ORIGINAL ARTICLE

Components of the metabolic syndrome: abdominal obesity and arterial hypertension in the context of the risk of oncological pathology

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ABSTRACT

Introduction

Metabolic syndrome (MS) is the most important risk factor for cancer, although the full relationship between MS and cancer remains far from resolved. A number of studies have been conducted that indicate a certain connection between hormonal and inflammatory changes in adipose tissue and cancer.

Objectives

The aim of the paper was to study was to investigate the incidence of cancer in patients with MS lasting more than 10 years, and the degree of dependence on its components: abdominal obesity (AO) and arterial hypertension (AH).

Methods

For comparison by the same parameters data from patients without MS were analyzed. The crosstabulation method was used to estimate the odds ratio (OR) of carcinogenesis and 95% confidence intervals (95% CI).

Results

It was found that in patients with a duration of MS of 13.5±2.41 years, the initiation of oncological diseases was observed in every fifth participant, while in the absence of MS in every fourteenth patient.

Conclusion

AO is associated with an increased risk of developing hypertension, and both of these conditions are associated with an increased risk of cancer of various localization. The greatest risk was found in MS with grade I obesity in combination with hypertension, as well as with the patient's age.

Keywords

metabolic syndrome; cancer; arterial hypertension; abdominal obesity.

INTRODUCTION

Metabolic syndrome (MS) is a global problem of our time. Representing a set of disorders of carbohydrate, lipid and purine metabolism, MS contributes to the development of early atherosclerosis, increases the risk of diabetes mellitus (DM) and cardiovascular diseases (CVD)[1]. The uncorrected prevalence of MS among the adult population is 40%, but there is serious concern about an increase in the absolute number of patients with MS by 50% in the next decade[2,3].

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Currently, there are several alternative definitions of MS, but the unifying criterion for all is abdominal obesity (AO), which is determined by an increase in visceral fat, decreased sensitivity of peripheral tissues to insulin, hyperinsulinemia. According to the World Health Organization (WHO), more than 1.9 billion people over the age of 18 are overweight, of which 650 million are obese[2]. At the same time, the frequency of obesity in the world community varies. For example, in Japan, 3.7% of the population is obese, in the Russian Federation - 19.6%, in the USA - 38.2% of citizens[4,5].

The development of primary hypertension (AH) accounts for about 90-95% of cases of stable increase in blood pressure. One of the main and independent risk factors for AH is obesity. In the presence of obesity, the risk of developing AH reaches 90%. AH is associated with an increased likelihood of developing certain types of cancer and with a higher mortality rate from cancer[4,33]. Thus, there is a close relationship between AO, AH and oncopathology.

Obesity, being a risk factor for socially significant diseases, also contributes to an increase in overall mortality. A prospective follow-up for the period 1971-1994 in the USA showed a reduction in life expectancy by 9.4 years in people suffering from obesity of varying degrees[6]. In this regard, the world community is somewhat wary of the increase in the prevalence of obesity, which, according to preliminary WHO forecasts, may amount to 1.5 billion by 2030[5]. It is proved that AO is associated with the risk of an increase in mortality from cancer by more than 30%[1,5-7]. Therefore, timely correction of risk factors and components of MS is considered the main task in the strategy of reducing the risk of developing socially significant diseases, including cancer. Despite the fact that there is a large evidence base on the relationship between obesity and carcinogenesis, some issues still require further study.

The aim of this study was to determine the probability of developing cancer in patients with MS, as well as with a combination of AO and one of the components of MS - arterial hypertension (AH).

Materials and methods: An observational retrospective study involving 1993 patients was conducted at the clinical base of the Department of Outpatient Therapy of the First Sechenov Moscow State Medical University (Sechenov University). The main group consisted of 994 patients (289 men and 705 women). The average age of participants in the main group at the time of selection for the study was 62.48±13.49 years (from 20 to 87 years). A mandatory criterion for inclusion in the study was the presence of MS in patients for 10 years or more, so at the selection stage, attention was paid to anthropometric data (waist size, height, and BMI) and the components of MS (hypertension, hyperglycemia, hypertriglyceridemia, and HDL reduction).

The comparison group consisted of 999 patients (261 men and 738 women), whose average age corresponded to the average values in the main group. A mandatory criterion for selecting patients in the comparison group was the absence of MS, based on the determination of waist size and body mass index. To diagnose MS, we used the recommendations of experts of the Russian Society of Cardiology (RSC) on the diagnosis and treatment of MS (2009, second revision). MS was diagnosed in patients with signs of AO (waist size >94 cm in men and >80 cm in women) in combination with 2 or more additional criteria[8]: blood pressure ≥140/90 mm Hg or treatment of previously diagnosed hypertension; increased triglycerides (TG) more than 1.7 mmol / l; reduced cholesterol high-density lipoproteins (HDL) of less than 1.2 mmol / l in women and less than 1.0 mmol/l in men; impared fasting glycemia(IGF), impaired glucose tolerance (IGT), combined violation of IGF/ IGT. When selecting patients for the comparison group, changes in one or two parameters corresponding to additional MS criteria were allowed. In the comparison group, a similar assessment of the levels of laboratory parameters and the above-mentioned chronic diseases was carried out. The manifestation of oncological diseases both in the main group and in the comparison group was determined taking into account the updated data of outpatient records. Data on malignancies were confirmed by a centralized review of morphological reports. All patients were registered on an outpatient basis with an oncologist.

Statistical analysis was carried out in accordance with the set goal using parametric and nonparametric statistical methods of the SPSS 22.0 program (SPSS Inc, USA) for Windows (Microsoft Corporation, USA). The percentage ratio, mean value, and standard deviation (M±σ) were calculated for numerical variables. To

identify the relationship between MS and cancer of any localization, the crosstabulation method was used. Proportionate risk models were used to estimate OR and 95% CI for the various associations compared.

Additionally, cancer risk in patients with MS was assessed by adjusting for age (up to 55 years, 55-74 and 75 and older) and the degree of obesity (I degree BMI 30-34 kg / m2, II degree BMI 35-39 kg / m2, III degree BMI 40 kg / m2 and above). The comparison group studied the association of hypertension with the risk of cancer in three age groups. The statistical significance of differences between categorical variables was checked using the Pearson chi-square test. The p-value<0.05 was considered statistically significant.

Ethical purity: The study was approved by the local ethics committee 1-st Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University) 06.04.2023, protocol number № 06-23.

RESULTS

The clinical and demographic characteristics of the study participants presented in **Table 1** indicated the predominance of female representatives in both the main group (70.9%) and the comparison group (73.87%). The average waist circumference (WC) was 103.8±10.50 cm, the average BMI 36.05±4.12 kg / m^2. In the comparison group, patients did not have AO, the average WC was 84±9 cm. In the main group is obese grade I was determined in 49.9% of participants, and grade II and III obesity was determined in 29.4% and 20.7%, respectively.

In the main group, the cancer process in MS developed in 185 patients with a BMI of ≥30.0 kg / m2, while a strong correlation was observed taking into account the grade of obesity (**Table 2**). According to the results of a multivariate analysis, the probability of developing cancer in individuals suffering from grade I obesity (n=496) increased compared to other grades up to 65.4% (OR-2.188; 95%CI-1.568–3.053; p <0.05). In patients with grade II (n=292) and grade III (n=206) obesity, the association with oncogenesis was revealed to a much lesser extent: in patients with grade II (n = 292) and grade III (n = 206) cancer is likely in 17.8% of cases (OR-0.461; 95%CI-0.308–0.691; p <0.05), in grade III - in 16.8% (OR - 0.729; 95% CI - 0.479–1.111; n/a), respectively.

Table 1:Characteristics of study patients

Indicators	The main group (patients with MS)	The comparison group (patients without MS)
Number of observations	994	999
Age (years)	62,48±13,49	64,05±19,75
Men/Women, n	29,1/70,9 (289/705)	26,13/73,87 (261/738)
Leading MS criterion: waist circumference, cm	103,8±10,50	84±22
Increase in BP, %	77,91 (774)	70,97 (709)
BMI (kg / m^2)	36,05±4,12	27,46±2,47
Grade I obesity (30-34. 9 kg / m^2), %	49,90	No
Grade II obesity (35-39. 9 kg / m^2), %	29,38	No
Grade III obesity (≥40 kg / m^2), %	20,72	No

Note: Proportions and sample sizes were specified for categorical variables, and averages and standard deviations were specified for continuous variables. MS – metabolic syndrome; BP – blood pressure; BMI – body mass index.

Table 2: The probability of oncogenesis in metabolic syndrome depending on obesity grade

Parameters			Cancer		Total
			No	Yes	
Obesity	I grade	Quantity	375_a	121_b	496
		%	46,4%	65,4%	49,9%
	II grade	Quantity	259_a	33_b	292
		%	32,0%	17,8%	29,4%
	III grade	Quantity	175_a	31_a	206
		%	21,6%	16,8%	20,7%
Total		Quantity	809	185	994
		%	100,0%	100,0%	100,0%

Parameters	Cancer		Total
	No	Yes	
Chi-square criteria	Meaning	Degree of freedom	p
Pearson's Chi-square	22,981	2	0,000
Likelihood ratios	23,651	2	0,000
Linear-linear relationship	13,864	1	0,000
Number of valid observations	994		

Note: Each subscript denotes a subset of cancer categories with column proportions that do not differ significantly from each other at the p-value threshold of 0.05.

The study found a significant association between the grade of AO and the risk of developing cancer pathology. In the comparison group, it was determined that in the absence of AO, the cancer process developed much less frequently – in 73 cases out of 999.

When analyzing the risk factors for oncogenesis, attention is paid to the association of neoplastic processes and hypertension. During follow - up, the neoplastic process was initiated in 161 patients, while in the absence of hypertension (n=220) - in 24 patients. The result of a multivariate analysis of the association of neoplastic processes and MS criteria such as AH and AO grade is presented in **Table.3.** Cancer more often developed in patients with hypertension and grade I obesity-26.5% (104 patients), in patients with grade II and III obesity – 14.2% (31 patients) and 16.1% (26 patients), respectively. It should be noted that a persistent increase in blood pressure over 140/90 mm Hg in the absence of antihypertensive therapy increases the chances of carcinogenesis in patients with MS by 2 times (OR-2.145; 95% CI-1.357-3.391; p <0.001).

Table 3: Multivariate analysis of the association of neoplastic process and MS components (AH, obesity grade)

Parameters				Cancer		Total
				No	Yes	
I grade of obesity	AH	No	Quantity	86_a	17_b	103
			%	22,9%	14,0%	20,8%
		Yes	Quantity	289_a	104_b	393
			%	77,1%	86,0%	79,2%
	Total		Quantity	375	121	496
			%	100,0%	100,0%	100,0%
II grade of obesity	AH	No	Quantity	70_a	2_b	72
			%	27,0%	6,1%	24,7%
		Yes	Quantity	189_a	31_b	220
			%	73,0%	93,9%	75,3%
	Total		Quantity	259	33	292
			%	100,0%	100,0%	100,0%
III grade of obesity	AH	No	Quantity	40_a	5_a	45
			%	22,9%	16,1%	21,8%
		Yes	Quantity	135_a	26_a	161
			%	77,1%	83,9%	78,2%
	Total		Quantity	175	31	206
			%	100,0%	100,0%	100,0%

Note: Each subscript indicates a subset of cancer categories where the column proportions do not differ significantly from each other at the level of 0.05. MS – metabolic syndrome; AH – arterial hypertension.

When analyzing the comparison group, it was found that even in the absence of MS, hypertension is a powerful risk factor for cancer development. Out of 999 people, hypertension was detected in 709. At the same time, 84.9% of 73 patients with oncopathology suffered from hypertension (n=62) **(Table 4).**

The study revealed a significant relationship between hypertension and the risk of developing cancer. We obtained a multiple increase in the risk of cancer in patients with hypertension, even in the absence of MS.

Table 4. The probability of oncogenesis in the presence of hypertension in patients without MS.

Parameters			AH		Total
			No	Yes	
Cancer	No	Quantity	279	647	926
		%	30,1%	69,9%	100,0%
	Yes	Quantity	11	62	73
		%	15,1%	84,9%	100,0%
Total		Quantity	290	709	999
		%	29,0%	71,0%	100,0%
Chi-square criteria					
	Meaning	Degree of freedom.	Asymptotic significance (2-sided)	Exact significance (2-sided)	Exact significance (1-sided)
Pearson's Chi-square	7,450[a]	1	,006		
Continuity adjustment[b]	6,737	1	,009		
Likelihood ratios	8,382	1	,004		
Fischer's exact criterion				,007	,003
Linear-linear relationship	7,443	1	,006		
Number of valid observations	999				

Note: MS – metabolic syndrome; AH – arterial hypertension

Taking into account the fact that age and gender are independent risk factors for oncogenesis, we calculated the risk of cancer development for three age groups of patients of each gender: for persons under 55 years old, for patients from 55 to 74 years old, and for representatives over 75 years old (**Tables 5, 6).** Gender analysis is showed that the probability of oncogenesis in men with MS in the age group of 55 years and less is low (the asymptotic significance according to the Pearson chi-square criterion is 0.008), the highest probability of oncogenesis is observed in the middle age group, while in the age group of 75 years and older, it increases by 1.2 times (OR=1.165; 95%CI-0.602–2.255; p=0.039). In women with MS, cancer development at a young age is also unlikely (OR=0.104; 95% CI-0.014–0.788; p=0.04), which is greatest in the age group of 55-74 years, and increases 1.5 times in the group over 75 years (OR=1.522; 95%CI-0.645-3.591; p=n/a). In general, there were no significant differences in the risk of cancer development between men and women in age groups, but it was noted that women with MS have a higher risk of cancer than men.

Table 5. Relationship of age and gender of MS patients with the development of neoplastic processes

Age group	All patients		Cancer patients	
	Men (n)	Women (n)	MEN (n)	Women(n)
Up to 55 years old	9,96% (99)	25,45% (253)	0,54% (1)	8,1% (15)
55-74 years old	10,46% (104)	32,7% (325)	19,46% (36)	36,76% (68)
75 years and older	8,65% (86)	12,78% (127)	9,73% (18)	25,41% (47)
Total	29,1% (289)	70,9% (705)	29,73% (55)	70,27% (130)
	100% (994)		100% (185)	

Note: MS is a metabolic syndrome

Table 6. Association of the age of MS patients and cancer

Parameters			Cancer		Total
			No	Yes	
Age groups	Up to 55 years old	Quantity	333_a	19_b	352
		%	41,2%	10,3%	35,4%
	56-74 years old	Quantity	330_a	99_b	429
		%	40,8%	53,5%	43,2%
	Over 75 years old	Quantity	146_a	67_b	213
		%	18,0%	36,2%	21,4%
Total		Quantity	809	185	994
		%	100%	100%	100%

Note: Each subscript indicates a subset of cancer categories in which the column proportions do not differ significantly from each other at the level of 0.05. MS – metabolic syndrome.

We determined the frequency of hypertension among men and women in different age groups. In the group of men under 55 years of age, the incidence of hypertension was 65% (n=65), among women – 61% (n=156); in the group of 56-74 years among men, 90% (n=94), among women – 81% (n=263); in the group over 75 years of age among men, 94% (n=81), among women 90% (n=115). The comparison group also analyzed the relationship between the age of patients, as an independent factor, with the risk of developing cancer and frequency of hypertension occurrence in different age groups. A correlation similar to the results obtained in the main group was revealed **(Table 7).** The incidence of hypertension by age group was distributed as follows: in the group under 55 years of age, it was 48% (n=150) among women and 62% (n=25) among men; in the group of 56-74 years, 85% (n=230) among women and 80% (n=113) among men; in the group older than 75 years 74% (n=113) among women and 97.5% (n=78) among men.

Table 7. Association of cancer risk with patient age

Parameters			Cancer		Total	
			No	Yes		
Age-group	55 or less	Quantity	303	10	313	
		%	96,8%	3,2%	100,0%	
	56-74	Quantity	352	37	389	
		%	90,5%	9,5%	100,0%	
	75 or more	Quantity	271	26	297	
		%	91,2%	8,8%	100,0%	
Total		Quantity	926	73	999	
		%	92,7%	7,3%	100,0%	
Chi-square criteria						
	Meaning	Degree of freedom	Asymptotic significance (2-sided)	Exact significance (2-sided)	Exact significance (1-sided)	Discrete probability
Pearson's Chi-square	11,524[a]	2	,003	,003		
Likelihood ratios	13,193	2	,001	,002		
Fischer's exact criterion	12,839			,002		
Linear-linear relationship	7,130[b]	1	,008	,008	,005	,002
Number of valid observations	999					

Additionally, the study analyzed the dependence of the localization of the cancer process on the presence of certain MS criteria in the main group of patients. Prostate cancer in men (33 cases out of 185), uterine and breast cancer in women (31 and 30 cases, respectively), kidney cancer (15 cases), colorectal cancer (16 cases) and lung cancer (10 cases) were found to be the most common. In general, the prevalence of cases of oncopathology by localization in MS **(Table 8)** corresponds to the general epidemiological data[9]. Multivariate statistical analysis did not reveal any differences in the relationship between tumor localization and certain components of MS, and they were also not detected in the comparison group.

Table 8. Quantitative characteristics of cancer processes by localization

Parameters	Main group		Comparison group	
Type of cancer process	Women, n/% of the total	Men, n/% from the total	Women, n/% of the total	Men, n/% of the total
Prostate cancer	-	33/17,8%	-	12/16,44%
Uterine cancer	31/16,8%	-	3/ 4,12%	-
Breast cancer	30/16,2%	-	16/22%	-
Kidney cancer	13/7%	2/1,1%	4/5,5%	1/1,4%
Colorectal cancer	11/6%	5/2,7%	5/6,8%	3/ 4,1%
Lung cancer	5/2,7%	5/2,7%	1/1,4%	2/2,74%
Stomach cancer	2/1,1%	1/0,5%	3/ 4,1%	2/2,74%
Skin cancer	7/3,8%	1/0,5%	5/6,8%	2/2,74%
Other types of cancer	31/16,8%	8/4,3%	11/15%	3/ 4,12%
Total n/% of the total	185/18,6%		73/7,3%	

DISCUSSION

Recent studies have supplemented the scientific understanding of the direct dependence of mortality on overweight, among which the leading role is played by systemic subclinical inflammation of the adipose tissue.10 According to experts of the World Cancer Research Foundation (WCRF), systemic inflammation contributes to cell metaplasia and increases the risk of developing 12 types of cancer: colorectal cancer, ovarian cancer, breast and endometrial cancer, cancer of esophagus, stomach, pancreas, gallbladder, liver, kidney, prostate, oral cavity, pharynx and larynx [1, 5, 11]. Therefore, when studying obesity and the associated cardiovascular, cardiometabolic and oncological risks, maximum attention is paid to the collection of anamnesis, the amount of adipose tissue, its distribution and type. Thus, our study established a significantly significant dependence of the risk of developing oncological pathology on the degree of AO, where the highest risk was observed in patients with grade I obesity.

The main peak in the development of obesity occurs at the age of 45-55 years - during the beginning of hormonal and metabolic restructuring of the body, thereby contributing to the creation of prerequisites for the initiation of systemic inflammation. Chronic metabolic disorders accompanied by hyperinsulinemia contribute to a decrease in the production of IGF-binding proteins, leading to an increase in the level of biologically active insulin-like growth factor (IGF-1) in the blood, which increases inflammation in adipose tissue. Adipokines of adipose tissue, cytokines, angiogenic factors (vascular endothelial growth factor VEGF and apelin (AGTR1)) they influence the initiation of carcinogenesis in obesity. Therefore, a timely combined assessment of BMI and OT is advisable to clarify the phenotype of obesity and the associated cancer risk [4, 12, 13].

With a more detailed analysis, gender differences in the risk of mortality among women and men were also established, which does not contradict the results of recent studies: for women, obesity is one of the leading risk factors for both general mortality and cardiovascular mortality, while for men it is only cardiovascular[14]. However, the unfavorable epidemiological situation that has been developing in recent decades, associated with urbanization and, as a result, physical inactivity,

threatens with an additional risk not only of CVD, but also an increase in premature mortality in both men and women.

Currently, cardioncological syndromes (COS) with a five-level classification system are used to differentiate the types of relationship between oncological diseases and CVD [15]. In particular, in patients with cardiovascular dysfunction, COS type III is characterized by a pro-oncogenic environment created by the release of cardiokines and high oxidative stress. У пациентов с ССЗ развивается тканевая гипоксемия из-за эндотелиальной дисфункции и недостаточного капиллярного кровотока. Patients with CVD develop tissue hypoxemia due to endothelial dysfunction and insufficient capillary blood flow. Tissue hypoxia contributes to the production of induced factor 1-alpha (HIF-1a), which is overexpressed in many types of cancer. In addition, HIF-1a performs several leading functions that contribute to the progression of cancer: changing the pathways of apoptosis, stimulating angiogenesis, enhancing glucose metabolism as the main substrate for tumor growth[16]. In addition to tissue hypoxia, an important role in the development of cancer in patients with hypertension is played by the release of cardigans, which are considered to be pro-oncogenes [17, 18]. A meta-analysis of 13 prospective studies showed an association of AH with certain types of cancer. Men suffering from AH are at a higher risk of developing prostate cancer, women are at a higher risk of developing breast and cervical cancer, liver cancer, pancreatic cancer, colorectal cancer and melanoma compared to the category of people without AH [19, 20, 21, 22]. In addition, regardless of gender, hypertension is a leading risk factor for brain cancer and kidney cancer, taking into account the proven role of the renin-angiotensin-aldosterone system (RAAS) and paracrine mechanisms of its locally formed components in the pathogenesis of cancer of these localizations[16]. The local paracrine and autocrine effect of RAAS components on adipocytes, whose activity is especially high in the kidneys, gastrointestinal tract, brain, adipose tissue, stimulates subclinical inflammation and thereby increases cardiometabolic and oncological risks [11, 21].

Pathophysiological parallels of the mutual influence of cancer and high blood pressure have long been the object of scientific research by many scientists. For the first time, the link between hypertension and carcinogenesis was shown by a group of scientists led by Professor Dyer in 1975. In her prospective fourteen-year study involving 1,233 men, she demonstrated the association of high systolic and diastolic blood pressure with a high risk of cancer mortality[23]. The results of another prospective cohort study showed an absolute association of AH with an increased probability of cancer development regardless of its course (stable, controlled, uncontrolled): patients with AH had a high risk of mortality from cancer of any localization (up to 15%) compared with patients without AH with normal blood pressure[24]. Further, studies by scientists Silveira E, et al and Kaprin A. et al proved a higher risk of carcinogenesis (56-68%) in patients with AH than with other CVD [25, 26].

Based on the results of our scientific work, a significantly significant relationship was shown between AH and the risk of developing oncological diseases, both in the main group and in the comparison group, which explains the commonality of cancer and AH risk factors and common pathophysiological mechanisms in the genesis of these diseases (systemic inflammation, apoptosis disorders, an increase in the number of reactive oxygen species and oxidative stress)[27]. We also found a high incidence of cancer with increasing age, both in the male and female populations, reaching maximum values in the age groups over 70 years. According to the latest statistics, every year in Russia the number of newly diagnosed oncological diseases increases. So, in 2021, 600,000 new cases of cancer were detected (337.1 people per 100,000 population) [28]. At the same time, people over 60 years of age were more likely to get cancer: the incidence in men was 72.1%, in women - 65.8%. The maximum level was observed in the group of people over 70 years of age (1406.6 cases per 100,000 population). The prevalence of oncological diseases in this group is explained by the duration of exposure to carcinogenic factors (ultraviolet radiation, tobacco smoke, household and industrial chemicals, trans fats, viruses, chronic diseases, metabolic disorders), as well as the accumulation of genetic mutations with age, the number of which each person doubles every 8 years[29, 30].

With age, the prevalence of AH increases, which does not depend on income level and is the same in low-, middle- and high-income countries [31, 32]. The increase in the frequency of hypertension with age has been confirmed by the results of numerous population studies. Since the observed increase in life expectancy is accompanied by an aging population, in the near

future, an increase in the number of both new cases of hypertension to 1.5 billion patients and 33 cancer is predicted[33], which determines the high relevance of the problem we are covering.

CONCLUSION

The results of our research complement the presentation in the field of the studied problem. MS is equally a risk factor for CVD and cancer. AO is associated with an increased risk of developing cancer of various localization, while the greatest risk is associated with grade I obesity, metabolic disorders, and the age of patients. The presence of CVD, in particular AH, increases the risk of developing cancer even in the absence of metabolic disorders, and in the presence of MS, the probability of developing a tumor process doubles.

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Authors' contribution:

concept and design of the study — M. Osadchuk, O. Mitrokhina, I. Vasileva;

collection and processing of material—O. Mitrokhina, I. Vasileva;

statistical data analysis—O. Mitrokhina, I. Vasileva;

writing the text — I. Vasileva, O. Mitrokhina;

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