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REPRODUCTIVE FACTORS AND COLORECTAL CANCER RISK. Case - control study.

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Summary.

Colorectal cancer is one of the most common cancers worldwide. The role of the female sex hormones in the etiology of the disease is very intriguing. Reproductive factors are surrogate measure of lifetime exposition to the sex hormones.

Purpose: Our aim is to investigate the association between the reproductive factors and colorectal carcinoma risk.

Materials and methods: We include 234 Bulgarian women in our study – 117 cases with colorectal cancer and the same number of healthy controls. Cases are divided into three groups according to the localization of the tumor. We conduct case-control study, using questionnaires about reproductive factors. We use the following statistical methods – descriptive, variational analysis, binary logistic regression.

Results: We observed that only the age at menopause is associated with colorectal cancer risk, and this factor has strongest protective effect in the proximal colon (**95% CI** - 0,051-0,781, **OR** – 0,200, **p – 0,021).**

Conclusion: Analyzing our data we observed that among Bulgarian women the only reproductive factor that show association with the risk of colorectal cancer is the age at menopause.

Keywords: colorectal cancer, reproductive factors, risk factors, age at menopause.

INTRODUCTION:

Colorectal cancer is one of the commonest malignancies worldwide. The incidence is highest in developed countries, but recently its prevalence also increases in developing countries. [1] It is the second reason for deathcause by malignant disease in Bulgaria, according to the last statistical data. Many experimental and observational studies explored the association between colorectal cancer risk and certain risk factors. The role of the female sex hormones in the etiology of the disease is very intriguing. Reproductive factors are surrogate measure of life time exposition to the sex hormones. Theinformationabouttheroleofthesefactorsincolorectalcancergenesis is inconsistent. Most of the studies demonstrate that the colorectal cancer risk is lower in women with later age at menarche and at menopause. [2] The number of liveborn children is also important and the risk decreases with the birth of five or more children, or if the interval between the first and last birth is shorter. [2, 3] The younger age of first birth [3, 4] and longer lactation are taken as a protective factors. [1, 2] Some studies find, that body mass index and hormone therapy use may modify the association of these factors with colorectal cancer risk. [2, 5] Another studies demonstrate different results for the certain subsite of the carcimon in the colon. [3,6] There are researches that observed conflicting results or null association between reproductive factors and colorectal cancer risk. [5,7, 8]

With respect to hormone therapy use (as a hormone replacement therapy or oral contraceptive), data are also inconsistent. Duration of the use, composition of the therapy (estrogen only, or estrogen with progestin) and years since last use are of great importance. [3] Some studies reported hormone therapy as a factor decreasing the incidence of colorectal carcinoma. [9], and others restricted this effect only to the progesterone containing drugs. [2]

In this study we define as reproductive factors the age at menarche and menopause, number of children, age at first and last birth, duration of lactation (average for each child and for lifetime), and female sex hormone use (as hormone replacement therapy or as oral contraceptive), duration of use and the time past since the last use.

PURPOSE:

To investigate the association between colorectal cancer risk and reproductive factors. and to evaluate the influence of the cancer subsite (proximal, distal colon and rectum) on this association.

MATERIALS AND METHODS:

We conducted case-control study. We evaluate 234 Bulgarian women, on age from 22 to 86, with average age 62,69±11,32. Patients are divided into two groups – 117 cases (with colorectal cancer) and the same number of healthy controls. Cases are distributed by tumor subsite – proximal, distal colon and rectum. All participants are statistically uniform by age. Each participant complete questionnaire about reproductive factors mentioned above, by the help of trained interviewer. The questionnaire includes questions about: All data are statistically managed by IBM SPSS Statistics 22.0 program. We accept $p < 0,05$ as a level of significance, wherein we reject the null

hypothesis. There were used the next statistical methods: descriptive, variational analysis and binary logistic regression.

RESULTS:

Conducting our study we obtain the following results, in table appearance,:

Table 1. Colorectal cancer risk according to age at menarche

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Age at menarche	All	Between 13 and 16 years/ before 13 years	0,852	0,405	1,795	0,674
		After 16 years/ before 13 years	0,486	0,153	1,546	0,222
	Proximal colon	Between 13 and 16 years/ before 13 years	1,053	0,321	3,458	0,932
		After 16 years/ before 13 years	1,562	0,342	7,131	0,565
	Distal colon	Between 13 and 16 years/ before 13 years	0,599	0,239	1,503	0,275
		After 16 years/ before 13 years	0,139	0,015	1,255	0,079
	Rectum	Between 13 and 16 years/ before 13 years	1,146	0,387	3,397	0,806
		After 16 years/ before 13 years	0,250	0,026	2,438	0,233

Table 2. Colorectal cancer risk according to number of children

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Number of children	All	1/0	1,067	0,310	3,673	0,919
		2/0	0,844	0,260	2,744	0,778
		3/0	3,333	0,599	18,543	0,169
	Proximal colon	1/0	0,800	0,135	4,745	0,806
		2/0	0,896	0,169	4,745	0,897
		3/0	0,000	0,000	,	0,999
	Distal colon	1/0	1,100	0,192	6,286	0,915
		2/0	0,818	0,154	4,353	0,814
		3/0	7,000	0,861	56,895	0,069
	Rectum	1/0	1,300	0,231	7,315	0,766
		2/0	0,818	0,154	4,353	0,814
		3/0	3,000	0,312	28,841	0,341

Table 3. Colorectal cancer risk according to age at first birth

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Age at first birth	All	Increasing with 1 year	1,035	0,969	1,106	0,306
	Proximal colon	Increasing with 1 year	1,030	0,921	1,152	0,604
	Distal colon	Increasing with 1 year	1,018	0,923	1,123	0,717
	Rectum	Increasing with 1 year	1,064	0,976	1,160	0,158

Table 4. Colorectal cancer risk according to age at last birth

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Age at last birth	All	Increasing with 1 year	1,051	0,990	1,115	0,102
	Proximal colon	Increasing with 1 year	1,032	0,929	1,147	0,555
	Distal colon	Increasing with 1 year	1,063	0,973	1,161	0,176
	Rectum	Increasing with 1 year	1,075	0,992	1,165	0,078

Table 5. Colorectal cancer risk according to lactation

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Lactation	All	Yes/No	1,031	0,349	3,047	0,957
	Proximal colon	Yes/No	1,071	0,211	5,435	0,934
	Distal colon	Yes/No	0,905	0,222	3,682	0,889
	Rectum	Yes/No	1,179	0,233	5,957	0,842

Table 6. Colorectal cancer risk according to lifetime duration of lactation

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Lifetime duration of lactation	All	Increasing with 1 month	1,021	0,996	1,045	0,098
	Proximal colon	Increasing with 1 month	1,021	0,983	1,060	0,280
	Distal colon	Increasing with 1 month	1,031	0,997	1,065	0,072
	Rectum	Increasing with 1 month	1,016	0,982	1,050	0,368

Table 7. Colorectal cancer risk according to lactation average per child

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Lactation average/child	All	Increasing with 1 month	1,006	0,950	1,065	0,841
	Proximal colon	Increasing with 1 month	1,019	0,939	1,104	0,656
	Distal colon	Increasing with 1 month	1,008	0,934	1,087	0,841
	Rectum	Increasing with 1 month	0,992	0,920	1,071	0,844

Table 8. Colorectal cancer risk according to hormone therapy use (as a replacement therapy or oral contraceptives)

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Hormone therapy use	All	Yes/No	1,298	0,466	3,611	0,618
	Proximal colon	Yes/No	0,964	0,191	4,874	0,965
	Distal colon	Yes/No	0,753	0,150	3,773	0,730
	Rectum	Yes/No	2,269	0,676	7,614	0,185

Table 9. Colorectal cancer risk according to duration of hormone therapy use

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Duration of hormone therapy use	All	Increasing with 1 month	0,991	0,963	1,018	0,504
	Proximal colon	Increasing with 1 month	0,900	0,705	1,149	0,397
	Distal colon	Increasing with 1 month	1,006	0,972	1,041	0,724
	Rectum	Increasing with 1 month	0,988	0,954	1,024	0,518

Table 10. Colorectal cancer risk according to years past since last hormone therapy use

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	Top boarder	
Years since last hormone therapy use	All	Increasing with 1 year	0,949	0,859	1,049	0,303
	Proximal colon	Increasing with 1 year	0,001	0,000	,	0,997
	Distal colon	Increasing with 1 year	1,043	0,888	1,225	0,606
	Rectum	Increasing with 1 year	0,930	0,812	1,066	0,299

From the statistical analysis it table appearance it is obvious that reproductive factors such as age at menarche, number of children, age at first and last birth, lactation (lifetime duration, and average per child), hormone therapy use - duration and years since last use, have no significant association with colorectal cancer risk. There is no significant threshold for duration of hormone therapy use and years since last use. Only the age at menopause may be reported as statistically reliable protective factor, if the woman undergo menopause at 50 or more years versus before 40 years. The association is stronger for the proximal colon – about 80% (**95% CI** - 0,051-0,781, **OR** – 0,200, **p – 0,021)** (table.11).

Table 11. Colorectal cancer risk according to age at menopause

Factor	Localization	Comparing	OR	95% CI		p
				Low boarder	To boarder	
Age at menopause	All	Between 50 and 40 years/ before 40 years	0,867	0,289	2,598	0,798
		After 50 years/ before 40 years	0,420	0,142	1,244	0,118
	Proximal colon	Between 50 and 40 years/ before 40 years	0,600	0,161	2,234	0,446
		After 50 years/ before 40 years	0,200	0,051	0,781	0,021
	Distal colon	Between 50 and 40 years/ before 40 years	0,722	0,157	3,316	0,676
		After 50 years/ before 40 years	0,633	0,144	2,779	0,545
	Rectum	Between 50 and 40 years/ before 40 years	1,750	0,323	9,469	0,516
		After 50 years/ before 40 years	0,650	0,118	3,590	0,621

DISCUSSION:

There are different mechanisms underlying the association between reproductive factors and colorectal cancer risk. These factors are surrogate measure for the lifetime exposure to estrogen, whereas serologic studies usually demonstrate the estrogen levels at certain time. [8] Exogenous and endogenous hormones play a different role in the colorectal carcinogenesis, it is supposed. [7] Most of the studies connect high levels of endogenous estrogen with increased risk of colorectal cancer. [5,10] Exogenous estrogen is considered to play a protective role in colorectal cancerogenesis via different mechanisms. One of these mechanisms is indirectly by decreasing insulin like growth factor I (IGF- I) [11] and secondary bile acid. The last are potentially damaging for the colon mucosa and may increase the initiation and promotion of the malignant growth. The estrogen has direct effects also, as a regulator of the colon epithelium cell growth, and inhibitor of the carcinoma cell proliferation. [12] It is establish that in the carcinoma tissue there is higher level of activity of estradiol, compared with nonmalignant tissue and that carcinoma tissue has two fold higher levels of total estrogen, compared with normal colon mucosa. [13]. Low concentration of intratumoral estrogen, are reported to have statistical significant connection with better prognosis of the disease. [7] Estrogen performed its action by connecting with estrogen receptors. Estrogen receptor beta (ESR ^{2}) is the major estrogen receptor in the human colon. It is supposed that the protective effect of estragen is mediated of this receptor.[14] As for conflicting data about the role of estrogen in developing CRC, they can be explained with

different expression of this receptor in the tumor tissue.[15]

Conflicting data in the available literature demonstrate that there are another hormonal and physiological mechanisms related with colorectal carcinogenesis, which may underlie the association between reproductive history and colorectal cancer.[2, 7, 11] Other heredity factors and factors from lifestyles may modify this association. [9] Additional researches exploring the influence of these confounders are needed.

CONCLUSION:

Conducted case-control study demonstrates the association between reproductive factors and colorectal cancer risk, among Bulgarian women. There is no such study in Bulgaria so far. We find that the only factor that was inversely related with this kind of carcinoma and may serve as a protective is the age of menopause, if it it occurred at 50 or more years. The most significant is the protective effect in the proximal colon.

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