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Clinical and phenotypic variants of hereditary and sporadic colorectal cancer in young patients

Relevance: *In the Republic of Kazakhstan, colorectal cancer (CRC) ranks third in the structure of oncological pathology. In 2008-2019, the CRC incidence in the Republic was growing each year. There is an upward trend in CRC incidence among young people. Cohort studies show that, in young patients, CRC is characterized by distal localization of the tumor process, advanced stages of the disease, an aggressive course, and low tumor differentiation. The known association of phenotypic signs with clinical characteristics of the disease, such as the response to therapy and survival rates, urges addressing this problem. The phenotypic and molecular genetic aspects of CRC in young people have not been systematically studied in Kazakhstan.*

The purpose of the study *was to compare the phenotypic features of hereditary and sporadic colorectal cancer in young patients and patients over 65 years.*

Results: *The study involved 185 patients aged 17 to 50 years (Group 1) and 112 patients aged 65 to 85 (Group 2). In Group 1, a locally advanced process (stage III) was 14.8% more often than in Group 2; stage IV was 1.23 times more common in men; and multiple primary tumors were 3.1% more often, with a prevailing metachronous course. In Groups 1 & 2, most tumors were localized in the rectum; 84.8% and 78.6% of tumors, respectively, occurred in the left half of the colon. The frequency of right-sided tumors increased with age modified by gender (in Group 2). Hereditary burdened anamnesis was detected in 14.6% patients before 50 (6.57% more than in Group 2); family history of CRC – in 4.8% patients. The latter is consistent with published data. The studied syndromic variants met the diagnostic criteria for familial adenomatous polyposis, Lynch syndrome, Peutz-Jeghers syndrome, and familial type X colorectal cancer.*

Conclusion: *The increase in CRC incidence at the age of 50-70 years is explained by the effectiveness of screening. However, the upward trend for the age below 50 needs a detailed study of etiological (dietary, environmental, behavioral, hereditary) factors. Effective early diagnostics requires considering the phenotypic characteristics and hereditary history associated with a high risk of CRC onset.*

Keywords: *colorectal cancer (CRC), young age, phenotype, familial variants, sporadic variants.*

Introduction: Till today, we have accumulated a large amount of systematized data on the fundamental aspects of clinical [1] and molecular-genetic patterns of the development of sporadic and hereditary forms of colorectal cancer (CRC) [2]. The phenotype of the disease remains clinically underestimated since the tumor localization, shape, and growth direction largely determine the disease symptoms, progress patterns, metastasis direction, and possible complications. In addition, the clinician deals with the phenotype at all stages of diagnostic examination and further treatment of a patient. According to modern concepts, a phenotype is "a set of external and internal characteristics of an organism, that arise due to individual development based on the genotype and its reaction with environmental factors" [3]. Patients from Asian, African, and western countries demonstrate phenotypic differences in CRC characteristics and the frequency of phenotypic features [4-8].

Though a phenotype characterizes an individual organism, the share of patients with different disease stages is one of the key indicators of cancer epidemiology and phenotype [9]. Comparative studies show that young patients are mostly (up to 70%, according to some authors) diagnosed with stages III and IV of the disease, which are "late" or "advanced" stages [10, 11]. In turn, such phenotypic characteristics of "aggressiveness" as mucus production, relatively rapid tumor growth, and low degree of differentiation are due to specific genotypic differences, including the effects of *de novo* mutations. A high share of advanced stages in young patients may indicate an aggressive nature of the disease and poor oncological alertness of physicians at various stages of the diagnostic process [12].

Correct determination of tumor differentiation degree is important for prognosis. Usually, high-differentiated tumors are associated with a more favorable prognosis than low-differentiated cancer. Several reviews indicate a rela-

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tively high (~ 50%) incidence of high-differentiated tumors in young people [13]; others show no difference in this indicator between cohorts of young and elderly patients [14]. Some studies from Middle East (Iran, Israel) and Southeast Asia (Taiwan) report the prevalence of advanced stages and low tumor differentiation in young patients compared with elderly patients [15-17].

The current increase in the incidence of multiple primary tumors (MPT) of the colon is associated with increased overall cancer incidence. MPTs of the colon currently account for about 17% of all detected MPTs. A recent study showed that most cases are diagnosed in the first two years, or 5 to 10 years after surgery for the first tumor [18]. There is evidence that patients with metachronous multiple primary CRC are younger than patients with synchronous or solitary cancer. In contrast, synchronous colon cancer is more common in people over 75 years than in young and mature ages. At that, synchronous MPTs are more frequent in men than in women [19]. Microsatellite instability in synchronous multiple primary CRC is found in 10-30% of cases and is considered one of the specific characteristics of the phenotype. The emergence of MPTs is associated with aberrant expression of the p53 gene. Mutations in this suppressor gene are associated with left-sided localization and a low degree of tumor differentiation, and a tendency to the deep invasion of the intestinal wall [19].

The primary tumor localization and the response to antitumor therapy depend on CRC molecular pathogenesis [20]. For example, cetuximab effectively treats metastatic tumors with a wild-type KRAS gene and left-sided localization, while bevacizumab delivers a better response in right-sided tumors. This affects the objective overall survival indicators [21]. In general, CRC tends for distal localization (about 90% of primary cases) in countries with low incidence rates (certain regions of Southeast Asia) and an increased share of right-sided tumors in countries with high incidence rates (USA, Europe, Japan, South Korea). These patterns are probably associated with racial and ethnic characteristics, as well as a decrease in rectum cancer incidence (due to screening programs) and an increased share of elder people in the population (population aging). Some works devoted to the genetic mechanisms underlying the development of "proximal" and "distal" tumors (splenic flexure of the colon is a conditional boundary) highlight that these mechanisms are gender-mediated [22].

Nelson and Saltzstein showed an increase in the share of proximal tumors with age, the so-called "age shift to the right" [23, 24]. The age of this shift varies greatly with gender and ethnicity. O'Connell evidenced the dominance of left-sided localizations in young patients [25]. The general trend for Asian cohorts is a large share of tumors in the distal colon (> 65%) in both age groups. European researchers report different shares of right- and left-sided tumor localization, with a high frequency of right-sided tumors in young and elderly patients [14].

Nearly every third CRC case is associated with hereditary factors. Up to 30% of CRC cases are "familial forms" with a "family aggregation" of cases of the disease in several generations, but with no mutations in known genes that determine a hereditary predisposition to CRC [26]. Hereditary forms of CRC include CRCs with known mutations in susceptibility genes. About 5% of all pathogenetic conditions forming the basis for CRC are inherited in an autosomal dominant manner.

Patients with a hereditarily burdened anamnesis (HBA) represent a heterogeneous group that includes hereditary and familial variants of CRC of a syndromic and non-syndromic nature. The polymorphism of genes mediating the organism's interaction with environmental factors is actively studied in sporadic CRC, including in young patients [27-29]. A twofold and threefold increase in CRC risk has been proven in individuals whose close relatives have CRC.

The purpose of the study was to compare the phenotypic features of hereditary and sporadic colorectal cancer in young patients and patients over 65 years.

Materials and methods: The study involved 185 patients aged 17 to 50 years examined and treated at the Kazakh Institute of Oncology & Radiology (Almaty, Kazakhstan) and oncological centers of the regions and the cities of Almaty, Nur-Sultan, and Shymkent (Group 1). The group included 98 (53%) men and 87 (47%) women. The average age of the patients was 41.1±0.52 years (men – 40.54±0.76, women – 41.71±0.70). Figure 1 shows the distribution of Group 1 patients by the age of the disease onset.

The control group (Group 2) involved 112 patients aged 65 to 85 years, including 48 (43%) men and 64 (57%) women. The average age of patients was 71.9±0.52 years (men – 71.9±0.76, women – 71.8±0.70).

The material for clinical and phenotypic analysis was the clinical and phenotypic characteristics of the disease, extracted from patient medical records (form No. 003/u), outpatient medical records (form No. 025/y), and electronic resources of information support of the oncological service (hospital cancer registries and the electronic register of cancer patients).

In cases observed after 2017, the tumor process staging followed the AJCC Cancer Staging System classification, edition 8 (2017) [30].

Histological typing of tumors was based on the pathomorphological examination of surgical and biopsy material by the pathomorphologists of the Almaty Oncology Canter, the Kazakh Institute of Oncology & Radiology, and regional oncological centers.

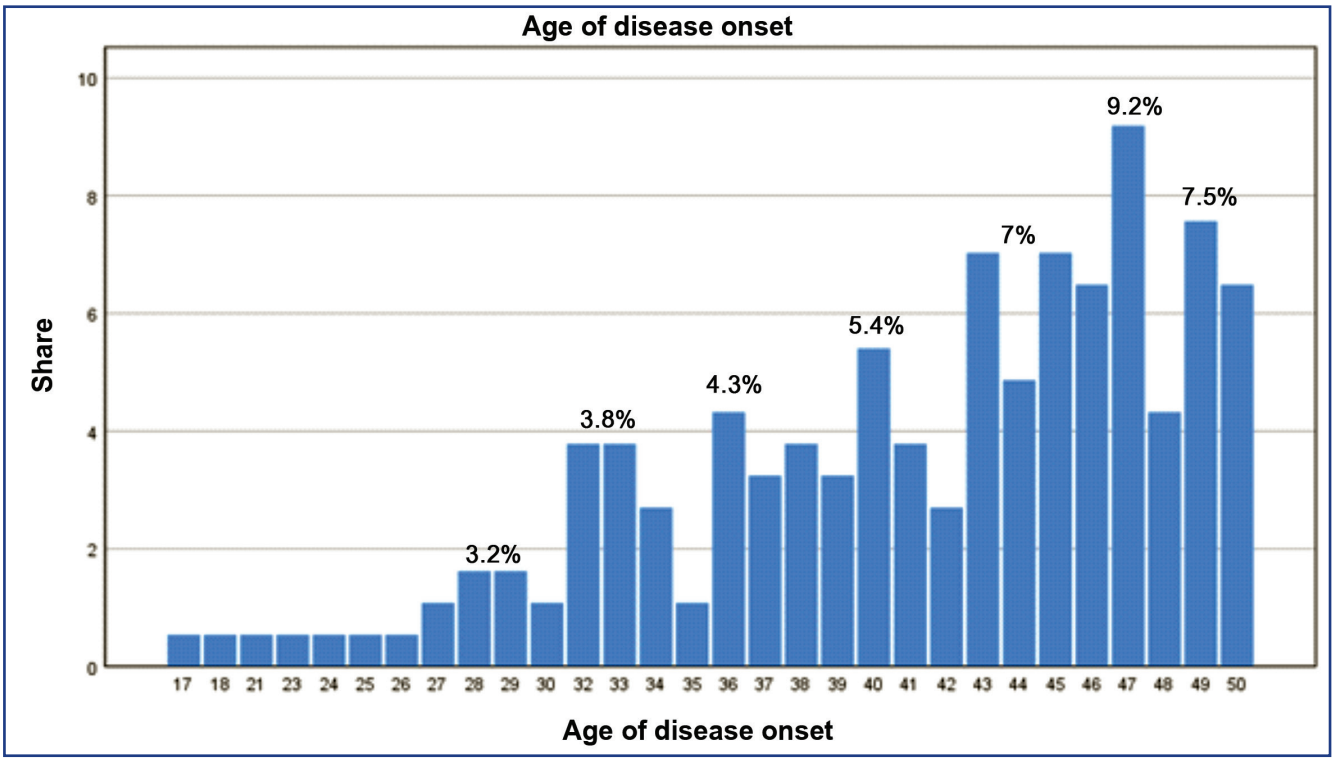


Figure 1 – Distribution of Group 1 patients by the age of the disease onset (n=185)

The patient examination included major established clinical methods and instrumental methods: endoscopic ultrasound, CT, MRI (procto- and colonoscopy). Intraoperative data, the results of pre- and postoperative pathomorphological and IHC tests were assessed. If there was a family history of CRC or other cancers, information about the patient and his/her relatives was analyzed using clinical genealogical methods and the compilation of genealogical charts under generally accepted principles [31].

Results and Discussion:

Most (85.4%) cases of CRC in young patients were sporadic. Sporadic variants of CRC are polygenic diseases. Their frequency was mainly determined by lifestyle, which is supposed to determine health status by 50-60% and the resulting conventional risk factors [32]. The survey data for most patients (14.6% of patients had a family history of cancer) suggested that significant reasons for the early development of sporadic CRC might be a sedentary lifestyle, smoking, and a diet with an excess of "red meat" and low content of vegetable fiber. The latter is typical for a traditional Kazakh diet, particularly for the northern regions of the Republic of Kazakhstan.

Distribution by the disease stage

In Group 1, the stage distribution was as follows: Stage 0 – 1 (0.5%), Stage I – 8 (4.3%), Stage II – 61 (33%), Stage III – 77 (41.6%), Stage IV – 33 (17.8%) patients. Five patients with MPT with different stages of the disease were excluded from the comparative analysis. In Group 2, the stage distribution was as follows: Stage 0 – 4 (3.6%), Stage I – 7 (6.3%), Stage II – 52 (46.4%), Stage III – 30 (26.8%), Stage IV – 19 (16.9%) patients.

Comparing the number of cases by stage of the disease in the study groups showed the prevalence of stage III in Group 1 (41.6%) and stage II in Group 2 (46.4%). At the same time, the number of stage III cases in Group 1 exceeds that in Group 2 by 14.8%. However, the number of stage II cases is less by 13.4%. There was an equivalent number of stage IV cases in both groups (17.8% and 16.9%, respectively) (Figure 2). However, the distribution by gender in the subgroup of patients with stage IV in Group 1 was uneven.

When assessing the differences in the number of cases of stages II and III between age groups, the $\chi 2$ criterion was 14.56, and the number of degrees of freedom was 3 ($p = 0.00237$). Thus, the analysis of the distribution by stages of the disease revealed the predominance of a locally advanced process (stage III) in Group 1 (41.6%) compared to Group 2 (26.8%), and an excess of 27.3% in the frequency of stage IV in men in Group 1.

The log-likelihood function of Bayesian statistics revealed the probability of a stage-gender relationship in Group 1, reflecting the difference in the number of stage IV cases in men and women, with a 27.3% prevalence of cases in men (Figure 3).

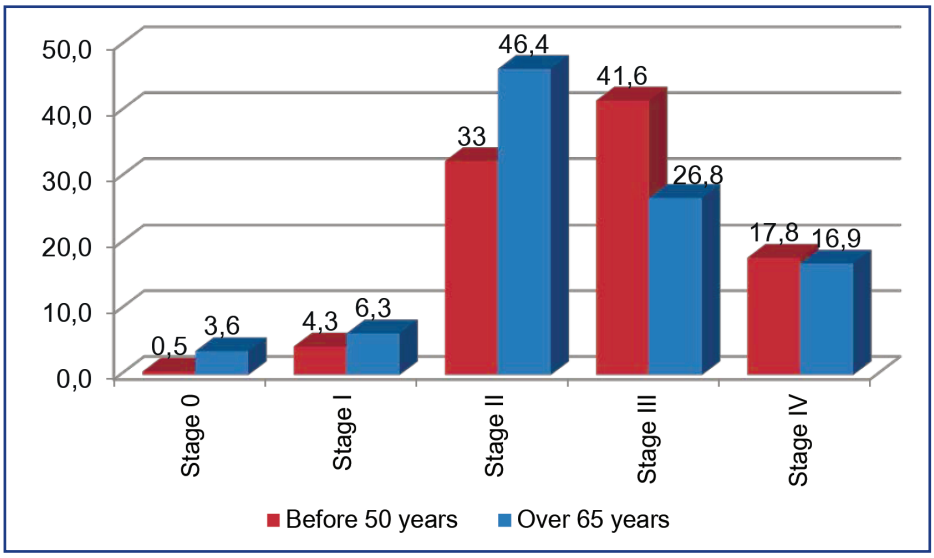


Figure 2 – Comparison of the number of cases by stage in the study groups (%)

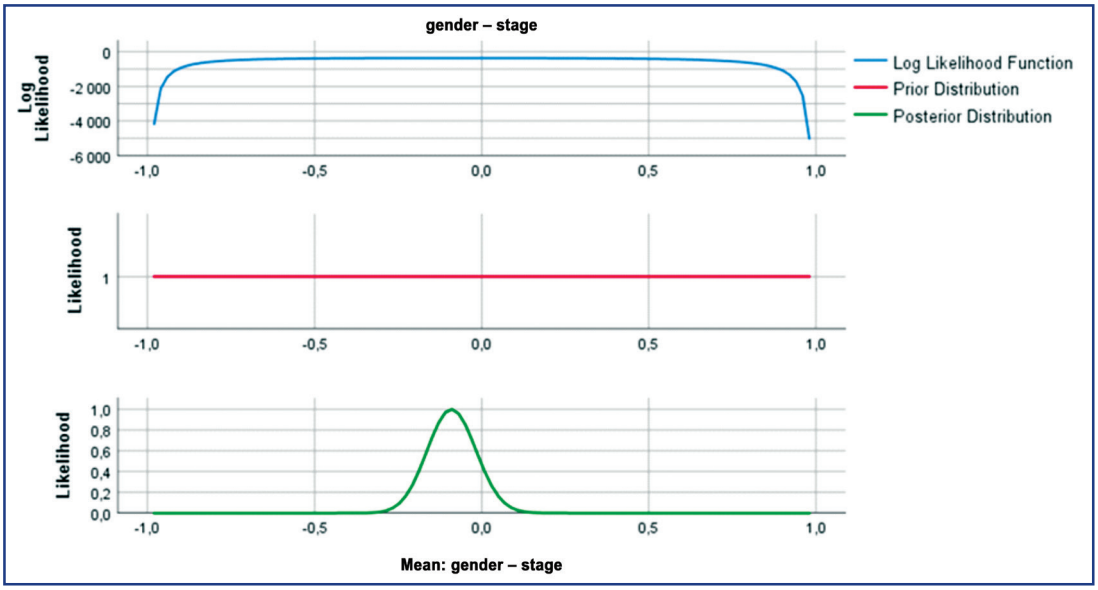


Figure 3 – The posterior distribution of the probability of association of the stage indicator with gender in Group 1 (age before 50)

Distribution by the tumor histological structure

Figures 4 and 5 show the distribution of cases by the histological structure of tumors in both groups. The predominant histological variant of tumors was adenocarcinoma, with a moderate degree of differentiation (G2).

In Group 1, only 21 (11.4%) tumors were mucus-producing. Signet ring cell adenocarcinoma and squamous cell carcinoma were detected in 2 (1.1%) cases each. Dark cell adenocarcinoma, small cell carcinoma, and non-Hodgkin lymphoma occurred in 1 case each (0.5%, 1.5% in total).

In Group 2, the mucinous component was found in 8 cases (7.1%); no signet ring cell carcinomas were reported (Figure 5).

Modern concepts attribute mucoid (colloid) adenocarcinoma and signet ring cell carcinoma to low-differentiated tumors [33], which are quite frequent in young people. A colloid tumor produces a lot of mucus, which causes cell disaggregation in the pri-mary lesion. In contrast, a signet ring cell tumor is associated with massive intramural growth, making it difficult to choose the boundaries for bowel resection. A signet ring cell tumor metastasizes faster and spreads to surrounding organs and tissues, producing relatively little damage to the mucous membrane. This feature complicates both the X-ray and endoscopic diagnostics of the tumor.

In the study groups, there was no significant difference in the frequency of various histological types of tumors. A statistically insignificant difference in the incidence of ad-enocarcinomas of the mucous membrane was found, with a 4.3% higher share in Group 1.

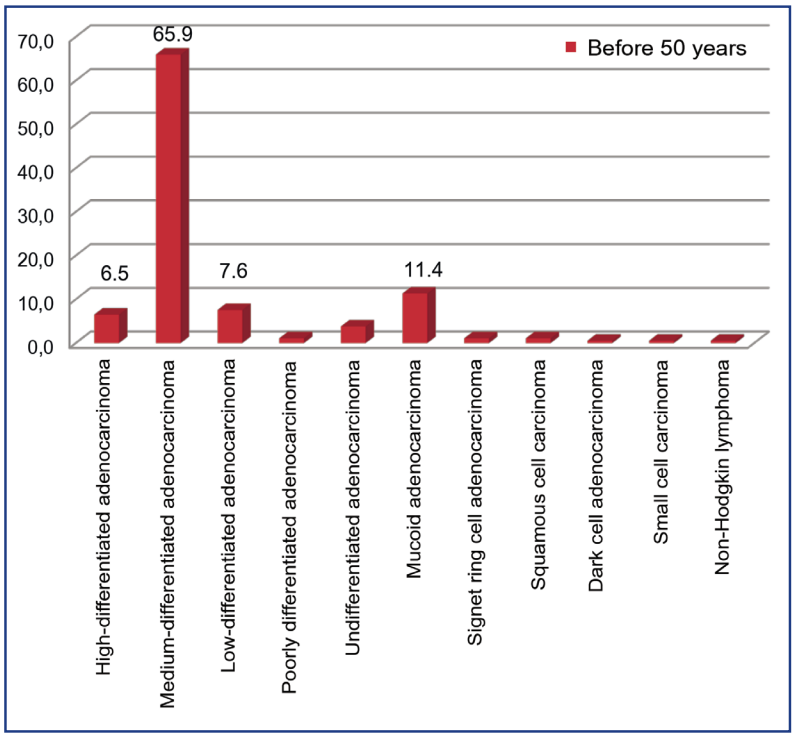


Figure 4 – Distribution of cases in Group 1 (before 50 years) by the tumor histological structure, %

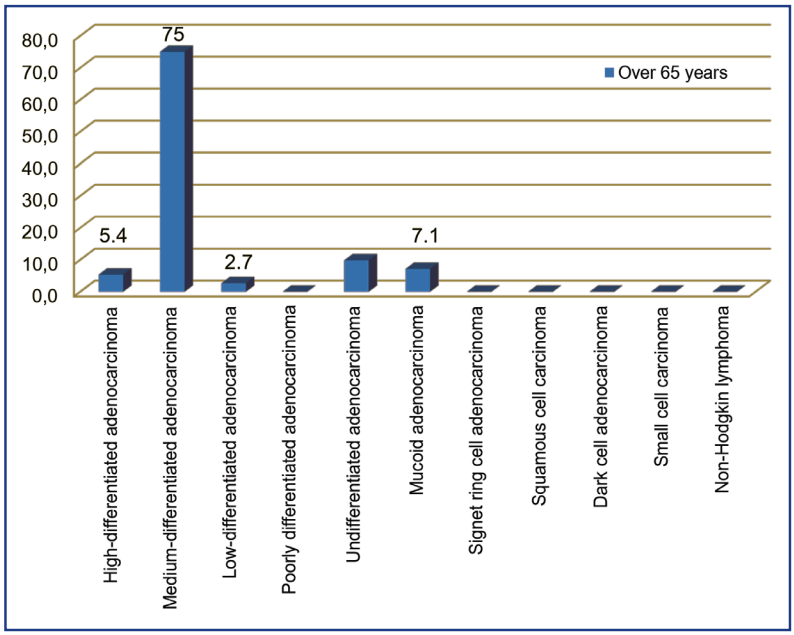


Figure 5 – Distribution of cases in Group 2 (over 65 years) by the tumor histological structure, %

Multiple primary tumors and colonic obstruction

MPTs were reported in 14 (7.56%) patients before 50 years. In 6 cases, tumors occurred in different parts of the colon (3 cases of synchronous cancer, 3 cases of metachronous cancer). In 8 cases, tumors occurred in the colon and other organs (1 case of synchronous cancer, 7 cases of metachronous cancer). In 2 cases, MPTs developed against the background of hereditary tumor syndromes (Table 1).

We analyzed the combination of the tumor process with the local tumor spread and colonic obstruction.

Only in 12 (6.5%) patients before 50, the tumors invaded the adjacent structures (Table 2).

The disease was accompanied by an intestinal obstruction in 44 cases (23.7%).

In Group 2, MPTs were reported in 5 patients (4.46%). Metachronous tumors occurred in the colon – 4 cases (sigmoid colon cancer and hepatic flexure cancer, rec-

tosigmoid cancer and sigmoid colon cancer, sigmoid colon cancer, and mid-ampullar rectal cancer, CRC and transverse colon cancer) and the bladder – 1 case (CRC).

In patients over 65 years, the tumors invaded the adjacent structures and organs in 10 (8.92%) cases: the parietal peritoneum and paranephric fat; stomach and small intestine; the uterus with appendages and perivesical fat; the uterine tube; the small intestine and the fundus of the bladder; the right ovary, right ureter, and small intestine; the mesocolon; the uterus, left appendages small intestine loops; the seminal vesicles; and the cervical stump and bladder (1 case each). The disease was accompanied by an intestinal obstruction in 37 cases (33%).

Thus, MPTs in young patients occurred 3.1% more frequently than in elder patients (over 65 years), with a predominance of a metachronous process. Colonic obstruction of tumor origin, one of the main complications of the disease, was observed in almost a quarter of young patients and 10% higher in elderly patients. The differences in the frequency of obstruction between the groups of young and elderly patients were statistically insignificant.

Table 1 – Primary multiple tumors in Group 1 (before 50 years, n=14)

Localization of the primary tumor	Multiple primary tumors (MPT)		
	Synchronous	Metachronous	
MPTs localized in the colon			
Splenic flexure cancer		Sigmoid colon can-cer (FAP syndrome)	
Rectosigmoid cancer	Splenic flexure cancer		
Ascending colon can-cer	CRC		
Sigmoid colon cancer	Hepatic flexure can-cer		
Sigmoid colon cancer		Ascending colon cancer	
Ascending colon can-cer		Descending colon cancer	
Total MPTs in the colon (n)	6		
MPTs localized in the colon and other organs			
Ovarian cancer		Breast cancer	Sigmoid colon can-cer (type X CRC (FCCTX)
Rectal cancer	Cancer of the cortex of both adrenal glands		
Descending colon can-cer		Ovarian cancer	
Sigmoid colon cancer		Central lung cancer	
Sigmoid colon cancer		Thyroid cancer	
Gastric cancer		Rectosigmoid cancer	
Thigh soft tissue sar-coma		CRC	
Endometrial cancer		Low-ampullar rectal cancer	
Total MPTs in the co-lon and other organs (n)	8		
Total MPT cases (n)	14		

Table 2 – Tumor local spread in Group 1 (before 50 years, n=12)

Primary tumor localization	Primary tumor invasion area	n; %
Sigmoid colon cancer, CRC	Small intestine	3; 1.62%
Sigmoid colon cancer, CRC	Bladder	3; 1.62%
CRC	Uterus	1; 0.54%
Sigmoid colon cancer	Anterior abdominal wall	1; 0.54%
CRC	Vagina	1; 0.54%
CRC	Anal canal	1; 0.54%
Cecum cancer	Right ureter, duodenum	1; 0.54%
CRC	Vagina, cervix, parietal peritoneum, cecum, appendix	1; 0.54%

Tumor localization.

Figures 6 and 7 show the tumor localizations in Groups 1 and 2, respectively.

In Group 1, the tumors in distal regions prevailed (157 of 185 cases), with an uneven distribution of right-sided tumors in men and women. In that group, tumors with right-sided and left-sided localizations accounted for 14.05% and 84.85%, respectively (excluding MPTs localized in different halves of the colon). In Group 2, an uneven distribution of right-sided tumors localization was also gender-dependent. In that group, tumors with right-sided and left-sided localizations accounted for 21.4% and 78.6%, respectively (Table 3).

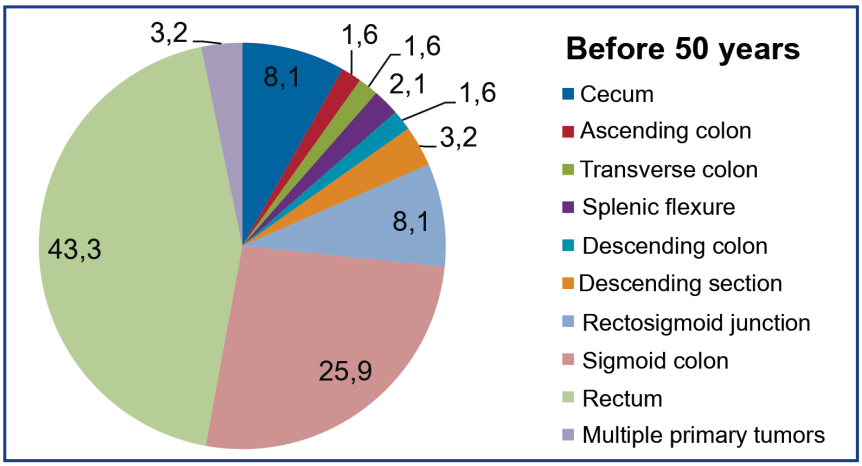


Figure 6 – Distribution by tumor localization in Group 1 (before 50 years), %

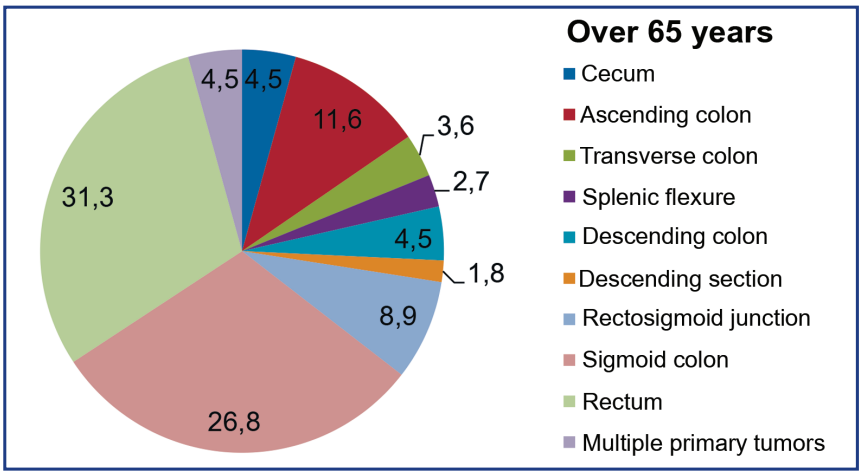


Figure 7 – Distribution by tumor localization in Group 2 (over 65 years), %

Table 3 – Distribution of right-sided and left-sided tumors in the study groups, by gender, %

	Before 50 years		Over 65 years	
	Right colon	Left colon	Right colon	Left colon
Male	8.7	43.7	6.2	36.6
Female	5.5	42.1	15.2	42

The Fisher's criterion (p-value) of 0.017 when assessing the differences between age groups indicated a significant difference in the number of right-sided tumors. The probability of a relationship between the right-sided tumor localization and gender revealed using the log-likelihood function of Bayesian statistics showed a statistically insignificant difference in the number of cases, with a predominance of 23.07% in men (Figure 8).

Comparing the two groups by tumor localization revealed an uneven distribution of tumors in the right and left halves of the colon in men and women by age (Figure 9). The Fisher's criterion (p-value) of 0.03498 indicated significant differences between the study groups in the number of right- and left-sided tumors in men and women. In that case, gender acted as a modifier of the age effect on tumor localization in the right side of the colon.

Thus, the rectum was the dominant site for tumor localization in both age groups, with most tumors occurring in the left half of the colon. The number of cases of right-sided tumors increased with age. The difference in left-sided tumor frequency in men was higher (by 7.1%) in Group 1. In Group 2, in contrast to the younger group, right-sided tumors were more frequent in women (15.1%, vs. 6.2% in men) and were more frequent in general (21.4 % vs. 14.2% in the younger group). The data obtained argue the importance of total colonoscopy in CRC diagnostics and screening, particularly for elder patients, and the advisability of determining the hemogaptoglobin complex in feces as a more sensitive screening method (compared to hemoccult test and iFOBT) for detecting proximal tumors [34].

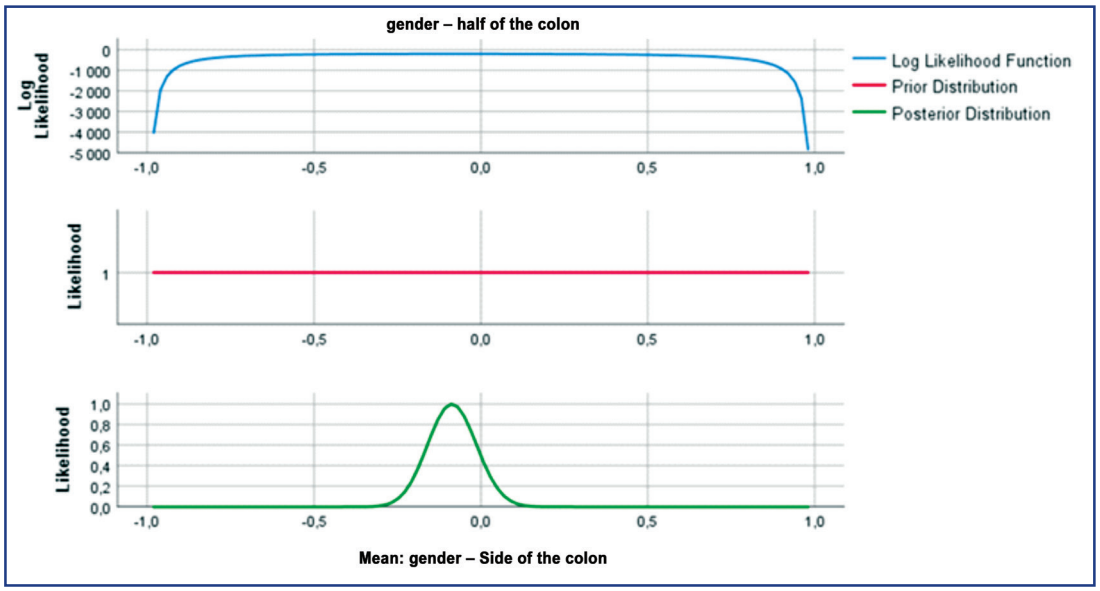


Figure 8 – Posteriori probability distribution of the relationship between tumor localization and gender

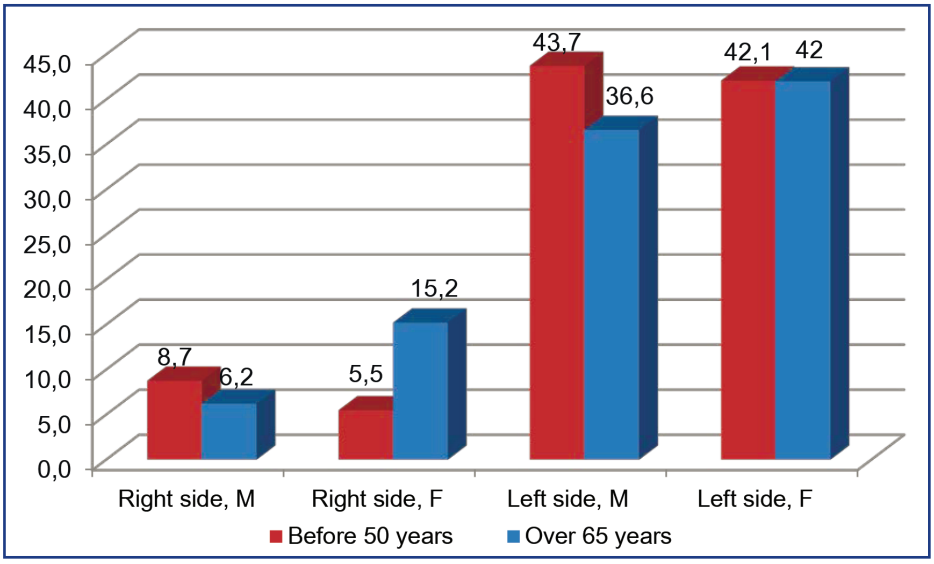


Figure 9 – Distribution of right- and left-sided tumors in the study groups, by gender, %

Hereditary history in the study group

HBA was revealed in 27 (14.6%) young patients, including two patients with MPTs.

Sporadic CRC variants were detected in 158 (85.4%) patients, including 12 patients with MPTs, with no history of malignant neoplasms in their close relatives (Figure 10).

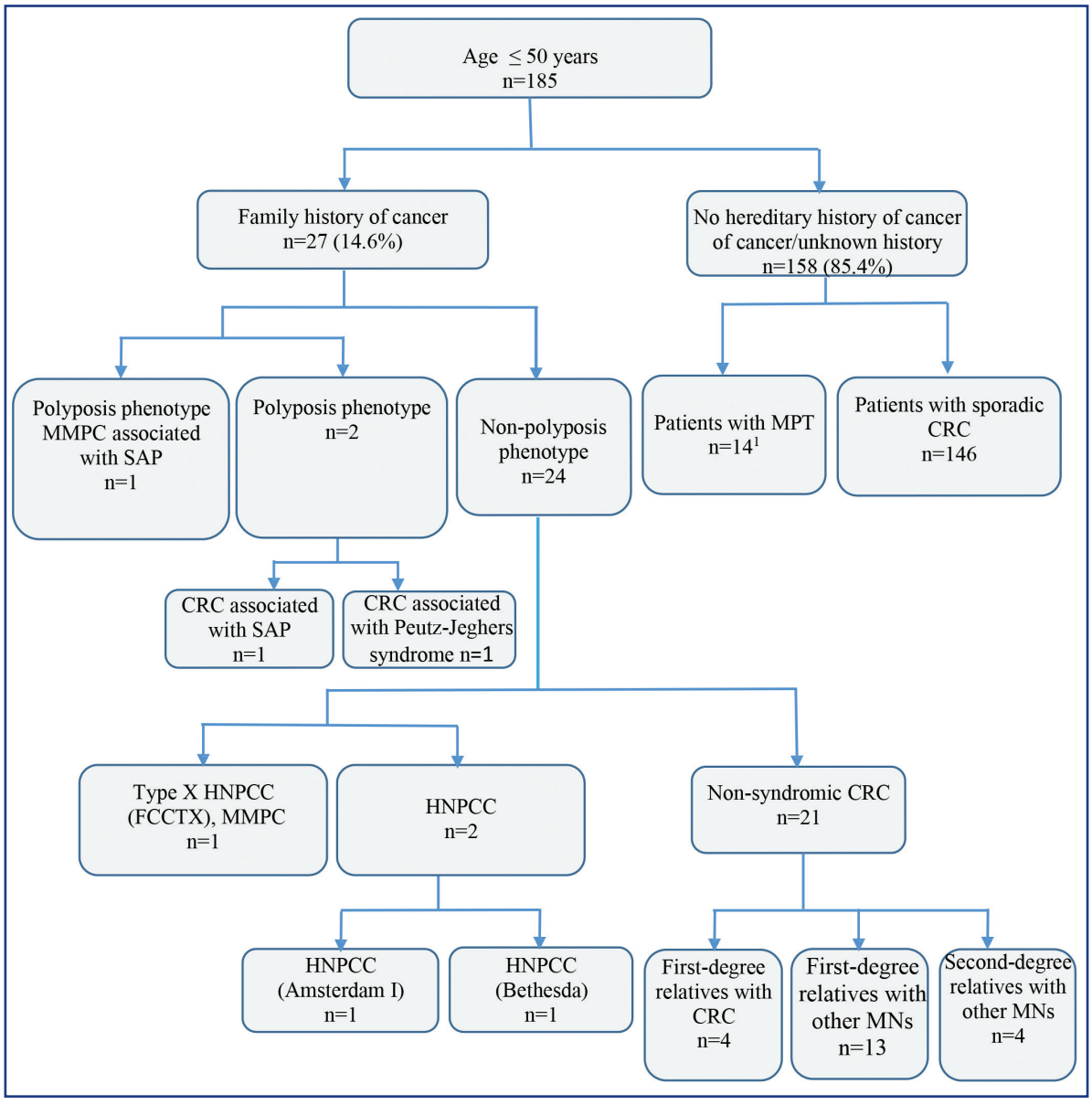
The clinical and genetic characterization of patients was performed using the method-ology proposed by Mork et al. [35]. In Group 1, the following hereditary variants of CRC of syndromic and non-syndromic nature were identified: familial adenomatous polyposis (FAP syndrome) of classical form – 2 patients, Lynch syndrome (hereditary non-polyposis CRC, HNPCC) meeting the clinical diagnostic criteria of Bethesda (2004) and Amsterdam I – 2 patients, metachronous multiple primary cancer (ovarian cancer (OC), breast cancer (BC) and sigmoid colon cancer – 1 patient (with familial non-polyposis type X CRC (FCCTX): OC in the patient's mother and maternal grandmother), and Peitz-Jeghers syndrome established clinically and morphologically – 1 patient.

The study of the family history of cancer did not reveal any association between the patient's diagnosis and the type of tumor in his/her relatives. However, the tumor pathology profile in the patients' relatives confirmed many studies on the relationship of CRC with BC, OC, and EC [2, 36].

The log-likelihood function of Bayesian statistics revealed a probable relationship be-tween the hereditarily burdened anamnesis and the male gender (Figure 11).

In addition to 6 syndromic variants (FAP, HNPCC, Peitz-Jaegers syndrome, FCCTX syndrome), in 21 cases, the

study of family history of cancer revealed various variants of possible familial nature of the disease. Tumors associated/not associated with CRC were identified in the patients' parents and siblings (Table 4). HBA outside the known hereditary tumor syndromes (CRC, EC, OC, BC, prostate cancer, lung cancer, gastric cancer, kidney cancer, or laryngeal cancer in the family history) was reported in 11.3% of 185 patients. This indicator was consistent with published data on CRC incidence at a young age without an identified genetic cause [37]. At the same time, the frequency of FAP syndrome and HNPCC coincided with the published data (~ 1% and 3-5%, re-spectively) [38, 39].



Abbreviations: HNPCC – hereditary non-polyposis CRC; MMPC – metachronous multiple primary cancer
Note: [1]HBA was also reported in 2 patients from the MPT subgroup.

Figure 10 – Clinical and genetic characteristics of Group 1 patients (before 50 years)

HBA was established in 9 (8.03%) patients aged 65-85, including one patient with MPT. No cases met the diagnostic criteria for hereditary tumor syndromes. Thus, the HBA frequency in Group 1 exceeds that in Group 2 by 6.57%.

It should be noted that, in some cases, the medical records of patients had no mention of HBA, while it was revealed by questioning. This indicates the importance of gaining a complete family history by clinicians, with the number of sick relatives of the proband, the degree of relationship, and (where possible) an accurate diagnosis. These data, in turn, ensure the applicability of clinical and genealogical research methods, the completeness of clinical diagnosis, and allows molecular genetic testing using certain diagnostic panels.

Table 4 – Cases of CRC associated with HBA

No.	Gender	Age	Diagnosis	Family history
1	Female	47	Rectosigmoid can-cer	Prostate cancer in father
2	Female	39	CRC	CRC in mother
3	Male	25	CRC	GC in father
4	Male	46	CRC	Kidney cancer in father
5	Female	47	CRC	BC in mother MDP cancer in father
6	Male	43	Cecum cancer	CC in mother GC in maternal grandmother
7	Female	48	Sigmoid colon cancer	Laryngeal cancer in father
8	Female	36	CRC	EC in mother
9	Male	46	CRC	LC in paternal grandfather, BC in paternal grandmother
10	Male	32	CRC	GC in father
11	Female	46	CRC	Prostate cancer in father
12	Female	49	Sigmoid colon cancer	CRC in mother
13	Female	40	CRC	CRC in mother
14	Male	32	Cecum cancer	GC in paternal grandmother Leukemia in paternal uncle
15	Male	32	Rectosigmoid can-cer	BC in maternal grandmother, CRC in maternal uncle
16	Female	49	Rectosigmoid can-cer	Brain tumor in aunt (father's sister)
17	Male	45	CRC	Gastric cancer in mother, paternal grandmother, paternal grandfather
18	Male	47	CRC	Cancer in father, cancer in brother (no exact data available)
19	Male	34	Sigmoid colon cancer	gastric cancer in paternal grandmother, uncle (father's older brother), uncle (1-st older brother of the mother), uncle (2-nd older brother of the mother), older brother
20	Male	29	Rectosigmoid can-cer	BC in older sister
21	Male	47	Sigmoid colon cancer	Prostate cancer in father

Abbreviations: PC – prostate cancer, GC – gastric cancer, EC – endometrial cancer, BC – breast cancer, CRC – colorectal cancer, MDP – major duodenal papilla

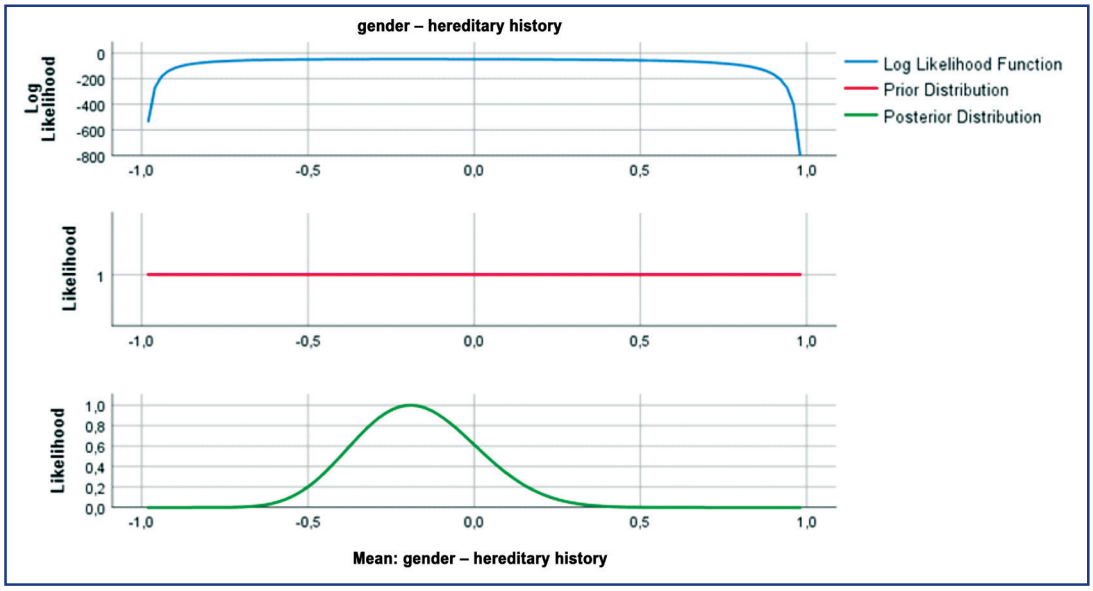


Figure 11 – Posteriori probability distribution of the relationship between HBA and the patient's gender

Conclusion: If the increase in incidence at the age of 50-70 years could be explained by screening efficiency, the etiological (dietary, environmental, behavioral, hereditary) factors in the age group before 50 require a detailed study.

Most of the investigated CRC cases refer to sporadic variants. However, in younger patients, the frequency of HBA cases of 14.6% was 6.57% higher than among elder patients aged 65-85. This fact evidences the need for molecular genetic studies of patients and their close

relatives to identify genetic changes being an etiological factor for CRC onset at a young age.

Questioning of most patients suggested that a sedentary lifestyle, smoking, and a diet with an excess of "red meat" and low content of vegetable fiber – which is typical for the traditional Kazakh diet, in particular, for the northern regions of Kazakhstan – could be the significant reasons for early development of sporadic CRC.

The conducted comparative analysis of phenotypic features revealed a predominance of a locally advanced process (stage III) in patients before 50. This actualizes the problem of early diagnostics and oncological alertness in this age group. Effective early diagnostics requires taking into account the patients' phenotypic characteristics and family history associated with a high risk of CRC.

We revealed a higher frequency of left-sided tumors in younger patients compared to patients aged 65 to 85. The age-related increase in the frequency of right-sided tumor localization actualizes the need for total colonoscopy for diagnostic and screening purposes in elderly populations.

The diagnostic criteria of several syndromes in the members of one family (the "overlapping phenotypes" phenomenon) or the presence of metachronous or synchronous tumors in the patient's individual history requires simultaneous assessment of multiple genes with known clinical effects. This is actual both for individuals not meeting standard diagnostic criteria and for those with previous ambiguous results for candidate genes in case their individual history indicates a hereditary predisposition to cancer.

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ТҰЖЫРЫМ

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Жас науқастардағы тұқым қуалайтын және спорадикалық колоректальды қатерлі ісіктің клиникалық-фенотиптік нұсқалары

Өзектілігі: *Қазақстан Республикасында онкологиялық патологияның құрылымында колоректальды қатерлі ісік (КҚІ) 3 орында тұр. 2008-2019 жылдары республикада колоректальды қатерлі ісік ауруының жыл сайынғы өсуі байқалды. Жастар арасында колоректалды қатерлі ісік ауруының жоғарылау тенденциясы байқалады. Когортты зерттеулер нәтижесінде жас пациенттерге ісік процесінің дистальды локализациясы, аурудың «кеш» кезеңдері, сонымен қатар аурудың агрессивті жүру және ісік дифференциациясының төмен дәрежесі тән екендігі дәлелденді. Аурудың клиникалық сипаттамалары бар фенотиптік белгілердің бірлестіктері белгілі: терапияға жауап және өмір сүру деңгейі, бұл осы проблеманың маңыздылығын анықтайды. Қазақстан Республикасында қазірге дейін жастар арасындағы КҚІ-тің фенотиптік және молекулалық-генетикалық аспектілері әлі жүйелі түрде зерттелген жоқ.*

Зерттеудің мақсаты: *50 жасқа дейінгі және 65-тен жоғары науқастардағы тұқым қуалайтын және спорадикалық колоректальды қатерлі ісіктің фенотиптік ерекшеліктерін салыстырмалы талдау.*

Нәтижелері: *Зерттеуге 17-50 жас аралығындағы 185 науқас (1 топ) және 65-85 жас аралығындағы 112 науқас (2 топ) қатысты. 1-топта 2-топпен салыстырғанда жергілікті дамыған үрдістің (III кезең) 14.8% артық екендігі анықталды. 1-топта IV кезең ерлерде әйелдерге қарағанда 27.3% жиі кездеседі. 1-ші топта 2-ші топпен салыстырғанда, артық бастапқы процестің метахронды сипатымен басым болатын көптеген алғашқы ісіктердің жиілігі бойынша 3,1%-ға артық. 1 және 2 топтарындағы ісіктердің басым орны тік ішек болып табылады, сәйкесінше 84.8% және 78.6% ісіктер тоқ ішектің сол жақ жартысында пайда болады. Пациенттердің жасының ұлғаюымен оң жақты ісіктер жиілігінің жоғарылау тенденциясы анықталды. Гендер оң жақ ішек ішіндегі ісік оқшаулауына жас әсерінің модификаторы ретінде қызмет етеді (2 топта). 50 жасқа дейінгі пациенттердің 14.6% -ында тұқым қуалайтын анамнез анықталды (2 топқа қарағанда 6.57% көп). Колоректальды қатерлі ісіктің отбасылық оқиға пациенттердің 4.8%-ында расталды, бұл жарияланған мәліметтермен сәйкес келеді. Зерттелген синдромдық нұсқалар отбасылық аденоматозды полипоз, Линч синдромы, Пейтц-Егерс синдромы және отбасылық Х колоректальды қатерлі ісік диагностикалық критерийлеріне сәйкес келді.*

Қорытынды: *Егер 50-70 жас аралығындағы топта аурудың жоғарылауы скринингтің тиімділігімен түсіндірілсе, онда 50 жасқа дейінгі топтың тенденциясы этиологиялық (диеталық, экологиялық, мінез-құлық, тұқым қуалайтын) факторларды егжей-тегжейлі зерттеуді қажет етеді. Ерте диагностиканың тиімділігі КҚІ дамуының жоғары қаупімен байланысты болатын пациенттердің фенотиптік сипаттамаларын және тұқым қуалаушылық оқиға ескеруді қамтиды.*

Түйінді сөздер: *колоректалды қатерлі ісік (КҚІ), жас кезең, фенотип, отбасылық нұсқалар, спорадикалық нұсқалар.*

АННОТАЦИЯ

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Клинико-фенотипические варианты наследственного и спорадического колоректального рака у больных молодого возраста

Актуальность: *В Республике Казахстан колоректальный рак (КРР) находится на 3 месте в структуре онкологической патологии. За период 2008-2019 гг. в Республике отмечен ежегодный рост заболеваемости КРР. Наблюдается тенденция роста заболеваемости КРР у лиц молодого возраста. В результате когортных исследований доказано, что для больных молодого возраста характерны дистальная локализация опухолевого процесса, «поздние» стадии заболевания, а также агрессивный характер течения и низкая степень дифференцировки опухолей. Известны ассоциации фенотипических признаков с клиническими характеристиками заболевания: ответом на терапию и показателями выживаемости, что определяет высокую значимость данной проблемы. Фенотипические и молекулярно-генетические аспекты КРР у лиц молодого возраста до настоящего времени не подвергались в Республике Казахстан систематическому изучению.*

Цель исследования: *сравнительный анализ фенотипических особенностей наследственного и спорадического колоректального рака у больных в возрасте до 50 лет и старше 65 лет.*

Результаты: *Обследованы 185 пациентов в возрасте 17-50 лет (Группа 1) и 112 пациентов в возрасте 65-85 лет (Группа 2). В Группе 1 выявлено превышение на 14.8% частоты местно-распространенного процесса (III стадии) по сравнению с Группой 2. В Группе 1, IV стадия встречалась у мужчин на 27.3% чаще, чем у женщин. В Группе 1 выявлено превышение частоты первично-множественных опухолей на 3.1% по сравнению с Группой 2, с преобладанием метахронного характера процесса. Доминирующим местом возникновения опухолей в Группах 1 и 2 была прямая кишка, 84.8% и 78.6% опухолей соответственно возникли в левой половине толстой кишки. Выявлена тенденция увеличения частоты правосторонних опухолей с увеличением возраста пациентов. Пол являлся модификатором эффекта влияния возраста (в Группе 2) на локализацию опухоли в правых отделах толстой кишки. Наследственно-отягощенный анамнез выявлен у 14.6% пациентов в возрасте до 50 лет (на 6.57% больше чем в Группе 2); КРР в семейном анамнезе был подтвержден у 4.8% пациентов, что согласуется с опубликованными данными. Исследованные синдромальные варианты соответствовали диагностическим критериям семейного аденоматозного полипоза, синдрома Линча, синдрома Пейтца-Егерса и семейного колоректального рака типа Х.*

Заключение: *Если для группы 50-70 лет рост заболеваемости КРР объясняется эффективностью скрининга, то тенденция для группы до 50 лет нуждается в детальном изучении этиологических (диетических, средовых, поведенческих, наследственных) факторов. Эффективность ранней диагностики предполагает учет фенотипических особенностей и наследственного анамнеза пациентов, которые ассоциированы с высоким риском развития КРР.*

Ключевые слова: *колоректальный рак (КРР), молодой возраст, фенотип, семейные варианты, спорадические варианты.*