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Review Article

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Obesity as a Relative Risk Factor for The Reproductive System Cancer.

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Summary

The article examines the possible effect of metabolites synthesized in adipose tissue on carcinogenesis, in particular in the organs of the reproductive system.

Keywords: Obesity, Breast cancer, Cervical cancer, Ovarian cancer, Corpus uteri cancer.

Obesity is a serious medical, social and economic problem in modern society. Its relevance is determined, first of all, by its high prevalence. According to epidemiological forecasts, while maintaining the existing rate of increase in obesity, it is assumed that by 2025 it will suffer from 30% to 50% of the population of economically developed countries [1]. Obesity is not just an excess of body fat, it is a complex pathology, which is currently regarded as a chronic recurrent disease that contributes to the manifestation and development of many concomitant diseases that shorten the life expectancy of a person and worsen its quality. When analyzing epidemiological data not only in our country, but also in the world (Figure 1), it can be concluded that, despite a large number of new developments, both in diet therapy and in drug treatment, the number of obese patients is increasing. in all age [2].

In the United States, this problem has reached the size of a national epidemic: 32% of the country's adult population is diagnosed with obesity, and 66.3% of adults and 17% of adolescents and young people aged 12 to 19 are overweight. Another 16% of young people are at risk of adding these statistics in the near future [3].

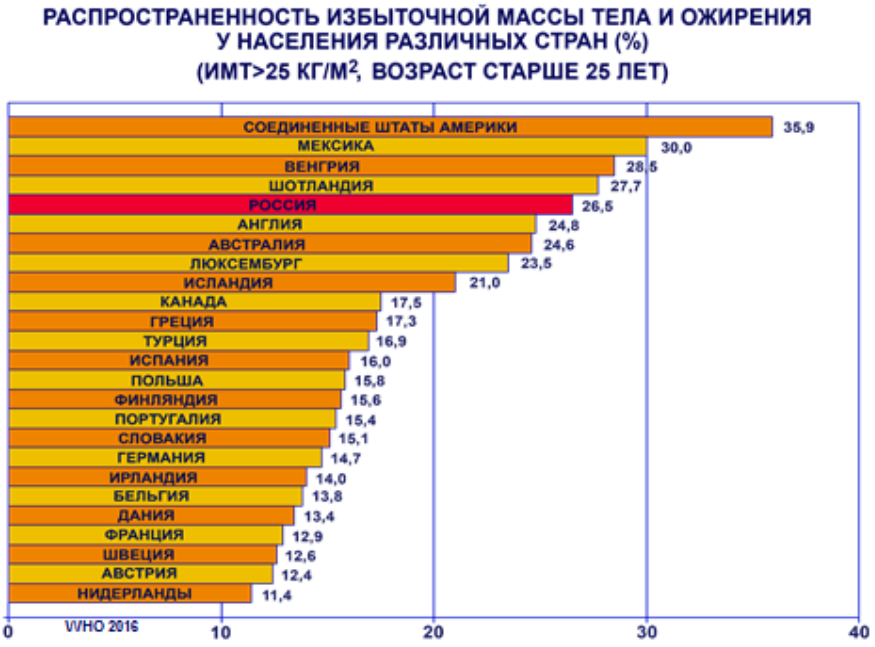

Figure 1: Rice.1 (https://www.statista.com/statistics/1065611/share-of-overweight-and-obese-people-worldwide/) [4].

At every stage of a woman's life, we are faced with such a complex pathological process as obesity. Numerous authors have described the effect of obesity on the reproductive system, menstrual cycle, gestation and pregnancy, psychological aspects of a woman's life, etc. at the same time, the combination of obesity with oncological diseases of the organs of the reproductive system, in particular, the cervix, mammary glands, ovaries, is not often covered. If we rely on statistical data, it has long been proven that the presence of excess body weight increases the risk of developing cancer of a particular localization. But the mechanisms of the effect of adipose tissue on various organs and systems are not described as the cause of malignancy. In our article, we would like to try to substantiate the possible impact of excess adipose tissue on the organs of the reproductive system based on an analysis of literature data and our own long-term experience in this area.

According to the International Agency for Research on Cancer, in 2016 more than 10 million people fell ill with malignant tumors in the world. In Russia, women are most often diagnosed with breast cancer. Cancer of the reproductive system occupies, in terms of frequency of occurrence, the fifth to eighth place [5-7].

According to the GLOBOCAN statistical service (2019), breast cancer ranks first in the structure of malignant neoplasms, cervical cancer is in fourth place, endometrial cancer is in sixth place, and ovarian cancer is in eighth place [8]. If we consider, in particular, neoplasms of the cervix, as one of the most important organs of the reproductive system, up to 529,800 cases are recorded annually in the world. Cervical cancer, this is 9% of all women with malignant neoplasms [9]. According to calculations, the incidence of cervical cancer by 2050 will double, reaching more than 1,000,000 new cases per year [10].

In Russia, 16,439 newly diagnosed cases of cervical cancer were registered in 2018. Malignant neoplasms of the cervix make up 5.2% and rank 6th after breast cancer (20.9%), skin cancer (16.7%), other localizations (10.2%), uterine body (8.0 %) and colon (7.4%) [11].

Undoubtedly, papillomavirus infection and the presence of dysplastic processes of varying degrees play a leading role in the pathogenesis of cervical cancer, but obesity, according to some researchers, is an additional factor of influence.

Before considering the processes occurring in adipose tissue, it is necessary to determine what types of obesity (gluteo-femoral and abdominal-visceral) and types of adipocytes (hypercellular-hypertrophic and hyperplastic) are currently identified. The nature of the distribution of fat is determined mainly by the hormones of the gonads and the adrenal cortex, and the conversion of androstenedione to estrone in adipose tissue plays a central role. A risk factor for cancer and other diseases associated with obesity is abdominal-visceral obesity, which is due to the specific anatomical and physiological properties of adipose tissue. It is better supplied with blood, metabolically most active, and adipocytes have a high density of beta-adrenergic receptors (stimulation of which leads to lipolysis) with a relatively low density of alpha-adrenergic receptors and insulin receptors (their stimulation suppresses lipolysis). The accumulation of adipose tissue in the thighs and buttocks is regulated mainly by the enzyme lipoprotein lipase; this area is characterized by the processes of lipogenesis, and the activity of lipolysis is low, and therefore, gluteofemoral obesity, as a rule, does not affect health and only affects the external appearance of a woman [12].

Intensive lipolysis of adipose tissue in the abdominal-visceral region leads to an increase in the content of free fatty acids in the systemic circulation, which causes metabolic disorders characteristic of abdominal obesity: insulin resistance, increased levels of glucose, insulin, VLDL-C and triglycerides in the blood [13].

A great difficulty in understanding obesity is created by the fact that adipose tissue is not metabolically homogeneous. In adipocytes there are alpha2- and beta-adrenergic receptors that promote lipolysis, the number and activity of which are not the same in adipocytes of different parts of the body, which creates the heterogeneity of adipose tissue. Differences were found in the action of insulin and catecholamines on fat depots of different localization. Parathyroid hormone causes lipolysis only in the fat depots of women and is intact in men. The sensitivity of fat in depots of different localization to lipolytic influences is heterogeneous. Fat breakdown occurs more actively in adipose tissue located in the chin, neck, supraclavicular and subclavian fossae. The most stable and difficult to decompose is the fat located on the anterior abdominal wall and especially in the buttocks. Abdominal depots undergo lipolysis more easily than subcutaneous ones. Different properties of fat deposits are due to the fact that the number of catecholamine receptors on the membranes of adipocytes located in the chin, neck, upper half of the chest, significantly exceeds the number of receptors in fat cells in the abdomen, buttocks, and thighs. It is clear that any methods of affecting adipose tissue cause lipolysis mainly in those fat deposits in which there are many catecholamine receptors, while the fat "apron" and "breeches" are practically not amenable to therapy. In addition to adrenergic receptors, the rate of lipolysis in fat depots is affected by different lipoprotein lipase activity: it is maximum in women in the thigh area, minimum in both women and men in the omentum.

For the assessment of obesity in relation to the risk of malignancy, both body mass index and the ratio of waist to hip circumference are decisive. Abdominal obesity is more often accompanied by the risk of developing malignant neoplasms. The increased risk of malignant neoplasms is caused by changes in hormonal status. There are several models to prove this, but steroid hormones play a key role. Adipokines in visceral adipose tissue increase the activity of aromatase in adipose tissue, especially with a high body mass index, which leads to an increase in the level of estrogen in blood serum and tissues [14]. In breast cancer, there was a 10-fold increase in the level of local estrusogenov, which proves the connection "tumor-adipocytes".

According to modern concepts, the main factor that stimulates the cells of estrogen-dependent organs and tissues (mammary glands, cervix, endometrium) to pathological growth is not the level of the main female hormone estradiol itself, but a disturbance in the balance of its metabolites - estrogens, which have a different ability to activate cell proliferation [15].

It has now been established that estrogens are catabolized in hydroxylation reactions with the formation of 2-hydroxyestrone (2-OHE1) and 2-hydroxyestradiol (2-OHE2), 16α-hydroxyestrone (16alpha-OHE1) and 16α-hydroxyestradiol (16alpha-OHE2). Of these substances, 2-hydroxyestrone and 16α-hydroxyestradiol are known to have estrogenic activity and are carcinogenic. In the model system of cells of the lobular-ductal epithelium of the mammary glands of mice and humans, it has been established that they have genotoxic properties. 2-hydroxy- and 4-hydroxyl metabolites are converted by the enzyme catechol-O-methyltransferase into anticarcinogenic metabolites (2-methoxyestrone and 2-methoxyestradiol, 2-hydroxyestrone and 2-hydroxyestradiol 3-methyl ether, 4-methoxyestrone and 4 methoxyestradiol, -hydroxyestrone and 4-hydroxyestrone 3-methyl ether) [16].

Thus, 2-hydroxylation and 16α-hydroxylation determine the ratio of carcinogenic and anticarcinogenic metabolites.

16α-OHE1 is a potent estradiol agonist. The activity of this metabolite is 8 times that of estradiol. Therefore, the high rate of formation of this metabolite in a woman's body causes a state of hyperestrogenism, despite the normal concentration of estradiol in the blood.

There is also evidence that the 16alpha-OHE1 metabolite has the ability to cause various genotoxic damage to DNA molecules, which can lead to the malignancy of target cells [17].

Since adipocytes accumulate androgens and aromatize them into estrogens, it is possible to define adipose tissue as the main depot of estrogen metabolism.

Metabolic syndrome with hyperinsulinemia leads to an increase in the production and level of insulin-like growth factor-1, which has a mitogenic effect and potentiates the effect of estrogens on receptors. Hyperinsulinemia also leads to a decrease in the level of sex-steroid-binding globulin, which in turn leads to an increase in free steroid hormones (for example, with a BMI> 30, the number of free estrogens and testosterone increases 2-3 times). An increase in leptin secretion, which correlates with the number of adipocytes, leads to an increase in leptin receptors in breast tissue (in 92% of breast cancers) and a low survival rate in this category of patients. The Framingham study [18].

Showed an increased risk of breast cancer in obese women. A relative risk of 1.8% was established for patients with grade III obesity. Similarly, an American study (495,477 women) confirmed the results of the Framingham Study, found a link between visceral obesity and tumor size, lymph node involvement and mortality. A relationship has been demonstrated between obesity and endometrial cancer. More than one third of endometrioid carcinomas can be associated with obesity. The relative risk in women with a body mass index of more than 30 compared with normal weight is 4.5% higher. In contrast to breast cancer, obesity-associated endometrial cancer occurs predominantly in women under the age of 50. The association of ovarian and cervical cancer with obesity has been proven, although less pronounced. The malignancy of adenomatous polyps of the colon is now considered proven; a lower rate of apoptosis in the intestinal mucosa has been revealed. This result suggests that insulin is able to accelerate the process of malignancy by inhibiting apoptosis. In a large study by Calle et al / USA [19, 20]. Over 16 years, more than 900 thousand patients were observed ... At the beginning of the observation, they did not have any neoplasms. During this time period, 57,145 deaths were reported from cancer. In grade III obesity, mortality from malignant neoplasms increased by 52% in men (RR = 1.52) and 62% in women (RR = 1.62). 14% and 20% of all cancer deaths in men and women, respectively, may be associated with overweight or obesity (Figure 2).

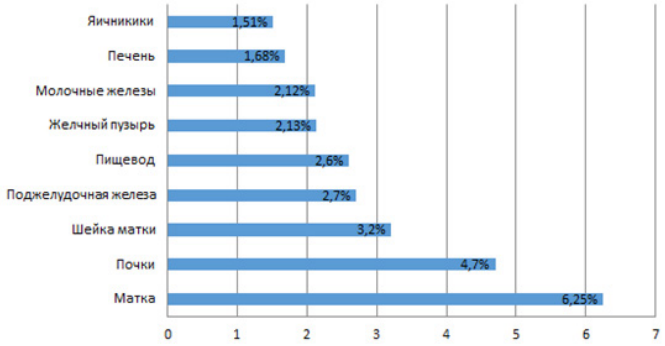

Figure 2: Rice. 2. Coefficient of the likelihood of developing cancer in women, BMI> 40 (cervix, liver, ovaries - BMI> 35; esophagus, gallbladder - BMI> 30) [21].

Obesity can be considered not only as a risk factor for the development of tumors and an aggravating criterion for treatment (surgery, chemotherapy and radiotherapy), but also as a negative prognostic factor for already diagnosed malignant neoplasms.

Estrogen metabolism is a very complex process that is clinically significant for the emergence and development of neoplasms of the female reproductive system. In order to expand our understanding of this process, it is necessary to understand exactly which links of this metabolic chain are disrupted, which will allow you to purposefully and effectively restore hormone metabolism. It is advisable to strengthen the measures of pathogenetic prevention (elimination of the factors of the onset of the disease), which will make it possible to achieve more significant progress in the prevention and treatment of neoplasms of the female genital organs. Weight loss (elimination of excess adipose tissue) can be one of the steps towards the prevention of malignant neoplasms of various localization, including reproductive organs.

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