract. 2017;23(5):594–9.
20. Martino A, Cammarota G, Cianci R, Bianchi A, Sacco E, Tilaro L, et al. High prevalence of hyperplastic colonic polyps in acromegalic subjects. Dig Dis Sci. 2004;49(4):662–6.
21. Wassenaar MJ, Cazemier M, Biermasz NR, et al. Acromegaly is associated with an increased prevalence of colonic diverticula: a case-control study. J Clin Endocrinol Metab. 2010;95(5):2073–9.
22. Colao A, Pivonello R, Auriemma RS, et al. The association of fasting insulin concentrations and colonic neoplasms in acromegaly: a colonoscopy-based study in 210 patients. J Clin Endocrinol Metab. 2007;92(10):3854–60.
23. Heine-Bröring RC, Winkels RM, Renkema JM, et al. Dietary supplement use and colorectal cancer risk: a systematic review and meta-analyses of prospective cohort studies. Int J Cancer. 2015;136(10):2388–401.
24. Rokkas T, Pistiolas D, Sechopoulos P, Margantinis G, Koukoulis G. Risk of colorectal neoplasm in patients with acromegaly: a metaanalysis. World J Gastroenterol. 2008;14:3484–9.
25. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care. 2003;26(12):3320–5.
26. Koksal AR, Ergun M, Boga S, et al. Increased prevalence of colorectal polyp in acromegaly patients: a case-control study. Diagn Ther Endosc. 2014;2014:1–4. https://doi.org/10.1155/2014/152049.
27. Yamamoto M, Fukuoka H, Iguchi G, et al. The prevalence and associated factors of colorectal neoplasms in acromegaly: a single center based study. Pituitary. 2015;18(3):343–51.
28. Bhansali A, Kochhar R, Chawla YK, Reddy S, Dash RJ. Prevalence of colonic polyps is not increased in patients with acromegaly: analysis of 60 patients from India. J Gastroenterol Hepatol. 2004;19(3):266–9.
29. Øines M, Helsingen LM, Bretthauer M, Emilsson L. Epidemiology and risk factors of colorectal polyps. Best Pract Res Clin Gastroenterol. 2017;31(4):419–24.
30. Haumaier F, Sterlacci W, Vieth M. Histological and molecular classification of gastrointestinal polyps. Best Pract Res Clin Gastroenterol. 2017;31(4):369–79.
31. Delhougne B, Deneux C, Abs R, et al. The prevalence of colonic polyps in acromegaly: a colonoscopic and

pathological study in 103 patients. J Clin Endocrinol Metab. 1995;80(11):3223–6.
32. Williams GT. Metaplastic (hyperplastic) polyps of the large bowel: benign neoplasms after all? Gut. 1997;40(5):691–2.
33. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopicpolypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329(27):1977–81.
34. Eminler AT, Sakalli M, Irak K, et al. Colonoscopic polypectomy results of our gastroenterology unit. J Acad Gastroenterol. 2011;10(3):112–5.
35. Jenkins PJ, Fairclough PD, Richards T, et al. Acromegaly, colonic polyps and carcinoma. Clin Endocrinol (Oxf). 1997;47(1):17–22.
36. Simmons JG, Pucilowska JB, Lund PK. Autocrine and paracrine actions of intestinal fibroblast-derived insulin-like growth factors. Am J Physiol. 1999;276:G817–G27.
37. Leavitt J, Klein I, Kendriks F, Gavaler J, Van Thiel DH. Skin tags: a cutaneous marker for colonic polyps. Ann Intern Med. 1983;98(6):928–30.
38. Beitler M, Eng A, Kilgour M, Lebwohl M. Association between acrochordons and colonic polyps. J Am Acad Dermatol. 1986;14(6):1042–4.
39. Agarwal P, Rai P, Jain M, Mishra S, Singh U, Gupta SK. Prevalence of colonic polyp and its predictors in patients with acromegaly. Indian J Endocrinol Metab. 2016;20(4):437–42.
40. Szojda MM, Cuesta MA, Mulder CM, Felt-Bersma RJ. Review article: management of diverticulitis. Aliment Pharmacol Ther. 2007;26(Suppl 2):67–76. https://doi.org/10.1111/j.1365-2036.2007.03491.x.
41. Sonnenberg A, Turner K, Genta RM. Ethnic variations in the occurrence of colonic neoplasms. United European Gastroenterol J. 2017;5(3):424–31.
42. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N Engl J Med. 1999;340(2):101–7.
43. Kunzmann AT, Coleman HG, Huang WY, Kitahara CM, Cantwell MM, Berndt SI. Dietary fiber intake and risk of colorectal cancer and incident and recurrent adenoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Clin Nutr. 2015;102(4):881–90.
44. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM, American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009. Am J Gastroenterol. 2009;104(3):739–50. https://doi.org/10.1038/ajg.2009.104.