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HEREDITARY FACTOR AND RISK OF THYROID CANCER.

(Literature Reviews)

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Thyroid cancer is the most common oncological pathology of endocrine organs.

Despite the relatively modest place (1-2%) in the general structure of malignant tumors, the problems of the pathogenesis of thyroid cancer are extremely relevant in recent decades, due to the trend of increasing prevalence of this disease. Thus, in the period from 1995 to 2008, the incidence of thyroid cancer in the world and in Russia increased from 2.8 to 6.3 cases per 100,000 population. In most countries of the world, the incidence of thyroid cancer increases by 4% annually [11, 55].

2019 year More than 230 cases of cancer a were registered in the Republic of Uzbekistan in 2019 более 230 the thyroid gland. In the structureof oncology, it makes up 0.9% , the incidence rate per 100 thousandepeoplея was 0.7 (M. N.Tillyashaykhov, 2019).

According to A.Mericansky About the cancer center OIn fact, approximately 17,000 new cases of thyroid cancer are reported annually in the United States. Themost frequent pathohistological forms of thyroid cancer are papillary and follicular adenocarcinomas, which account for 50-60% and 10-20% of all thyroid malignancies, respectively.

Differentiated forms of thyroid cancer are characterized by a long, asymptomatic course, calculated over years. At the same time, in a fairly large number of patients (up to 20%), the first symptoms of the disease may be associated with the appearance of metastases to the cervical lymph nodes, lungs, and bone tissue. At the same time, the primary tumor may not be detected by routine examination methods, since the size of the primary focus is often less than 1 cm, and significant lung damage or the development of pathological bone fractures at the sites of metastasis of tumor cells in the so-called "latent" cancer are not only unexpected forms of pathology, but also lead to delayed inadequate treatment. The problems of the etiology and pathogenesis of thyroid cancer, the pathogenetic justification of new principles for diagnosing the disease, the development of neoplastic metastasis processes, and the evaluation of the effectiveness of complex therapy require further consideration, despite a significant number of works by domestic and foreign authors devoted to this problem [9, 24, 28, 37, 38].

The classification of thyroid tumors developed by WHO (1989) is based on the development of neoplasms from two types of follicular cells (A and B), parafollicular C cells and non-thyroid cells. A-cells under the influence of carcinogenic factors are a source of development of differentiated forms of thyroid cancer, in particular papillary and follicular adenocarcinoma, as well as undifferentiated cancer. B cells that are absent in the thyroid gland under normal conditions occur more often in autoimmune diseases of the thyroid gland, from which, in turn, follicular and papillary thyroid cancer can form. C-cells are a source of medullary cancer formation [37, 44].

Papillary and mixed papillary-follicular cancers account for about 60% of all malignant thyroid diseases. Meanwhile, follicular cancer is less common than papillary cancer and mainly occurs in elderly and senile individuals [10, 37, 48].

A point of view is expressed regarding the molecular and cellular mechanisms of carcinogenesis under the influence of polycyclic aromatic hydrocarbons. The latter have

the ability to convert visible radiation into ultraviolet radiation, which induces the development of mutations and oncogenic transformation of cells [23, 35].

In studies Bartschby H. Bartsch (2004) concerning the role of N-nitrosamine compounds in the pathogenesis of cancer of various localization, it was shown that nitrosamine loading in humans is not only alimentary exogenous, but also occurs in the process of enhanced endogenous synthesis of nitric oxide (NO) in the body during chronic inflammatory processes with the participation of inducible NO synthetase.In turn, NO is a source of formation of carcinogenic nitrosamines, reactive acid-d-and nitrogen-containing compounds that damage DNA.

A number of studies have suggested the role of random somatic mutations in thyroid epithelial cells in their oncogenic transformation and subsequent development of thyroid cancer. In accordance with this concept, most cases of breast cancer, regardless of the histological variant, are sporadic. However, according to the results of observations by other authors, individual families can detect from 2 to 8 relatives suffering from thyroid carcinoma. Such inherited cases are referred to as familial variants, which account for up to 35% of cases in medullary cancer and 2.5-6.3% in papillary and follicular thyroid cancer. Moreover, cases of familial non-mullary thyroid cancer differ from sporadic ones by a more aggressive course, a pronounced tendency to multifocal growth, and extrathyroid invasion.

Familial papillary adenocarcinoma The thyroid gland accounts for about 5% of all papillary adenocarcinomas and, unlike sporadic adenocarcinomas, is clinically more aggressive. The researchers report that familial papillary adenocarcinoma tends to be a bilateral, multi-focus lesion, often with vascular invasion and metastasis to regional lymph nodes. In this pathology, the probability of relapse and long-term metastasis is higher than in sporadic forms [13, 30, 52].

A detailed study of the role of hereditary factors in the etiology and pathogenesis of medullary thyroid cancer is presented in the works of G. V. Rumyantseva et al., (2006, 2007) and a number of other authors [44]. As is known, medullary thyroid cancer is a rare disease that accounts for only 5-7% of all cases of thyroid cancer, and the sporadic form of medullary thyroid cancer is observed in 70-80% of cases, while the main (hereditary) with autosomal dominant inheritance type is noted in 20-30% of cases.

The clinical picture of hereditary medullary thyroid cancer is characterized by earlier cell malignancy, multicentric tumor growth, and damage to both lobes of the thyroid gland.

The familial form of medullary thyroid cancer is caused by mutations in the RET proto-oncogenelocated in the central region of the 10 pair of chromosomes encoding tyrosine kinase. Mutations in the RET proto-oncogene increase tyrosine kinaseactivity, inducing the development of medullary thyroid cancer, pheochromocytoma, or parathyroid adenoma. Currently, the diagnosis of familial medullary thyroid cancer is made only in cases where there are more than 10 carriers of RET mutations in the family (sick and healthy) [23, 38].

Subsequent studies revealed that thyroid cancer is familial in 6.7 % of cases: medullary thyroid cancer was hereditary in 26.5% of patients, papillary thyroid cancer in 4.3% [38]. Genetic screening among blood relatives with medullary thyroid cancer allowed us to diagnose the disease at the preclinical stage of the tumor and conduct preventive surgical treatment.Screening of components of multiple endocrine neoplasiasyndrome increased its detectability by 1.8 times. Germinal mutations of the RET proto-oncogene in patients with hereditary medullary thyroid cancer were more often localized in the 634th codon (in 63.6% of cases), with this mutation the most aggressive course of the disease was noted.

Currently, there is no doubt that the basis of malignant neoplasms is damage to the genetic apparatus in the germinal (sexual) or somatic cells, which makes these cells sensitive to the effects of external carcinogenic factors that can activate the malignancy process. Depending on which cell the initial mutation occurred in - sexual or somatic, cancer can be hereditary or non-hereditary. The genes responsible for transformation are normal cellular genes involved in controlling cell division, growth, and differentiation, but changing these genes ultimately leads toun controlled cell division.

In hereditary forms of the tumor, the initial changes (mutations) occurring in germinal cells will be detected in all cells, including in peripheral blood cells. However, the initial mutation in the germ or somatic cell is not sufficient to cause a tumor. If a similar mutation of an alternative gene occurs in a homologous chromosome, a malignant transformation may develop. All this also applies to hereditary forms of thyroid cancer.

According to modern concepts, thyroid cancer is a heterogeneous disease in terms of histogenesis, tumor structure, and etiological factors.

The first works related to the elucidation of the role of hereditary factors in the development of A-cell thyroid cancer were devoted to the description of families in which there was an accumulation of papillary-follicular or papillary thyroid cancer (PTC) among relatives of the 1st degree of kinship[16]. Familial variants of PTC and follicular thyroid cancer (FSC) account for 3-7% of all cases of these tumors. In such families, 2-4 relatives affected by similar tumors are detected, and in some-up to 8 affected relatives. [5]. The clinical picture and prognosis of familial PTC do not differ from those for sporadic forms of this disease.

However, population-based studies have shown that families with several cases of these cancers have already been identified have an 8.6-fold higher risk of developing cancer in their relatives than in the control group[9]. This risk increases when both parents develop thyroid cancer. In addition, the involvement of hereditary factors in the development of these cancers was confirmed by observations of papillary adenocarcinoma in monozygotic twins with subsequent development of bilateral breast cancer. The molecular defect responsible for the development of these forms of diseases is still unknown, but an active search for candidate genes is underway. Recently, data were published on the localization of the gene on the short arm of chromosome 19 (19p13.2)[6], responsible for the development of thyroid tumors, and the gene on the long arm of chromosome 14 (14q31), responsible for the development of multi-node goiter [12]. In addition, a gene on the long arm of chromosome 1 (lq21) associated with familial PTC in combination with kidney cancer is localized[14].

Hereditary variants also include the so-called "cancer family" syndromes, in which, along with breast, intestinal, stomach, endometrial and other neoplasms, several members of the same family are diagnosed with PPHD or FPHD. The most well-known is the association of A-cell thyroid cancer with familial полипозомcolon polyposis and its variants such as syndromesGardner's, Turkota. Thyroid cancer in the syndrome Gardner ('s disease (adenomatosis of the colon, skin fibroids and epidermoid cysts) occurs with a frequency of 1-3% of cases. Young women (20-30 years old) are more often affected. (the ratio of women to men is 10: 1). In most cases, the tumor in combination with these syndromesи- is multicentric and in 2/3 of cases precedes the detection of intestinal polyps. These features indicate the expediency of periodic examination of the colon in young patients affected by thyroid cancer, in order to detect intestinal adenomatosis, and, conversely, in patients with familial polyposis of the colon, a thorough examination of the thyroid gland is recommended. A number of patients with PTC associated with these syndromes have mutations in the APC (adenomatous poliposis coli) gene located in the long arm of chromosome 5 (5q21) and a number of other genes[17].

Hereditary forms of thyroid cancer include from 20 to 30% of cases of medullary thyroid cancer (MCT), which occurs due to the inheritance of a mutation in the RET proto-oncogene. In rare cases, inheritance can be discussed in papillary and follicular thyroid cancer. Based on the data of epidemiological studies, it can be concluded that some hereditary predisposition to thyroid cancer may also exist in patients who developed the disease after radiation exposure in childhood.

Medullary thyroid cancer (MCT) originates from parafollicular or C-cells and accounts for 5-10% of all thyroid cancers. Hereditary MCC accounts for 20-30% of all cases of this cancer. It can be inherited by an autosomal dominant type, being either an independent disease-a familial form (CMSC), or occur within the framework of the syndrome of multiple endocrine neoplasms (MEN) of types 2A or 2B.Identification of hereditary Breast cancer has been alleviated in recent years by direct genetic analysis of the RET proto-oncogene1,2. (*Proto-oncogenes are nucleotide sequences in the human genome that are homologous to the genome sequences of oncogenic viruses).

The gene responsible for the development of MCT was discovered in the cetromeric region of chromosome 10 in 1987, 5,6,7, and hereditary mutations of the RET protooncogene in MEN-2A, MCTCC, and MEN-2B were described in 1993, 5,6,7. The RET protooncogene consists of 21 exons and encodes the structure of the tyrosine kinase receptor. This membrane-associated receptor contains a caderin-like region in the extracellular domain, a cysteine-rich region located directly above the membrane, and an intracellular tyrosine kinase domain.

Mutations in these codons are found in more than 95% of cases of hereditary forms of MEN-2A and CCTCT. In addition, there have recently been reports of rare mutations, such as 9-base pair duplication in exon 8 in13CCTG13. In those rare cases where no mutation of the RET proto-oncogene was detected in the familial form MRCC, it was usually only a few members of the same family who were affected. De novomutations (for example, not detectable in parents) are detected in 4 to 10% of cases of MEN-2A and CCTCC and are localized in the allele, inherited from the patient14's father14.

Point mutations of the RET proto-oncogene lead to unregulated activation of the tyrosine kinase receptor. Mutations in both the extraa- (codon 634) and intracellular domains (codon 918) of tyrosine kinase lead to transformation of NIH 3T3 cells. Transgenic mice that receive a gene with codon 634 mutation in the calcitonin promoter region of C cells develop C-cell hyperplasia and MCT2121. Finally, these mutations were detected in the sporadic form of MCTC.

The earliest histological change that is detected in hereditary C-cell diseases of the thyroid gland is C-cell hyperplasia, which can be detected immunohistochemically using antibodies to calcitonin. C-cell hyperplasia can also occur in other diseases of the thyroid gland, for example, in thyroiditis or in cells adjacent to follicular tumors. Distinguishing between C-cell hyperplasia and a population of C-cells with a size corresponding to the upper limit of normal can be difficult. C-cell hyperplasia is not detected only in a small number of patients with CCTG. On the other hand, it is detected only in a small number of cases with sporadic MTC 22, 23.

The sequence of stages of histological changes in C-cells is characterized as hyperplasia, nodular hyperplasia, microscopic carcinoma, and finally, an obvious tumor. The familial form of MTC develops from C-cell hyperplasia and is a bilateral and multicentric tumor, while sporadic Breast cancer is usually a single tumor that affects one lobe of the thyroid gland.

In many families, the only manifestation of a mutation in the RET proto-oncogene is MCT. Clinically, breast cancer manifests itself at an older age and with mutations in exons 13 and 14 has a relatively more favorable prognosis compared to breast cancer in

MEN-2A9.

It remains definitively unclear whetherли Breast cancer is an independent disease or it is a variant of the MEN-2A syndrome, in which the genotype features cause a delay in the manifestation of its other components.

MEN-2B syndrome is represented by a combination of MSCC, pheochromocytoma, ganglioneuromatosis, marfanoid changes, and skeletal pathology. Hyperparathyroidism in this syndrome is almost never observed29. MSCT in MEN-2B flows significantly more aggressively than in MEN-2A. It develops at a younger age, usually up to 10 years, and often reveals the germination of the thyroid capsule, as well as regional and distant metastases.

The first step in the examination of a patient with MEN-2A or CCTCT is genetic analysis of the RET proto-oncogene (Figure 1). Since all known mutations are localized in exon 7, it is most justified and practical to conduct targeted research of this exon using polymerase chain reaction (PCR) or direct sequencing (*determination of the nucleotide sequence) of DNA. If a mutation is detected, a targeted examination of all relatives of the first degree of kinship is necessary to identify the carrier of the pathological gene. The test is performed after receiving the patient's informed consent and is repeated twice on different blood samples, in order to eliminate the possibility of laboratory error.

In the family in which the mutation was detected, 50% of relatives are not carriers of the pathological gene and their risk of developing the disease does not exceed that in the general population. These individuals do not need further and repeated examination. There are two fundamental approaches to individuals who have been diagnosed with a mutation.

In families with mutations in exons 13 or 14, C-cell pathology manifests later, usually at the age of 30-40 years, and the course of MCT is more often less aggressive. Therefore, in individuals with these mutations, it was suggested that a pentagastrin test should be performed annually, starting at the age of 10 years, and thyroidectomy should be performed only if pathological results of the pentagastrin test are detected.

Treatment of breast cancer involves surgical removal of all the tissues changed by the tumor process in the neck. Before this, it is necessary to reliably exclude a pheochromocytoma from the patient. A number of studies have shown that the survival rate of patients with breast cancer largely depends on the adequacy of surgical intervention. The latter implies a total thyroidectomy with bilateral removal of the cervical lymph nodes. Total thyroidectomy is indicated for both hereditary and sporadic forms of breast cancer.

In most cases, when the hereditary form is determined by bilateral C-cell hyperplasia, which can be a source of MSCC; in 5% of seemingly obvious sporadic cases, a hereditary form of MSCC is detected during further examination; finally, even with confirmed sporadic forms of the disease, the bilateral nature of the lesion occurs in 30% of cases. Removal of lymph nodes is indicated due to the fact that metastases in them are detected in 10% of cases with a primary tumor diameter of less than 1 cm and in 90% of cases with a palpable tumor. It is necessary to remove the lymph nodes and fiber of both the anterior and lateral areas of the neck from both sides.

Familial cases of PTC and FTC account for 3-7% of these tumors. Usually, 2 to 4 cases can be identified in a family, but the literature describes up to 8 cases of thyroid cancer in one family, while other family members may have had benign thyroiddiseases37-46. Recently, a French family with benign and malignant thyroid tumors with 47 cell47oxyphilia and a family with PPH and 48 papillary renal neoplasia was described48.

In most of the described familial cases of PTC, an association was found with autosomal dominant inheritance of some gene with low penetrance. In fact, it is most

likely a complex interplay of phenomena such as genetic heterogeneity, polygenic inheritance, and the additive effects of genotype and environmental factors. An active search for localization of candidate genes for familial forms of thyroid canceris underway. Recently, the localization of the gene responsible for the development of thyroid tumors with oxyphilia cells on chromosome47 19p13.2, as well as the proposed localization of the multi-node goiter (MNG1) gene in one Canadian family on chromosome 14q31, were published. However, in most cases of familial forms of PTC, mutations in these regions of the genome were not detected41. Finally, the gene for the familial form of PTC in combination with kidney cancer was localized on chromosome481q21.

The risk of developing thyroid tumors for individuals who underwent radiotherapy for cancer in childhood was 3 to 10 times greater than for individuals who were treated with ionizing radiation for benign tumors. This risk was 5 times greater for children treated for neuroblastomathan for children who received radiotherapy for other malignancies54.54 Epidemiological studies have shown that some people who have been exposed to radiation in childhood have a high risk of developing thyroid tumors.

Thus, the analysis of literature sources showed, that hereditary factors have a certain significance in the development of thyroid cancer. Genetically determined thyroidtumorsчаются differ in their own ways clinical treatment, in determining the tacticsa of treatmentя and prognosis of the disease.

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