**INTRODUCTION**

Colorectal cancer (CRC) is the second of the fourth most common cancer in industrialized countries, leading to mortality. In Ukraine, the incidence of malignant tumors of colon is 28.3 per 100,000 males, rectum and anus is 27.2 per 100,000 males; the incidence of malignant tumors is 19.7 per 100,000 females and is 15.1 per 100,000 females, respectively. Worldwide incidence of malignant tumors of the colon, rectum and anus is 16.2 per 100,000 males, and is 15.9 per 100,000 males, respectively, and is 11.8 per 100,000 females and is 9.2 per 100,000 females, respectively, and is significantly lower than in Ukraine [1]. In Europe (in Germany and Norway), the highest incidence rate of CRC among men is 43—59 per 100,000 individuals and among women is 27—37 per 100,000 individuals per year and approximately correspond to the number of patients in the USA [2]. Mortality in patients with colon cancer is 41.8% and for rectal cancer is 32.9%. Almost half of patients dies in the first year after diagnosis confirmed. The incidence of CRC increases after 50 years to 160 or more cases per 100,000 people, and at the age over 60 years it increases to 259 cases [3]. In Ukraine, 15,000—17,000 new cases of CRC are diagnosed annually. The highest mortality rate was observed in the age group of individuals over 60 years (56—60%) [4]. In patients with hereditary CRC the manifestation of the disease is characterized by a younger age, a high penetrance of the disease, the prevalence of tumors with low differentiation, appearance of metastases both before treatment and after surgery and lower rate of three-years survival [5]. The etiologies of the remaining 20—30% of inherited CRCs are not completely understood. According to the literature data the diseases with highest risk of CRC includes hereditary polyposis syndromes, most often familial adenomatous polyposis (FAP), Lynch syndrome and inflammatory bowel disease [6]. In patients with FAP the risk of CRC occurrence is approach to 100%, and in patients with Lynch syndrome the risk of CRC is less and accounts to 50—70%. Approximate 25% of patients with colorectal phenotypes indistinguishable from FAP and its attenuated form — AFAP, can be associated with biallelic inherited mutations of BER (base excision repair) gene, MUTYH (human MutY homolog) in the absence of demonstrable inherited mutations of APC gene. The established role of MUTYH is BER of adenine residues that have been misincorporated opposite guanine or 8-oxoG [7]. In 60—70% of patients with MUTYH-associated polyposis (MAP) CRC diagnosed at an average age of 47 years [8]. The risk of CRC in patients with Lynch syndrome younger than 45 years increases in 3 times in comparison to the general population rate [9].

**Aim:** to analyze the distribution of males and females by the age of colorectal cancer (CRC) onset with and without hereditary predisposition to the disease to identify individuals at risk group. **Subjects and methods:** the medical records and the genealogical information of 182 patients with CRC were analyzed, including 94 males and 88 females. «Positive» familial anamnesis for CRC was confirmed in 61 probands: 40 patients to met 1—2 of Amsterdam criteria for Lynch syndrome, 9 patients to met 3 Amsterdam criteria, 7 patients had familial adenomatous polyposis, 3 patients had familial CRC-associated inflammatory bowel diseases, 1 patient had MUTYH-associated polyposis, 1 patient had Peutz — Jeghers syndrome. **Results:** age manifestation of the disease varied in regarding patient’s gender and family history. In probands with «positive» familial anamnesis for CRC the peak age of the disease onset was 5 years lower for both genders, compared to the age of individuals without family history. The average age of CRC onset in probands of both genders with «positive» familial anamnesis for this disease was statistically significant lower, than in patients without family history. The statistically significant difference for the average age of the CRC manifestation between males and females without family history was revealed. **Conclusion:** thus, the study of gender and age—CRC is one of the urgent problems of modern medicine. A precise understanding age of inherited CRC manifestation of patients with CRC is important for identifying at-risk individuals, improving cancer surveillance and prevention strategies, and developing better diagnostic and therapeutic approaches.

**Key Words:** colorectal cancer, familial anamnesis, age manifestation of the disease, gender.
It is known that 10–15% of deaths from the inflammatory bowel disease — ulcerative colitis and Crohn’s disease, caused by CRC. Patients with cancer associated with ulcerative colitis at 10–15 years younger compared with patients with sporadic CRC, and for terms of 5-year survival the difference between the two groups were didn’t observed [10].

The aim of this research is to analyze the distribution of males and females by the age of CRC onset with and without hereditary predisposition to the disease to identify individuals at risk group.

**SUBJECTS AND METHODS**

During the 2002–2014 years it was analyzed the medical records and genealogical information in 182 patients with CRC, including 94 males and 88 females. The diagnosis was established using clinical, endoscopic, radiological and laboratory methods. All diagnoses were morphologically confirmed. Patients were residents of the six regions of Ukraine: Lviv, Ivano-Frankivsk, Ternopil, Volyn, Vinnytsia and Zakarpattya. The collection of genealogical information in 3–4 generations was carried out using a single registration of probands according to the appropriate ethical requirements. The mode of inheritance of the diseases was determined using clinical, genealogical, laboratory and literature (OMIM) database. The age of CRC onset in cases with familial anamnesis of cancer was evaluated in the probands only and does not take into account the age manifestation of the disease in their relatives. Selection of patients in the group of high risk of Lynch syndrome was performed according to 1–3 Amsterdam diagnostic criteria.

«Positive» familial anamnesis for CRC was confirmed in 61 patients. Its including cases, when recurrence of cancer within the family in one or more of first degree relatives and in subsequent generations, was established. Of these, 40 patients (15 males and 25 females) to met 1–2 of Amsterdam criteria for Lynch syndrome, 9 patients to met 3 Amsterdam criteria, and thus confirmed Lynch syndrome (4 males and 5 females). Only 1 patient of these group had Lynch syndrome I and other patients have Lynch syndrome II. The selection of the group of patients with Lynch syndrome I was carried out considering accordance Amsterdam I diagnostic criteria that includes three basic requirements:

- onset of CRC in at the least 3 individuals spanning two generations (FAP should be excluded);
- at least one of these individuals is the first-degree relative of the other two;
- at least one of the individuals must have a diagnosis prior to age 50 years [11].

Selection of patients in the risk group of Lynch syndrome II carried out with regarding supplemented, i.e. Amsterdam II criteria. Requirements include, in fulfilled to the same 3 diagnostic criteria I, some additions: Lynch syndrome II should be suspected in probands and their relatives with CRC/or extracolonic cancers (endometrial, hepatobiliary system, stomach, small intestine, skin, genitourinary cancer) [12]. In 1997, the National Can-

**RESULTS AND DISCUSSION**

Patients with CRC were symbolically divided into two groups regarding patient’s familial history of the disease: without familial anamnesis for the disease were 121 (66.5%) patients (group 1) and with hereditary predisposition for the disease were 61 (33.5%) patients (group 2) (Table 1).

<table>
<thead>
<tr>
<th>Patient’s gender (number of patients)</th>
<th>CRC patients without family history to the disease (group 1), absolute number (%)</th>
<th>CRC patients with family history to the disease (group 2), absolute number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n = 94)</td>
<td>69 (57)</td>
<td>25 (41)</td>
</tr>
<tr>
<td>Females (n = 88)</td>
<td>52 (43)</td>
<td>36 (59)</td>
</tr>
<tr>
<td>Total</td>
<td>121 (100)</td>
<td>61 (100)</td>
</tr>
</tbody>
</table>

The I stage of tumor process was identified in 7 (5.8%) patients, the II stage were in 81 (67.0%) patients, the III stage were in 23 (19.0%) patients, and the IV stage were in 10 (8.2%) patients of the total number of patients without family history of CRC. Among patients with hereditary predisposition for CRC the I stage of tumor pro-
Early tumor stages (I + II) were diagnosed in 88 (72.7%) patients of the group 1 and later tumor stages (III + IV) have 33 (27.3%) individuals, compared to the number patients of the group 2 — 37 (60.6%) and 24 (39.4%) patients, respectively. Thus, in patients with a family history of CRC were diagnosed more advanced forms of the disease.

The distribution of males and females by age at the onset of CRC is shown on Fig. 1.

![Fig. 1](image-url)  
**Fig. 1.** The distribution of males and females by age manifestation for the CRC

Age manifestation of the disease was varied in relation of patient’s gender. The largest number of males was observed at the age from 65 to 74 years, which were on 15—20 years later than females. Females were ill at an earlier age starting from 25 years. At the age of 25–29 years were observed 3 (3.4%) females with CRC unlike male patients — 2 (2.1%) were registered starting at the age of 35–39 years. The number of female patients at the age of 35–39 years and of 40–44 years were 5 (5.6%) and 6 (6.8%) individuals, respectively, exceeded in twice the number of male patients at the same age — 2 (2.1%) and 3 (3.2%) individuals, respectively. The incidence of CRC in males at the age of 70–74 years was twice higher, than in females: 19 (20.2%) male patients and 9 (10.2%) female patients, respectively. According to the data of Bulletin of the National Cancer Registry in Ukraine, the frequency of females at the age of 25–29 years with cancer of the colon and rectum was higher (1.8/100,000), than males (0.8/100,000), but at the age of 80–84 years the frequency of cancer of the same localization was higher in males (109.8/100,000), than females (22.1/100,000) [11].

The number of male patients aged over 80 years was exceeded the number of female patients: 9 (9.6%) males and 5 (5.7%) females. Wider range age (25–86 years) of CRC onset was observed in females, unlike males (35–82 years). The incidence of CRC after 80 years in females decreased to the level of the age group of 30–39 years unlike males: 5 (5.7%) females and 9 (9.6%) males. According to the literature data sporadic colon cancer progresses stepwise from adenoma to carcinoma, with a latency period that may last decades and with highest incidence during advancing age [14], it is conceivable that tumors start developing slowly before menopause, but rapidly progress with cessation of ovarian estrogen production [14, 15]. In the observed group 8 (9.1%) female patients at the age range of 45–49 years were found, and the maximum number — 14 (15.9%) females, were found at the age of 50–54 years. A stable high level of CRC incidence (10.0—11.0% of females) was observed in patients at 55—74 years. It was known that antiproliferative effects of 17β-estradiol are mediated through the estrogen receptor (ER)-β, which is the predominant ER subtype in the human colon mucosa [16]. In addition, there is evidence to suggest that the chemopreventive effect of estrogen against CRC is mediated in part through vitamin D receptor (VDR)-activated antiproliferative intracellular signaling. Early during tumor progression human colorectal cancer cells express high levels of the CYP27B1-encoded 25-hydroxyvitamin D-1α-hydroxylase, the enzyme that synthesizes the active vitamin D metabolite, 1,25-dihydroxyvitamin D₃, (1,25 (OH)₂D₃), which when bound to its cognate receptor, the VDR, effectively inhibits proliferation and promotes differentiation in human colon cancer cells [17]. Estrogens have been shown to increase VDR and CYP27B1 expression and activity in human colon cancer cells. Thus, activation of ER-β causes antitumor effect. Estrogens increase the potential antiproliferative effect of vitamin D hormone [17—21]. However, women are protected from more aggressive cancer in the colon though not in the rectum until well after menopause. This likely reflects the differential sensitivity of the mucosa at these sites against the anticancer effects triggered by activation of ER-β [22].

The manifestation of the disease occurred in females at a younger age, ranging from 25 years, that is on 11 years earlier, than in males. The maximum number of men — 6 (24.0%) patients was observed at the age range of 65—69 years that more than twice exceeded the number of women — 4 (11.0%) patients. The number of patients of both genders in older age (over 75 years) was lower (5.6%), than in patients without family history (6.8%, see Fig. 1). The male patients at this age range (Fig. 2) never found in like to male patients without the family history of CRC (6.4%, see Fig. 1).

In probands with «positive» familial anamnesis the peak age of the disease manifestation was lower by 5 years for both genders: in males is 65—69 years, and in females is 45—49 years, compared with age of individuals with—
out family history (in men is 70–74 years and in women is 50–54 years). The analysis of distribution on age and gender of CRC onset in probands with «positive» familial anamnesis for CRC, is shown on Fig. 2.

Among the 182 probands «positive» familial anamnesis was found in 61 (33.5%) patients: in 25 males and 36 females. In 7 (11.5%) relatives of probands the disease repeated in three generations. Recurrence of CRC in 2–3 generations of families allows to confirms an autosomal dominant mode of inheritance of the disease in some patients. The frequency of various diseases of colon, associated with CRC and family history of this disease, is shown in Fig. 3.

It was determined (see Fig. 2) that among patients with family history of CRC 18 (29.5%) individuals had monogenic diseases of colon, such as: Lynch syndrome — 9 (14.8%), FAP — 7 (11.5%), MAP — 1 (1.6%) and Peutz — Jeghers syndrome — 1 (1.6%). Among them were 7 males and 11 females. Inflammatory bowel disease ulcerative colitis and Crohn’s disease, associated with CRC, was found in 3 (4.9%) patients with hereditary predisposition to CRC. The familial cancer was the most common in this group of probands and was diagnosed in 40 (65.6%) patients. According to the literature data, of common malignancies, CRC has one of the largest proportions of familial cases. Kindred and twin studies estimated that approximately 30% of all CRC cases are an inherited form of the disease [23]. It is known that in Lynch syndrome patients there is a different lifetime risk and earlier age of manifestation for CRC — especially in MSH6 mutation carriers, in men and women [24].

In 25 (41.0%) males and in 36 (59.0%) females «positive» familial anamnesis for CRC was confirmed (p > 0.05). It was observed 69 (57.0%) males and 52 (43.0%) females without family history of CRC (p > 0.05). Despite the lack of a statistically significant difference between the groups of males and females, probably due to the small number of patients in groups, the distribution of cancer cases in the observed families demonstrates the tendency, called the Carter effect [25]. It means that the individuals of gender, which is less affected, have a higher hereditary predisposition compared with patients of the gender, which is often affected. It is known that the incidence and mortality in men by 30–40% higher than in women, despite fluctuations depending on age [1, 24].

There was established statistically significant difference of the age of CRC onset regarding the hereditary predisposition to the disease. Males and females with family history of CRC had lower average age of manifestation of the disease than in patients without a «positive» familial anamnesis. In male patients with family history of CRC the average age of the CRC onset was 50.9 ± 2.77 years that was approximately at 15 years less, than those without family history for the disease (66.2 ± 1.10 years). In women with familial history of CRC the difference of the average age of cancer onset was 50.9 ± 2.91 years less than more than 9 years, than those without a genetic predisposition to the disease — 60.2 ± 1.72 years (Table 3).

Table 3

<table>
<thead>
<tr>
<th>Gender</th>
<th>Family history of CRC</th>
<th>Average age of CRC onset (in years), M ± m</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>n = 69</td>
<td>66.2 ± 1.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n = 94)</td>
<td>n = 25</td>
<td>50.9 ± 2.77</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>n = 52</td>
<td>60.2 ± 1.72</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(n = 88)</td>
<td>n = 36</td>
<td>50.9 ± 2.91</td>
<td></td>
</tr>
</tbody>
</table>

n — the number of patients without family history of CRC; n — the number of patients with family history of CRC.

There was not confirmed statistically significant difference between the average age of CRC onset in patients of both genders with «positive» familial anamnesis of the disease. However, it was revealed a statistically significant difference (p < 0.01) for the average age of the CRC onset between males (66.2 ± 1.10 years) and females (60.2 ± 1.72 years) without family history.

Thus, the study of gender and age-CRC is one of the urgent problems of modern medicine. A precise understanding of the age of inherited CRCs manifestation is important for identifying at-risk individuals, improving cancer surveillance and prevention strategies, and
developing better diagnostic and therapeutic approaches. Studies of the cases of familial and inherited colon cancers have led to recommendations for colon cancer screening. Furthermore, genetic study among this group of patients improves our understanding of colon cancer risk, pathogenesis, and prevention.

CONCLUSIONS

1. Age of the CRC onset was varied in relation of patient’s gender and hereditary predisposition to the disease. In probands with family history of CRC the peak age of the disease onset was 5 years lower for both genders (65–69 years in males and 45–49 years in females), compared to the age of patients without family history (70–74 years in males and 50–54 years in females).

2. Among probands with family history of CRC 29.5% individuals have monogenic cancer syndromes of colon, such as: Lynch syndrome, FAP, MAP and Peutz–Jeghers syndrome. CRC-associated inflammatory bowel disease was found in 4.9% patients with familial amnesis for CRC.

3. The average age of CRC onset in probands of both genders with hereditary predisposition to this disease was the statistically significant lower, than in patients without family history.

4. The statistically significant difference for the average age of the CRC onset between males and females without family history of the disease was revealed.

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Результати: вік маніфестації захворювання варіював залежно від статі пацієнтів і спадкової обтяженності. У пробандів із сімейним анамнезом КРР віковий пік маніфестації захворювання був меншим на 5 років для обох статей порівняно з віком осіб без спадкової обтяженності. У пробандів із КРР чоловічої та жіночої статі зі спадковою обтяженностю цим захворюванням встановлено істотно менший середній вік маніфестації хвороби, ніж у хворих чоловіків і жінок без спадкової обтяженності. Між чоловіками і жінками без спадкової обтяженності КРР за середнім віком маніфестації хвороби встановлено статистично істотну різницю. Висновок: встановлення віку маніфестації спадкових варіантів КРР і статевих особливостей пацієнтів із цим захворюванням є важливим для виявлення осіб груп ризику, а також для покращення спостереження за пацієнтами із раком товстої кишки та відпрацювання превентивної стратегії для вдосконалення діагностики і лікувальних підходів.

Ключові слова: колоректальний рак, сімейний анамнез, вік маніфестації хвороби, стать.

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