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***Retrospective Cohort Study***

**Adenoma and advanced neoplasia detection rates increase from 45 years of age**

Karsenti D *et al*.ADR and NDR according to age

David Karsenti, Gaelle Tharsis, Pascal Burtin, Franck Venezia, Gilles Tordjman, Agnès Gillet, Joelle Samama, Karine Nahon-Uzan, Philippe Cattan, Maryan Cavicchi

**David Karsenti, Gaelle Tharsis, Franck Venezia, Gilles Tordjman, Agnès Gillet, Joelle Samama, Karine Nahon-Uzan, Philippe Cattan, Maryan Cavicchi,** Digestive Endoscopy Unit, Clinique Paris-Bercy, Charenton-le-Pont 94220, France

**Pascal Burtin,** Digestive Endoscopy Unit, Institut Gustave Roussy, Villejuif 94800, France

**ORCID number:** David Karsenti (0000-0003-1487-2814); Gaelle Tharsis (0000-0002-6381-1359); Pascal Burtin (0000-0001-9241-2130); Franck Venezia (0000-0003-0732-8028); Gilles Tordjman (0000-0001-6343-4867); Agnès Gillet (0000-0003-4298-4573); Joelle Samama (0000-0002-0562-5830); Karine Nahon-Uzan (0000-0001-7195-2947); Philippe Cattan (0000-0002-9205-5337); Maryan Cavicchi (0000-0002-4062-4868).

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**Corresponding author: David Karsenti, MD, Doctor,** Digestive Endoscopy Unit, Clinique Paris-Bercy, 9 Quai de Bercy, Charenton-le-Pont 94220, France. karsenti@club-internet.fr

**Telephone:** +33-143967850

**Fax:** +33-143967851

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**Abstract**

***BACKGROUND***

Colonoscopy is considered a valid primary screening tool for colorectal cancer (CRC). The decreasing risk of CRC which is observed in patients undergoing a colonoscopy is correlated to the adenoma detection rate (ADR). Due to the fact that screening programs usually start from the age of 50, very few data are available on the risk of adenoma between 40 and 49yoa. However, CRC incidence is increasing in young populations and it is not uncommon in routine practice to detect adenomas or even advanced neoplasias during colonoscopy in patients under 50yoa.

***AIM***

To compare ADR and advanced neoplasia detection rate (ANDR) according to age in a large series of patients in routine colonoscopy.

***METHODS***

All consecutive patients who were scheduled for colonoscopy were included. Exclusion criteria were: Patients scheduled for partial colonoscopy or interventional colonoscopy (for stent insertion or stenosis dilation). Colonoscopies were performed in our unit by a team of 30 gastroenterologists in 2016. We determined ADR and ANDR in each age group in the whole population and in the population with average risk of CRC (excluding patients with personal or family history of advanced adenoma or cancer).

***RESULTS***

6027 colonoscopies were performed in patients with a median age of 57 (range, 15-96). ADR and ANDR were 28.6% and 9.7%, respectively, in the whole population. When comparing patients in the 40-44yoa (*n* = 382) and 45-49yoa intervals (*n* = 515), we observed a strong increase in all parameters from 45yoa, with ADR rising from 9.7% in 40-44yoa to 21.2% between 45 and 49 (*P* < 0.001) and ANDR increasing from 3.1% in 40-44yoa to 6.4% between 45 and 49 (*P* < 0.03). As regards patients in the 50-54yoa interval (*n* = 849), we did not observe a statistically significant increase in ADR and ANDR between 45-49yoa and 50-54yoa. In the population with average risk of CRC, ADR and ANDR were still significantly higher in patients aged between 45 and 49 compared to patients aged between 40 and 44.

***CONCLUSIONS***

This study shows a significant two-fold increase in ADR and ANDR from 45yoa.

**Key words:** Colorectal cancer; Screening; Adenoma detection rate; Colonoscopy; Cohort study

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**Core tip:** Despite the fact that the incidence of colorectal cancer (CRC) before 50yoa seems to have increased in the last decade, we have very few data on adenoma and advanced neoplasia before 50yoa. This is the first large study to evaluate adenoma detection rate (ADR) and advanced neoplasia detection rate (ANDR) in patients under 50yoa in routine colonoscopy in average-risk and high-risk patients for CRC. This study shows a significant two-fold increase in ADR and ANDR from 45yoa, whether or not there was a personal or family history of polyp or cancer. Such high rates from 45yoa could be taken into account for CRC screening campaigns.

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**INTRODUCTION**

Colorectal cancer (CRC) is one of the most frequently occurring cancers worldwide, and the second most common cause of cancer-related deaths[1,2]. It is now well established that screening programs can reduce CRC mortality through detection of both precancerous lesions and early-stage cancer[3-8]. Different modalities are available, ranging from stool-based tests (guaiac test, immunochemical test or DNA assays) to endoscopy with varying sensitivity and specificity[9,10]. The choice of method usually depends on each national screening program policy. Whatever the method used, most scientific organizations recommend beginning screening at 50yoa in average-risk populations[11]. Colonoscopy is considered a valid primary screening tool for CRC when performed every 10 years, usually from 50yoa[11,12]. Optimizing the quality of screening colonoscopy is necessary to improve CRC prevention[13]. One of the best indicators of the quality of colonoscopy is the adenoma detection rate (ADR) which is correlated to the polyp detection rate and the mean number of adenoma per colonoscopy[14-16].

It may be worth discussing the age at which screening is begun. It is not uncommon in routine practice to detect adenomas or advanced neoplasias during colonoscopy in patients under 50yoa. Moreover, CRC incidence is increasing in young populations (particularly in the United States)[17], and non-negligible rates of colonic adenomas and advanced neoplasias have already been reported in patients aged 40 to 49 with a family history of cancer, at 13.3% and 3.4%, respectively[18]. However, due to the fact that screening programs frequently start from the age of 50, few recent data on the risk of adenoma in the 40-44yoa and 45-49yoa intervals are available. The only way to estimate the incidence of adenomas is to look at the risk in a population referred for colonoscopy for indications other than screening. The aim of the current study was to determine, in routine practice, adenoma and advanced neoplasia detection rates (ANDR) according to age in a large population of consecutive patients admitted for colonoscopy in our digestive endoscopy unit over a period of one year.

**MATERIALS AND METHODS**

This observational monocentric study was conducted in our unit from January 1, 2016 to December 31, 2016, by a team of 30 gastroenterologists. All patients were informed in writing of the use of their endoscopic procedure data for clinical research purposes and none expressed opposition. The data were retrospectively collected by extraction from our medical patient management software. Therefore, this retrospective study does not require approval from an ethics committee, in accordance with French ethics law. All authors declare that they have access to the study data and have reviewed and approved the final manuscript.

***Patients***

All consecutive patients who were scheduled for colonoscopy were included. Exclusion criteria were: patients scheduled for partial colonoscopy or interventional colonoscopy (for stent insertion, stenosis dilation or haemostasis).

***Data collection***

The following data were collected on dedicated software: Age, gender, indication for colonoscopy, preparation procedure and quality of preparation [assessed by the Boston Bowel Preparation Scale (BBPS)][19,20], caecal intubation, withdrawal time, number and size of polyps (< 1 cm or ≥ 1 cm) and polyp histopathology. Personal history of adenoma/cancer was defined as: Patient in whom a previous colonoscopy had found at least one adenoma or who was previously diagnosed with CRC. Family history of adenoma or cancer was defined as: patient with at least one first-degree relative diagnosed with CRC, patient with at least two second- degree relatives diagnosed with CRC or patient with at least one first-degree relative with adenoma whatever the age of the relative. Patients with personal or family history of adenoma or cancer were considered as high-risk patients for CRC while patients with other indications were considered as average-risk patients for CRC. We determined ADR (percentage of colonoscopies with at least one adenoma) and ANDR (percentage of colonoscopies with at least one advanced neoplastic lesion as defined below).

***Colonoscopy considerations***

The videocolonoscopes used were EVIS EXERA III CF-H190 (Olympus Co.) and more rarely EC-690 WM, and EC-600WM (Fujifilm Co.). Good preparation was defined as a BBPS score ≥ 6 with no sub-score < 2[14]. Withdrawal time was determined from the caecum to the anal verge, expressed in seconds and calculated on colonoscopies with no polyp.

***Histopathological considerations***

Adenomas were defined as tubular or tubulo-villous adenoma. Serrated polyps (SP) were defined as hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas. Hyperplastic polyps of the rectum and sigmoid colon were excluded, as they are not considered as at risk for CRC[21]. Advanced neoplasia was defined as grade 4 or grade 5 of the Vienna classification (grade 4 corresponding to a non-invasive high-grade neoplasia, *i.e*., high-grade adenoma/dysplasia, non-invasive carcinoma and suspicion of invasive carcinoma; grade 5 corresponding to an invasive neoplasia, *i.e*., intramucosal carcinoma, submucosal carcinoma or beyond) or polyp of 1 cm or more[22].

***Statistical analysis***

ADR and ANDR were analyzed in each age group in the whole population and also in the population with average risk of CRC (excluding patients with personal or family history of advanced adenoma or cancer). The NCSS v 10.0 was used to perform the statistical analysis. Quantitative variables were expressed as mean (SD) or as median and interquartile range (IQR). Qualitative variables were expressed as numbers and percentages. Continuous variables were compared using a Student’s *t* test or Wilcoxon–Mann–Whitney *U* test, as required. Categorical variables were compared using the chi-squared test or Fisher’s exact test, as required. Logistic regression analysis used a forward hierarchical stepwise method with switching to select independent variables related to ADR. All significant variables in the univariate analysis were included in the model and were retained at each step if *P* > 0.05. Odds ratios (OR) and 95% confidence intervals (CI) were given.

**RESULTS**

During the study period, 6335 colonoscopy procedures were performed. We excluded 278 sigmoidoscopies and 30 interventional procedures (Figure 1), leaving 6027 colonoscopies in 3308 women (54.9%) and 2719 men (45.1%) with a median age of 57 (range, 15-96: IQR 18). The indication for colonoscopy was a personal history of adenoma or cancer in 1512 patients, family history of adenoma or advanced adenoma or cancer in 2534, a positive fecal immunochemical test in 391, digestive symptoms or hematochezia in 2306, screening colonoscopy in 320 and other causes in 476 (mainly inflammatory bowel disease in remission follow-up, suspected colonic lesions after computed tomography scan and post-diverticulitis colonoscopy). Sub-optimal preparation was noted in 6.2% of the patients. Caecal intubation was obtained in 99%. Median withdrawal time was 470 seconds (range 55-3840; IQR 240).

***Results in the whole population***

Of the 6027 colonoscopies, 2054 detected 3914 lesions or polyps with adenomas in 2914 (74.5%), SP in 788 (20.1%) and other polyps in 212 (5.4%). ADR was 28.6% in this series. We found 690 advanced neoplasias in 584 patients leading to an ANDR of 9.7%. serrated lesion detection rare (SDR) was 9.2%. In the multivariate analysis (Table 1), the variables associated with a higher ADR were: A personal history of polyp or cancer (OR 1.5), a positive faecal immunochemical test (OR 2.7), male gender (OR 1.7) and the age of the patient (≥ 45yoa: OR 1.3). Colonoscopy for symptoms was associated with a lower risk of adenoma (OR 0.7).

***Results according to age intervals***

We looked at ADR and ANDR according to age with age intervals of 5 yr. The results are presented in Figure 2. ADR and ANDR markedly increased from 9.7% and 3.1% to 21.2 % (*P* < 0.001) and 6.4% (*P* < 0.03), respectively, between the 40-44yoa interval and the 45-49yoa interval (Figure 2). SDR also increased from 6% to 11.7 % (*P* < 0.005) between the 40-44yoa interval and the 45-49yoa interval. When considering only asymptomatic patients (*n* = 3267), ADR and ANDR also increased between the 40-44yoa interval and the 45-49yoa interval from 7.5% to 25.4% (*P* < 0.001) and 3.4% to 6% (*P* = 0.3), respectively.

A comparison of patients, colonoscopy data and detection rates between the 45-49yoa interval and after 50yoa is provided in Table 2. Regarding patients’ characteristics, the two groups were comparable, except for personal or family history of CRC or polyps and for a higher proportion of patients after 50yoa having no symptoms. Considering all patients above 50yoa (*n* = 4436), ADR and ANDR were significantly higher than in the 45-49yoa interval with 34.6% *vs* 21.2% (*P* < 0.001) and 11.8% *vs* 6.4% (*P* < 0.001), respectively. In contrast, SDR was not significantly different after 50yoa than in the 45-49yoa interval, with 10.1% *vs* 11.7 % (*P* = 0.32), respectively.

From the 584 patients diagnosed with an advanced adenoma during the study period, 71 underwent complementary treatment as surgery, chemotherapy, radiotherapy or combination. That shows that endoscopic resection was curative in 513 (88%) patients. Considering only patients under 50yoa, 10 out of 61 with advanced adenoma received additional treatment, giving a curative endoscopic resection rate of 51/61 (84%) (*P* = 0.7 compared to the whole population).

***Results in patients with average risk for CRC***

To rule out the possibility that our results were driven by patients at high risk for CRC, we looked at the results excluding patients with personal or family history of polyps or cancer. In this average-risk population, we also observed a significant increase in both ADR and ANDR between 40-44yoa and 45-49yoa, from 11% to 19% (*P* < 0.01) and 2.7 % to 6.4% (*P* < 0.05), respectively. The extent of the increase was therefore similar to that observed in the whole population (Figure 3).

**DISCUSSION**

This study demonstrated that adenoma and advanced neoplasia (*i.e*., polyp above 1 cm in size or adenoma with at least high-grade dysplasia) detection rates start to increase from 45yoa, with a two-fold increase compared to the 40-44yoa interval. These data were confirmed whether or not there was a personal or family history of polyp or cancer. Moreover, we did not observe any significant difference in ADR and ANDR between the 45-49yoa interval and the 50-54yoa interval in the whole population. Of note, the increase in the detection rates from 45yoa also concerned SP.

This is one of the first large studies to evaluate adenoma and ANDR in patients under 50yoa in routine colonoscopy in average-risk and high-risk patients for CRC. To our knowledge, work by Regula *et al*[18] is the only published study evaluating CRC screening in a young population from 40 to 66yoa. This very large Polish colonoscopy-based screening program on more than 50000 participants included patients from 40 to 49yoa, but only in cases of a family history of cancer of any type. These young patients constituted only 14.2% of the participants (*vs* 26.4% in our study). In the Polish study, ANDR and ADR were 3.4% and 8.5%, respectively. ANDR and ADR in our patients aged 45 to 49 were much higher at 9.7% and 21.2%, respectively. This discrepancy could be explained by the sharp rise in ADR between 40-44yoa and 45-49yoa and to a lesser degree by the high rate of completed colonoscopy (1% in our series *vs* 9% in the Polish study). However, the same difference can be observed after 50yoa, with ADR of 13.1% in the Regula study versus 34.6% in our patients, the latter being much closer to other published data[14].

A reduction in ADR and ANDR may have been expected by excluding patients with personal or family history of polyp or CRC as previously described[2,18], but this was not the case. As familial syndromes account for no more than 20% of young-onset CRC[23], the high rates of detection in our series could have minimized the difference between high-risk and average-risk patients. This study raises questions about screening in patients under 50yoa. Most scientific organizations such as the French Society of Digestive Endoscopy or the American College of Gastroenterology agree that colonoscopy or other methods of CRC screening programs for average-risk patients must enroll patients from 50 to 75yoa[3,5,15], but little is known about ADR and ANDR outside this range. Notably, the incidence of CRC before 50yoa seems to have increased in the last decade[2,17,23]. In two recent studies on approximately 600 patients each, young patients were diagnosed with significantly more advanced CRC in comparison to older patients[24,25]. Earlier screening might therefore improve disease stage on presentation and prognosis of CRC. Indeed, the United States multi-society task force on CRC recently recommended providing screening to African Americans as early as 45yoa[26], thus confirming the validity of rethinking the “50-year-old barrier”.

If adenomas are detected as early as 45yoa, they could be resected at 50yoa. While this assertion may be acceptable for small and low-grade dysplastic adenomas, it is highly questionable for advanced ones. However, the medical benefit of performing colonoscopy as early as 45yoa has to be balanced by the medico-economic feasibility of such a screening policy. Nevertheless, whatever the screening method, the high ANDR that we observed in young patients has to be taken into account in order to improve prevention of CRC and disease stage on presentation and prognosis.

Our study had some limitations. First, while this study has the advantage of describing “real-life” conditions, socio-economic level and environmental exposure as well as the way-of-life of a population of a major European capital could represent some biases compared to national screening campaigns which are more representative of the population of the entire country. Moreover, as 38% of our patients underwent colonoscopy because of symptoms, our population cannot be considered as a screening population. However, such symptoms are not known to increase the risk of polyps and were not correlated with a high ADR in the multivariate analysis in our series (OR 0.7). A personal or family history of polyp or CRC (defined as high-risk patients) may also bias the results. For this reason, we have detailed the results obtained for high-risk and average-risk patients. Yet, ADR and ANDR significantly increased in both populations (Figure 3). The number of patients in our study who underwent colonoscopy for screening was only 320 (approximately 5% of our population). Most of those patients were older than 50, as colonoscopy screening is not recommended for younger patients in France. The size of the screening population is too small to perform a reliable analysis. The conclusions of our study, as obtained on routinely explored patients, should therefore be transposed to screening with caution. In addition, it is well known that age is not the only risk factor for developing adenomas. It could therefore be speculated that other confounding factors could be associated with our ADR and ANDR. We acknowledge that we looked at neither ethnicity (which is not allowed in France) nor smoking or obesity, which are other known risk factors for CRC[27-30]. Nevertheless, we showed that age was an independent factor associated with a high ADR in the multivariate analysis (OR 1.3). Lastly, the colonoscopy quality criteria obtained in a single team such as ours with a long-standing awareness policy (sub-optimal preparation in only 6.2%, median withdrawal time of 490 s, caecal intubation rate of 99%) undoubtedly had a positive impact on detection rates and may thus moderate the reproducibility of these results.

To summarize, in this large monocentric cohort of consecutive colonoscopies, we found a two-fold increase in adenoma and ANDR from 45yoa, whether or not there was a personal or family history of polyp or CRC.

**ARTICLE HIGHLIGHTS**

***Research background***

Colonoscopy is considered a valid primary screening tool for colorectal cancer (CRC). The decreasing risk of CRC which is observed in patients undergoing a colonoscopy is correlated to the adenoma detection rate (ADR). Due to the fact that screening programs usually start from the age of 50, very few data are available on the risk of adenoma between 40 and 49yoa. However, CRC incidence is increasing in young populations and it is not uncommon in routine practice to detect adenomas or even advanced neoplasias during colonoscopy in patients under 50yoa.

***Research motivation***

It is well known that early detection of adenomas reduces the incidence of CRC and allows the diagnosis and treatment of cancer at earlier stages. As CRC is increasing in young populations, it is important to know at which age occurs the increase in the incidence of colonic adenomas and advanced colonic adenomas.

***Research objectives***

The purpose of this study is to compare ADR and advanced neoplasia detection rate (ANDR) according to age in a large series of patients in routine colonoscopy.

***Research methods***

All consecutive patients who were scheduled for colonoscopy were included in this observational monocentric study conducted in our unit by a team of 30 gastroenterologists.

***Research results***

6027 colonoscopies were performed in patients with a median age of 57 (range, 15-96). ADR and ANDR were 28.6% and 9.7%, respectively, in the whole population. When comparing patients in the 40-44yoa (*n* = 382) and 45-49yoa intervals (*n* = 515), we observed a strong increase in all parameters from 45yoa, with ADR rising from 9.7% in 40-44yoa to 21.2% between 45 and 49 (*P* < 0.001) and ANDR increasing from 3.1% in 40-44yoa to 6.4% between 45 and 49 (*P* < 0.03). In contrast, we did not observe a statistically significant increase in ADR and ANDR between 45-49yoa and 50-54yoa. When focusing on the population at average risk for CRC, ADR and ANDR were still significantly higher in patients aged 45 to 49 compared to patients aged 40 to 44.

***Research conclusions***

This study shows a significant two-fold increase in ADR and ANDR from 45yoa, whether or not there was a personal or family history of polyp or CRC.

***Research perspectives***

This study raises questions about screening in patients under 50yoa. The medical benefit of performing colonoscopy as early as 45yoa has to be balanced by the medico-economic feasibility of such a screening policy. Nevertheless, whatever the screening method, the high ANDR that we observed in young patients has to be taken into account in order to improve prevention of CRC, disease stage on presentation and prognosis.

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 **6,335 colorectal endoscopic procedures**

**308 exclusions**:

- 278 recto-sigmoïdoscopies

- 30 interventional procedures

 **6,027**

 **colonoscopies**

 **<45yoa**

 (n=1,076)

 **45-49yoa**

 (n=515)

 **≥50yoa**

 (n=4,436)

**High risk of CRC\***

**(n=248)**

**Average risk**

 **of CRC**

 **(n=828)**

**High risk of CRC\***

**(n=2082)**

**Average risk**

 **of CRC**

 **(n=2,354)**

**High risk of CRC1**

**(n=204)**

**Average risk**

 **of CRC**

 **(n=311)**

**Figure 1 Register flow chart.** Patients admitted, exclusions and breakdown of patients with high risk and average risk of colorectal cancer. 1Personal or family history of colonic polyp or colorectal cancer.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Age,** y (n)  | < 30 (252)  | 30-34 (182)  | 35-39 (260)  | 40-44 (382)  | 45-49 (515)  | 50-54 (849)  | 55-59 (856)  | 60-64 (828)  | 65-69 (775)  | 70-74 (537)  | 75-79 (339)  | > 79 (252)  |

**Figure 2 Adenoma and advanced neoplasia detection rates according to age.**

*Whole population*

*Average risk for CRC*

*ns*

*P*<0.001

*ns*

*P*<0.01

*P*=0.01

*P*<0.05

*P*<0.03

*P*<0.05

**Figure 3 Adenoma and advanced neoplasia detection rates in the 40-44yoa, 45-49yoa and 50-54yoa intervals, in the whole population and the average-risk for colorectal cancer population.**

*ns*

**Table 1 Multivariate analysis for adenoma detection rate in the whole population (*n* = 6027)**

|  |  |  |
| --- | --- | --- |
|  | **Univariate analysis** | **Multivariate analysis** |
| **Variable** | **Odds ratio** | ***P*** | **Odds ratio** | **95% CI** | ***P* value** |
| **Male gender** | 1.8 | 10-5 | 1.7 | 1.5–1.9 | 10-5 |
| **Age > 45** | 1.5 | 10-5 | 1.3 | 1.1–1.6 | 0.0005 |
| **Good prep** | 1.3 | 0.02 |  |  |  |
| **Screening** | REF |  | REF |  |  |
| **Family history** | 0.60 | 0.0006 | 0.65 | 0.5–0.0 | 0.004 |
| **Personal history** | 1.5 | 0.001 | 1.53 | 1.2–2.0 | 0.002 |
| **FIT +** | 2.7 | 10-5 | 2.7 | 1.9–3.6 | 10-5 |
| **Digestive symptoms** | 0.6 | 0.0005 | 0.7 | 0.5–0.9 | 0.02 |
| **Other indications** | 0.36 | 10-5 | 0.4 | 0.3–0.5 | 10-5 |

FIT: Fecal immunochemical test.

**Table 2 Comparison of patients’ characteristics, colonoscopy data and detection rates in the 45-49yoa interval and after 50yoa *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **45-49yoa****(*n* = 515)** | **≥ 50yoa****(*n* = 4436)** | ***P* value** |
| **Gender**, male/female, n | 236/279 | 2028/2408 | 0.98 |
| **Indications for colonoscopy** |  |  |  |
| Patients without symptoms | 268 (52) | 3,006 (68) | < 0.001 |
| High riskPersonal or family history of polyp | 204 (39.6) | 2082 (46.9) | 0.002 |
| Average riskDigestive symptoms Other | 311 (60.4)247 (48)64 (12.4) | 2354 (53)1430 (32.2)924 (20.8) | 1.48 |
| **Colonoscopy data** |  |  |  |
| Sub-optimal preparation | 30 (5.8) | 275 (6.2) | 0.84 |
| Mean number of polyps | 0.47  | 0.78  | - |
| Median withdrawal time, sec | 452 | 471 | 0.49 |
| **Histological data** |  |  |  |
| Polyp detection rate, % | 29.1 | 40 | < 0.001 |
| Adenoma detection rate, %  | 21.2 | 34.6 | < 0.001 |
|  Serrated polyp detection rate, % | 11.7 | 10.1 | 0.32 |
| Advanced neoplasia detection rate, % | 6.4 | 11.8 | < 0.001 |