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THE 15-YEAR RISK OF COLORECTAL CANCER: PROGNOSTIC SIGNIFICANCE OF RISK FACTORS FOR CHRONIC NON-COMMUNICABLE DISEASES WITH AGING

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Objective: to investigate the prognostic significance of risk factors for chronic non-communicable diseases in the development of colorectal cancer (CRC) in an ageing population cohort (Novosibirsk).

Materials and methods: The study was performed on a representative population sample (Novosibirsk) examined in the HAPIEE project (2003-2005). The analysis included 6061subjects, 152 of whom (73 men, 79 women) had an incident CRC diagnosed during the 15-year follow-up (2003-2015). Cases were identified by linking cancer registry with the cohort database, ICD-10 was used. We used Cox regression models to analyze the association between risk factors and CRC.

Results: The multivariable-adjusted 15-year risk of CRC in men was higher compared to women (HR=1.76; 95% CI:1.12-2.77). The risk of CRC was positively associated with age in both men (HR per year 1.11; 95% CI:1.07-1.15) and women (HR per year 1.09; 95% CI:1.05-1.14). In men with a positive family history of malignant neoplasms (MN) of any location, the risk of CRC was increased (HR=1.90; 95% CI:1.14-3.17). The presence of type 2 diabetes mellitus was associated with the risk of CRC in women (HR=1.97; 95% CI:1.10-3.53).

Conclusions: In studied population cohort aged 45-69, the risk of CRC is positively associated with male gender. Positive associations were also identified between CRC and age in both sexes, the family history of MN of any location in men, and the presence of type 2 diabetes in women.

Keywords: colorectal cancer, smoking, alcohol consumption, blood lipids, type 2 diabetes, body mass index.

Introduction. Today, oncological diseases occupy one of the main places in the overall structure of morbidity and mortality. However, cancer has been known since ancient times. The Ebers Papyrus, dated 1500 BC, contains the first descriptions of possible tumors of soft tissues, skin, uterus, stomach, and also the rectum. More precise evidence of the presence of tumors is provided by mummies. Not long ago, Zimmerman M.R. [18] described the first histologically confirmed case of rectal cancer, detected in an unnamed mummy of a man who lived in Doha in 200-400 AD. Despite centuries of effort to understand the nature of cancer and the undoubted colossal progress in the study of malignant tumors, questions still remain.

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Modern studies have identified a link between the occurrence of CRC and an increased body mass index (BMI) [9, 36], a diet low in dietary fiber [35] and high in red meat [36], cigarette smoking [46, 36], alcohol consumption [5], low physical activity [46, 36], a history of type 2 diabetes [53], a family history of CRC [36], and chronic bowel diseases [46]. Most of the identified risk factors for CRC are modifiable (more than 75%) - associated with the environment and lifestyle. However, the degree of influence of these factors on the risk of CRC varies in different populations, and the results of studies are sometimes ambiguous. For example, in the EPIC study, BMI was positively associated with colon cancer in men (29.4 kg/m^2 vs <23.6 kg/m^2, RR=1.55; 95% CI:1.12-2.15), but no significant association was found with rectal cancer (29.4 kg/m^2 vs <23.6 kg/m^2, RR=1.05; 95% CI:0.72-1.55). In contrast, in women in this study, BMI was not associated with either colon cancer (28.9 kg/m^2 vs <21.7 kg/m^2, RR=1.06; 95% CI:0.79-1.42) or rectal cancer. (28.9 kg/m^2 vs <21.7 kg/m^2, RR=1.06; 95% CI:0.71–1.58) [14]. In another study in women, both low BMI (<18.5 kg/m^2) and obesity (>= 30 kg/m^2) were positively associated with the risk of developing colon cancer. Moreover, low BMI was more associated with the proximal colon, and obesity with the distal colon [13]. There are also conflicting data regarding alcohol consumption. In the EPIC (Norfolk Intervention Study) study, total alcohol consumption did not influence the risk of developing CRC (HR=0.80; 95% CI: 0.51–1.26 for alcohol consumption ≥21 units/week or 24 g ethanol/day compared with non-drinkers), while daily consumption of ≥1 unit of wine (≥8 g ethanol/day) was inversely associated with the risk of developing CRC (HR=0.61; 95% CI:0.40–0.94) [11]. In another study (meta-analysis), an increase in the risk of CRC was found with moderate (>1–4 drinks/day, equivalent to 12.6–49.9 g/day of ethanol) and heavy (≥4 drinks/day, equivalent to ≥50 g/day of ethanol) alcohol consumption by 21% and 52%, respectively [5]. However, in the same study, according to the dose-risk analysis, a significant increase in the risk of CRC by 7% was found with consumption of 10 g of alcohol per day [5].

These data indicate the need for further research in this area, as it is not only of scientific interest, but also makes a practical contribution to the prevention of malignant neoplasms, especially for cancers (including colorectal cancer), where modifiable risk factors make a significant contribution to their occurrence, mainly at an older age, the correction of which will reduce morbidity and mortality from tumors of these localizations.

Objective: to investigate the prognostic significance of risk factors for chronic

non-communicable diseases in the development of colorectal cancer (CRC) in an ageing population (Novosibirsk).

Materials and methods: The work was carried out on a representative population sample (Novosibirsk), examined within the framework of the international project HAPIEE, 2003-2005 (the principal researchers of the Novosibirsk center are Prof. S.K. Malyutina, Academician of the Russian Academy of Sciences Yu.P. Nikitin). The basic study involved 9360 people aged 45-69 years, including 4266 men and 5094 women. The study protocol (dated 14.03.2002) was approved by the local ethics committee of The Research Institute of Internal and Preventive Medicine. Each participant in the study signed an informed consent before inclusion in the project. In the framework of this work, data from 6061 people were analyzed, of which 152 people (73 men and 79 women) were included in the main group, in whom "new cases of CRC were identified" during the follow-up period from 2003-2005, up to December 31, 2019, the comparison group included 5909 people (2287 men, 3622 women), in whom "CRC was not identified" during the same follow-up period. The analysis did not include 3299 people, among them: 2527 persons who died during the past follow-up period from various causes (except of fatal cases from CRC); 587 persons with new cases of cancer other than colorectal cancer, were identified during the follow-up period; as well as 185 persons with prevalent cancer of any localization diagnosed before inclusion in this study.

To identify all cases of cancer, the HAPIEE databases and data from the cancer registry were compared (the registry is maintained in the Research Institute of Internal and Preventive Medicine in cooperation with Novosibirsk Regional Clinical Oncologic Dispensary with the support of the RAS budget topic № FWNR-2024-0002). The diagnosis of CRC was established according to the codes of the International Classification of Diseases, 10th revision (ICD 10): C18 - colon; C19 - rectosigmoid junction; C20 - rectum. This work was carried out according to the design of a prospective cohort study and was supported by the Russian Science Foundation (20-15-00371-П).

The average follow-up period for men was 15.21±1.58 years, for women – 15.53±1.32 years.

At the stage of basic screening, socio-demographic data were collected, including information on alcohol consumption, smoking, level of education, presence of malignant neoplasms in first-degree relatives without specifying the localization of the process, anthropometric data, blood pressure (BP) was measured, and some biochemical parameters of the blood were determined.

Blood was collected from the cubital vein on an empty stomach. Blood serum samples were stored in a low-temperature chamber (-70° C). Determination of the levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) was carried out on KoneLab 300i (USA) autoanalyzer using Biocon kits (Germany). Low-density lipoprotein cholesterol (LDL-C) concentration was calculated using the formula of WT Friedewald et al. (1972) [24]: LDL-C=TC − (TG / 2.2 + HDL-C) (mmol/L). Serum glucose was converted to FPG using the formula of the European Association for the Study of Diabetes, 2007 [28]: FPG (mmol/L) = −0.137 + 1.047 × serum glucose (mmol/L). Blood pressure (BP) was measured three times (the average of three BP readings was analyzed) using an Omron M5-I automatic tonometer (Japan). Body weight was determined using a balance scale. Body mass index (BMI) was calculated using the formula: BMI = body weight (kg)/height2(m2). Height was measured with a vertical stadiometer. Waist circumference (WC) and hip circumference (HC) were measured with a tape measure: WC - in the middle between the lower edge of the costal arch and the sacral part of the ilium, HC - along the greater trochanter. All details of the study protocol have been published previously [19].

Statistical analysis was performed using SPSS v.13.0. The obtained data are presented as absolute and relative values, as well as M±SD, where M is the arithmetic mean, SD is the standard deviation. Statistical hypotheses about the type of distribution were tested using the Kolmogorov-Smirnov criterion. To compare two groups from populations with a normal distribution, Student's t-test for two independent samples was used. The Pearson $\chi 2$ criterion was used to compare categorical variables (tables 1 and 2 for men and women, respectively). The prognostic significance of the main risk factors in the development of CRC was assessed using Cox regression methods (proportional hazards models) in age-standardized and multivariate models for men (table 3) and for women (table 4). Model 0 included each studied factor separately adjusted for age. Model 1 included age, smoking status, and alcohol consumption (average dose per session). Model 2 included age, smoking status, alcohol consumption (average dose per session), education level, and family history of malignant neoplasms. Model 3 additionally included the following covariates: BMI, TG level, presence of hypertension, and presence of type 2 diabetes.

The critical significance level for testing statistical hypotheses in this study was taken to be 0.05.

Results and discussion. Over the 15-year follow-up period, the incidence rate of new CRC cases in the population cohort was 2.5% (3.1% for men and 2.1% for women). At the time of CRC diagnosis, the average age was 69.23±7.89 years in men and 69.85±7.98 years in women. The baseline characteristics of the survey participants are presented in tables 1 and 2. At the time of the baseline examination, both men and women who developed CRC during the follow-up period were more than 4 years older ($p<0.0001$) than men and women in the comparison group. The proportion of male patients with hypertension (HT) and with a family history of cancer of any localization was higher in the CRC group than in the comparison group ($p=0.012$ and $p=0.013$, respectively). The percentage of women with type 2 diabetes was higher in the group with CRC than in the comparison group ($p<0.0001$).

Next, we examined the results obtained in the Cox regression analysis. According to our study, the assessment of proportional hazards for both sexes established a positive significant association between CRC and male sex compared to females: HR=1.57; 95% CI:1.14-2.16 in Model 0 and HR=1.76; 95% CI:1.12-2.77 in Model 3. Our results are indirectly confirmed by published statistical data: in all regions of the world (Global Cancer Observatory, 2022), the incidence of CRC is higher in men than in women (1,069,446 versus 856,979 [21,9 versus 15,2 per 100,000 people]) [27]. In addition, according to McCashland TM, at al. (2001) the risk of developing polyps and colon cancer in men is higher than in women: 1,5 and 1,4 times, respectively [17], and in the study of Hsu SH, at al. (2022) the risk of CRC in men is more than 2 times higher than in women (HR = 2.119; 95% CI:1.386–3.241) [50]. At the same time, men have an 83% higher chance of progressive colorectal neoplasia to be detected than women [26]. These differences can be explained by the putative protective effect of estrogens in relation to the risk of CRC development in women [40], as well as the fact that men tend to smoke more often [2], consume more alcohol [25], and adhere

Table 1

The characteristics of men 45–69 years old at the baseline examination for those who developed (main group)/did not develop (comparison group) the incident colorectal cancer over a 15-year observation period (population cohort, Novosibirsk, 2003-2005)

Parameters/Examined		Comparison group (2287 men)	Main group (73 men)	p
Age at baseline examination, M(SD)		56.15 (6.77)	60.77 (6.97)	0.0001
Systolic blood pressure, mmHg, M(SD)		140.78 (22.07)	144.77 (21.26)	0.128
Diastolic blood pressure, mmHg,M(SD)		89.84 (12.75)	90.27 (10.97)	0.776
Cardiovascular diseases, n(%)		267 (11.7)	11 (15.1)	0.380
AH, n(%)		1355 (59.2)	54 (74.0)	0.012
Type 2 diabetes,n(%)		211 (9.4)	7 (10.0)	0.867
Presence of family heredity for cancer of any location, n(%)		453 (20)	23 (31.9)	0.013
Education:	Primary, n(%)	177 (7.7)	5 (6.8)	0.779
	Secondary, n(%)	771 (33.7)	19 (26)	0.171
	Professional, n(%)	503 (22)	23 (31.5)	0.055
	Higher, n(%)	836 (36.6)	26 (35.6)	0.869
Marital status:	Single/Not married, n(%)	58 (2.5)	0	0.168
	Married, n(%)	2006 (87.7)	64 (87.7)	0.991
	Live with a partner outside of marriage, n(%)	53 (2.3)	1 (1.4)	0.564
	Divorced or separated, n(%)	116 (5.1)	4 (5.5)	0.876
	Widower/Widow, n(%)	54 (2.4)	4 (5.5)	0.090
TC, mmol/l, M(SD)		5.98 (1.16)	6.16 (1.14)	0.199
HDL-C, mmol/l, M(SD)		1.48 (0.37)	1.54 (0.41)	0.166
LDL-C, mmol/l, M(SD)		3.82 (1.04)	3.94 (0.96)	0.365
FPG, mmol/l, M(SD)		5.94 (1.48)	5.89 (0.88)	0.809
TG, mmol/l, M(SD)		1.48 (0.81)	1.49 (0.91)	0.912
BMI, kg/m2, M(SD)		26.74 (4.25)	26.85 (3.76)	0.826
WC (cm), M(SD)		93.75 (11.69)	95.12 (10.12)	0.322
Alcohol consumption, average dose per session (g), M(SD)		52.90 (42.95)	53.36 (37.43)	0.929
Current smoker (at the time of baseline survey), n(%)		1042 (45.7)	25 (34.2)	0.056
Past smoker (quit smoking at some point before baseline), n(%)		558 (24.5)	21 (28.8)	0.393
Never smoked, n(%)		682 (29.9)	27 (37.0)	0.188
Average number of cigarettes per day currently smoked (at baseline), M(SD)		17.78 (8.38)	16.25 (7.65)	0.376
Average number of cigarettes per day, past smoking (quit smoking at some point before baseline survey), M(SD)		19.21 (11.13)	18.05 (7.26)	0.635

Note. In table 1-2: Data are presented in the form M (SD) - mean (standard deviation), as well as in the form of absolute and relative frequency - n (%).

to a diet with less fiber and more red and processed meat [6].

However, some studies show existing sex differences in terms of tumor localization in the colon and its histological type: women have a higher risk of developing right-sided colon cancer (RSCC) with a higher percentage of poorly differentiated and locally advanced tumors than men [16]. Many assumptions have been made about the reasons for such differentiation, but they require further research.

Age is the main risk factor for sporadic CRC. This neoplasia is rare under the age of 40 years, and more than 90% of all cases of detected CRC occur in people over 50 years of age. However, recently there have been reports of a steady increase in the number of new cases of CRC at a younger age (under 50 years) [34, 30]. Nevertheless, the risk of CRC increases with age, and the peak of the disease occurs at approximately the age of 70 years [1]. According to Hsu SH, at al. (2022) in individuals aged 46 to 54 years and over 55 years, the risk of developing CRC is 2.7 and 5.5 times higher than in individuals under 45 years of age [50]. In our study, the risk of CRC is positively associated with age in both men and women (tables 3 and 4).

In addition, we found an increased risk of CRC in men with a positive family history of malignant neoplasms of any localization, including colon and rectal tumors (table 3).

According to the published data, having a positive family history of CRC leads to an increased risk of developing this disease in a proband, while the strength of the association depends on the number of relatives with CRC and their degree of relationship with a proband, as well as the age at which the disease was diagnosed.

Table 2

The characteristics of women 45–69 years old at the baseline examination for those who developed (main group)/did not develop (comparison group) the incident colorectal cancer over a 15-year observation period (population cohort, Novosibirsk, 2003-2005)

Parameters/Examined		Comparison group (3622 women)	Main group (79 women)	p
Age at baseline examination , M(SD)		56.82 (6.92)	60.99 (6.68)	0.0001
Systolic blood pressure, mmHg, M(SD)		141.99 (24.68)	140.50 (20.95)	0.594
Diastolic blood pressure, mmHg, M(SD)		89.57 (13.11)	88.69 (11.66)	0.554
Cardiovascular diseases, n(%)		291 (8)	6 (7.6)	0.885
AH , n(%)		2328 (64.3)	58 (73.4)	0.093
Type 2 diabetes, n(%)		333 (9.4)	16 (21.3)	0.001
Presence of family heredity for cancer of any location, n(%)		935 (25.9)	26 (32.9)	0.159
Education:	Primary, n(%)	279 (7.7)	9 (11.4)	0.226
	Secondary, n(%)	1205 (33.3)	25 (31.6)	0.762
	Professional, n(%)	1135 (31.3)	24 (30.4)	0.856
	Higher, n(%)	1003 (27.7)	21 (26.6)	0.827
Marital status:	Single/Not married, n(%)	179 (4.9)	4 (5.1)	0.961
	Married, n(%)	2176 (60.1)	49 (62.0)	0.726
	Live with a partner outside of marriage, n(%)	62 (1.7)	1 (1.3)	0.762
	Divorced or separated, n(%)	528 (14.6)	11 (13.9)	0.870
	Widower/Widow, n(%)	677 (18.7)	14 (17.7)	0.827
TC, mmol/l, M(SD)		6.47 (1.29)	6.69 (1.29)	0.139
HDL-C, mmol/l, M(SD)		1.56 (0.34)	1.55 (0.39)	0.695
LDL-C, mmol/l, M(SD)		4.20 (1.16)	4.38 (1.13)	0.170
FPG, mmol/l, M(SD)		5.87 (1.42)	6.17 (1.36)	0.070
TG, mmol/l, M(SD)		1.55 (0.86)	1.66 (0.75)	0.247
BMI, kg/m2, M(SD)		29.89 (5.48)	30.13 (5.48)	0.702
WC (cm), M(SD)		90.91 (12.83)	92.74 (12.22)	0.210
Alcohol consumption, average dose per session (g), M(SD)		21.58 (16.65)	21.88 (15.58)	0.870
Current smoker (at the time of baseline survey), n(%)		387 (10.7)	4 (5.1)	0.108
Past smoker (quit smoking at some point before baseline), n(%)		152 (4.2)	2 (2.5)	0.463
Never smoked, n(%)		3079 (85.1)	73 (92.4)	0.067
Average number of cigarettes per day currently smoked (at baseline), M(SD)		8.82 (6.01)	7.33 (2.52)	0.669
Average number of cigarettes per day, past smoking (quit smoking at some point before baseline survey), M(SD)		6.77 (6.02)	3.50 (0.71)	0.445

In one study, the presence of first-degree relatives with CRC increased the risk of developing a tumor of this localization in a proband from 1.91 times in the presence of 1 first-degree relative with a history of CRC to 19.86 times in the presence of 5 or more first-degree relatives with this disease (individuals likely to have hereditary CRC syndromes). In addition, the presence of only second-degree relatives also increased the risk of this disease in a proband, but to a much lesser extent, and the presence of only third-degree relatives did not lead to a significant increase in risk. The totality and combination of the affected relatives in the family history of a proband led to an intermediate increase in the risk of CRC. [44]. In another study (meta-analysis), having a first-degree relative with a family history of CRC increased the risk of developing this malignant tumor by more than 2 times (RR=2.25; 95% CI: 2.00-2.53), having more than one relative with CRC by 4 times (4.25; 95% CI:3.01-6.08), and having a relative with this disease under 45 years of age by 3.8 times (3.87; 95% CI:2.40-6.22) [33]. Both women and men with a first-degree family history of CRC were at increased risk of CRC, and a family history of CRC in both men and women was associated with an increased risk of colon cancer, but not rectal cancer. The same study (a prospective study) showed that the relative risk of CRC associated with a family history of the disease was higher in younger participants and gradually decreased with age in both women and men.[3] Similar data were obtained in the work of Jung YS, at al., where it was noted that the risk of CRC in women with a

Table 3

15-year risk of incident colorectal cancer in men, results of analysis of prognostic predictors in Cox regression models

	Covariates	Model 0	Model 1	Model 2	Model 3
HR (95%CI)	Age, years (for 1 year)		1.1 (1.06-1.14)	1.11 (1.07-1.15)	1.11 (1.07-1.15)
	Smoking: Never smoked (reference)	1.0	1.0	1.0	1.0
	Current smoker	0.82 (0.47-1.43)	0.81 (0.46-1.41)	0.87 (0.49-1.53)	1.00 (0.56-1.79)
	Past smoker	0.97 (0.55-1.71)	0.96 (0.54-1.69)	1.01 (0.57-1.80)	1.01 (0.56-1.84)
	Alcohol, average dose, g/session:	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)
	Education: Higher education (reference)	1.0		1.0	1.0
	Secondary education	0.91 (0.50-1.64)		1.02 (0.55-1.86)	1.02 (0.54-1.91)
	Professional education	1.46 (0.83-2.56)		1.62 (0.91-2.86)	1.70 (0.95-3.05)
	Primary education	0.63 (0.24-1.65)		0.71 (0.27-1.89)	0.76 (0.29-2.04)
	Family history of any cancer: No (reference)	1.0		1.0	1.0
	Yes	1.83 (1.11-3.00)		1.82 (1.11-2.99)	1.90 (1.14-3.17)
	BMI < 25 kg/m² (reference)	1.0			1.0
	≥25 kg/m²	1.31 (0.77-2.24)			1.17 (0.65-2.11)
	TG level <1.7 mmol/l(reference)	1.0			1.0
	≥1.7 mmol/l	1.22 (0.73-2.02)			1.03 (0.58-1.83)
	HT BP < 140/90 mmHg without treatment (reference)	1.0			1.0
	BP ≥ 140/90mmrtst or treatment	1.64 (0.97-2.77)			1.48 (0.86-2.55)
	Presence of type 2 diabetes <7.0 mmol/l and no history of diabetes (reference)	1.0			1.0
	≥ 7.0 mmol/l or history of diabetes	0.93 (0.42-2.02)			0.86 (0.38-1.94)

Note. In table 3-4: Model 0 – standardization by age. Models 1-3 are multi-variant.

family history of CRC, compared with all women without a family history of CRC, gradually decreases with age from 1.92 (95% CI:1.55–2.38) at 40-49 years to 1.06 (95% CI:0.67–1.69) at ≥80 years. A similar trend was observed in men in this study from 1.58 (95% CI:1.27–1.96) at 40-49 years to 0.54 (95% CI:0.29–1.06) at ≥80 years [7]. In our study, women with first-degree relatives with cancer of any localization did not have an increased risk of CRC. This may be partly explained by the study design: the family history reflects the presence of not only CRC but also any other cancer in first-degree relatives, which may make our data less specific, since some types of malignancies do not increase the risk of developing CRC. Newschaffer CJ et al. reported that women with previous breast cancer were 5% less likely to develop colon cancer and 13% less likely to develop rectal cancer than women in the general population [47]. Most likely, the result obtained in the work of Newschaffer CJ et al. reflects the known negative effect of estrogens on breast carcinogenesis [48] and a possible protective effect on the occurrence of CRC [40]. On the other hand, there is a study (meta-analysis) confirming a significant association between the presence of a family history of CRC or any type of cancer with CRC, increasing the risk of developing malignant neoplasms of this localization (OR=2.12; 95% CI:1.65-2.73) [8]. However, this meta-analysis presents an assessment of the risk only for individuals of both sexes, but not separately for men and women, which, in our opinion, is important in this situation, given the obvious sex differences in the incidence of CRC.

We also found a positive association between the risk of CRC and the presence of type 2 diabetes in women (table 4). Our results are partially confirmed by numerous studies; however, there are differences in the information available to date. In some meta-analyses, the risk of CRC was increased in both women and men with type 2 diabetes, but the degree of association in women in some studies was higher than in men, [29] in others, the association of CRC with diabetes was more pronounced in men [20] or the risk was approximately the same in both sexes [56]. A prospective study by Campbell PT, at al. [45] reported an increased risk of developing CRC only in male patients with type 2 diabetes, but not in female patients. Other studies noted an increased risk of developing CRC among women with type 2 diabetes, but not among men

Table 4

15-year risk of colorectal cancer in women, results of analysis of prognostic predictors in Cox regression models

	Covariates	Model 0	Model 1	Model 2	Model 3
HR (95%CI)	Age, years (for 1 year)		1,09(1,05-1,13)	1,09(1,06-1,14)	1,09(1,05-1,14)
	Smoking: Never smoked (reference)	1.0	1.0	1.0	1.0
	Current smoker	0.75 (0.27-2.12)	0.68 (0.24-1.95)	0.68 (0.24-1.94)	0.55 (0.17-1.83)
	Past smoker	0.93 (0.22-3.84)	0.90 (0.22-3.74)	0.90 (0.22-3.75)	0.97 (0.23-4.03)
	Alcohol, average dose, g/session:	1.01 (0.99-1.02)	1.01 (0.99-1.02)	1.01 (0.99-1.02)	1.01 (0.99-1.02)
	Education: Higher education (reference)	1.0		1.0	1.0
	Secondary education	0.89 (0.50-1.60)		0.89 (0.49-1.59)	0.89 (0.48-1.65)
	Professional education	1.03 (0.57-1.84)		1.03 (0.57-1.86)	1.10 (0.60-2.02)
	Primary education	0.89 (0.40-1.99)		0.89 (0.40-2.00)	0.94 (0.42-2.13)
	Family history of any cancer: No (reference)	1.0		1.0	1.0
	Yes	1.41 (0.88-2.26)		1.42 (0.89-2.27)	1.42 (0.88-2.30)
	BMI < 25 kg/m2 (reference)	1.0			1.0
	≥25 kg/m²	1.13 (0.73-1.76)			1.04 (0.64-1.67)
	TG level <1.7 mmol/l(reference)	1.0			1.0
	≥1.7 mmol/l	1.54 (0.98-2.40)			1.39 (0.86-2.25)
	HT BP < 140/90 mmHg without treatment (reference)	1.0			1.0
	BP ≥ 140/90mmrtst or treatment	1.13 (0.68-1.88)			1.03 (0.59-1.79)
	Presence of type 2 diabetes <7.0 mmol/l and no history of diabetes (reference)	1.0			
	≥ 7.0 mmol/l or history of diabetes	2.25 (1.29-3.91)			1.97 (1.10-3.53)

[42]. The degree of association between CRC and diabetes depends on the duration of the latter: according to some data, the risk of CRC decreases after 8 years of type 2 diabetes compared to individuals without type 2 diabetes, the maximum increase in the risk of CRC is observed in individuals with a duration of type 2 diabetes of less than 3 years [56]. According to other data, the risk of CRC decreases in individuals with a diabetes duration of 10 years or more, and individuals with a type 2 diabetes duration of 2 to 5 years, compared with diabetes duration of 5 to 10 years, in this study are most susceptible to an increased risk of CRC (HR=2.55; 95%, CI: 1.77-3.67) [55]. In addition, methods of diabetes therapy are important: taking metformin reduces the risk of CRC in diabetes [41], while insulin treatment, on the contrary, increases the risk of CRC [31].

In our study, we did not identify an association between colorectal cancer and such factors as smoking, alcohol intake, BMI, hypertension, education level, and TG levels. There are reported evidences that either confirm or refutes the connection of the above mentioned factors with CRC.

In one meta-analysis, colorectal cancer was significantly associated with smoking in both former and current smokers, but the association with smoking was greater in colorectal cancer. Also in this study, smoking increased the risk of CRC in men in both former and current smokers; in women, the risk of CRC was increased only for former smokers [15]. Another meta-analysis (based on EMRO Eastern Mediterranean studies) found a significant association between smoking and CRC (OR=1.40; 95% CI:1.11–1.78). However, subgroup analysis revealed a negative correlation between CRC and current smoking, although the association was not significant (OR=0.94; 95% CI:0.59–1.51). Former smoking increased the risk of developing CRC, but was also not statistically significant (OR=1.53; 95% CI:0.96–2.45) [10]. One study shows a significant increase in the risk of developing colon cancer in women who smoke regularly, but not in men [51]. In addition, an increased risk of CRC has been reported to be associated with the number of cigarettes smoked per day, longer smoking period, or higher number of packs per year [15, 54].

One meta-analysis provided strong evidence of an association between moderate (2–3 drinks/day or 12.6–49.9 g/day ethanol) and high (≥ 4 drinks/day or ≥ 50 g/day ethanol) alcohol consumption and risk development of colorectal cancer in both men and women. In addition,

light (1 drink/day or less than 12.5 g/day of ethanol) alcohol consumption in women was a protective factor, while in men it increased the risk of CRC, but in both cases the results were not significant. [5]. In another meta-analysis, the risk of CRC was increased only in men and only with high alcohol consumption (>42 g/day ethanol); light/moderate alcohol consumption (1.1–28 g/day ethanol) reduced the risk of CRC in women (OR=0.88; 95% CI:0.82-0.95), as well as in men (OR=0.96; 95% CI:0.88-1.05) [37].

In other data (case-control), moderate alcohol consumption (12-35 g/day ethanol) compared with light (less than 12 g/day ethanol) was associated with a significantly reduced likelihood of developing colorectal cancer in men and women; conversely, high alcohol consumption (>48 g/day ethanol) was associated with an increased risk of CRC in men (OR=3.45; 95% CI:1.35–8.83) but not in women (OR=3.40; 95% CI:0.50-22.92) [4]. In Korea, any alcohol consumption, including even one alcoholic drink per day, is associated with an increased risk of developing cancer of the esophagus, stomach and colorectal cancer, however, subgroup analysis showed a significant increase in the risk of colorectal cancer in men with light/moderate and heavy alcohol consumption; in women the risk was reduced insignificantly [52].

There are not many studies related to hypertension and an increased risk of CRC. One meta-analysis reported an increased risk of CRC in men with hypertension, but not in women, and there were no significant associations between systolic blood pressure or diastolic blood pressure and the risk of CRC [8]. An association between blood pressure and the risk of colorectal cancer in men was also found in the Me-Can study (RR=1.10; 95% CI:1.02–1.18) [38] In contrast, in the EPIC study (European Prospective Investigation into Cancer and Nutrition), Christakoudi S, at al. reported that diastolic blood pressure was positively associated with the risk of colon cancer in both men and women, and systolic blood pressure was positively associated with the risk of CRC in men only. [12]. At the moment, the connection between hypertension and colorectal cancer is difficult to explain and requires additional research.

Educational data are inconsistent: in some reports, people with a college degree or higher had a lower risk of developing CRC than those with elementary school completion or less [21], these data are consistent with another study showing that the overall incidence of CRC was significantly higher among people with low levels of education or living in areas of low socioeconomic status [49]. According to other data (EPIC study - European Prospective Study of Cancer and Nutrition), the risk of CRC, especially in the proximal colon, is lower in subjects with a lower level of education compared with those with a higher level of education. [22].

Most reviews, articles, and meta-analyses report a positive association of BMI with CRC [43, 32], but Nilsen TI, at al. did not find an association between BMI and the risk of developing CRC, which is consistent with our study [42].

Elevated TG levels in the Me-Can study (cohort study) were associated with an increased risk of CRC, but only in men: RR=1.17; 95% CI:1.06–1.28 [38]; in another cohort study, high TG levels increased the risk of CRC [50], but this study did not analyze separately for each sex. According to Aleksandrova K, at al. (2011) an increased level of serum TG does not lead to an increased risk of developing CRC [39].

Limitations of the study. The study has several limitations, it concerns the modest number of men and women with CRC identified over the 15-year follow-up period, however, the study included all new cases of CRC that occurred in the cohort (9360) over the study period (average 15 years of follow-up); this increases the likelihood that we have obtained a representative sample of typical CRC for the population.

Conclusions

1. In the cohort 45-69 years old, the 15-year risk of developing colorectal cancer was higher in men compared to women.

2. CRC risk was positively associated with age in men and women.

3. In men with a positive family history of malignant neoplasms of any location in first-degree relatives, the risk of colorectal cancer was increased.

4. The presence of type 2 diabetes mellitus was associated with an increased risk of CRC in women.

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