DOI: https://doi.org/10.17816/2313-8726-2023-10-1-25-37

Phenomenon of hormone-dependent polyneoplasia of the female reproductive system

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ABSTRACT

BACKGROUND: Primary multiplicity of malignant tumors of the female reproductive system is the least studied area of clinical oncology. In addition, the steady rise in the number of patients and various localizations of polyneoplasia with lesions of the female reproductive organs necessitate a detailed study of this problem.

AIM: This study aimed to determine the incidence and risk factors and describe the clinical aspects of polyneoplasia of the female reproductive system for 2010–2021 in women seen at the Medical and Rehabilitation Center of the Ministry of Health of Russia, Moscow, and the University Clinical Hospital No. 4 of the I.M. Sechenov First Moscow State Medical University.

MATERIALS AND METHODS: We conducted a retrospective analysis of the case records of 147 patients with a confirmed diagnosis of polyneoplasia of the female reproductive system for 2010–2021, which accounted for 3.6% of all newly diagnosed neoplasms of the female reproductive system in the above medical institutions. Moreover, a continuous sampling method was used.

RESULTS: Breast cancer was the most frequent first tumor, combined with cancer of the contralateral breast in 27 (42.1%) patients, cancer of the uterine body in 4 (6.25%) patients, ovarian cancer in 4 (6.25%) patients, colon cancer in 4 (6.25%) patients, and thyroid cancer in 1 (1.5%) patient. Cancer of the uterine body was combined with breast cancer in 10 (35.7%) patients, ovarian cancer in 2 (7.1%) patients, thyroid cancer in 2 (7.1%) patients, and colon cancer in 3 (11.1%) patients. Endometrioid adenocarcinoma, pathogenic variant I was determined in 20 (71.4%) cases according to the histological structure. Thyroid cancer was detected in 7 (5.6%) cases; in all cases, it developed metachronously, and it was combined as the initial tumor with breast cancer in 1 (14.3%) case, uterine body cancer in 2 (28.5%) cases, and ovarian cancer in 1 (14.3%) case. As the second tumor, it was also combined with uterine body cancer in 2 (28.5%) cases and ovarian cancer in 1 (14.3%) case. The risk factors assessment led to the identification of several factors that are common in patients with hormone-dependent forms of primary multiple cancer, including obesity, diabetes mellitus, irregular menstrual cycle, history of proliferative diseases of the mammary glands, intake of thyroid drugs, uterine hyperplastic processes, and hypothyroidism.

CONCLUSIONS: Understanding the different aspects of the development and course of hormone-dependent polyneoplasia of the female reproductive system will help in developing approaches for follow-up monitoring of women who have been treated for a primary tumor and are at risk of developing a subsequent tumor of hormone-dependent organs, to prevent the recurrence of the disease and predict the subsequent tumor and ensure its timely detection.

Keywords: primary multiple cancer; mammary cancer; endometrial cancer; ovarian cancer; thyroid cancer; hormone-dependent polyneoplasia.

To cite this article:
Klyukina LA, Sosnova EA, Ishchenko AA, Davydov MM. Phenomenon of hormone-dependent polyneoplasia of the female reproductive system. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2023;10(1):25–37. doi: 10.17816/2313-8726-2023-10-1-25-37

Received: 12.11.2022 **Accepted:** 07.12.2022 **Published:** 17.03.2023

DOI: https://doi.org/10.17816/2313-8726-2023-10-1-25-37

Феномен гормонозависимых полинеоплазий органов женской репродуктивной системы

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АННОТАЦИЯ

Введение. Первичная множественность злокачественных опухолей органов женской репродуктивной системы представляет собой наименее изученную область клинической онкологии. Вместе с тем неуклонный рост числа больных, различные варианты локализаций полинеоплазий с поражением женских репродуктивных органов обусловливают необходимость детального изучения данной проблемы.

Цель работы — изучить частоту, проанализировать факторы риска и клинические особенности полинеоплазий органов женской репродуктивной системы за 2010–2021 годы у женщин, проходивших обследование и лечение в НМИЦ «Лечебно-реабилитационный центр» Минздрава России, Москва, и Университетской клинической больнице № 4 Первого Московского государственного медицинского университета им. И.М. Сеченова.

Материалы и методы. Методом сплошной выборки проведён ретроспективный анализ историй болезни 147 пациенток с верифицированным диагнозом полинеоплазий органов женской репродуктивной системы за 2010–2021 годы, что составило 3,6% всех впервые верифицированных новообразований органов женской репродуктивной системы в указанных выше лечебных учреждениях.

Результаты. Рак молочной железы чаще был первой опухолью и сочетался с раком второй молочной железы у 27 (42,1%) пациенток, с раком тела матки у 4 (6,25%), раком яичников у 4 (6,25%), раком толстой кишки у 4 (6,25%) и раком щитовидной железы у 1 (1,5%) пациентки. Рак тела матки чаще сочетался с раком молочной железы — у 10 (35,7%) пациенток, с раком яичников в 2 (7,1%) случаях, как и с раком щитовидной железы — 2 (7,1%) случая, а также зафиксированы 3 (11,1%) случая сочетания с раком толстой кишки. По гистологической структуре в 20 (71,4%) случаях определяли эндометриоидную аденокарциному, патогенетический вариант I. Рак щитовидной железы обнаружен в 7 (5,6%) случаях, во всех случаях развивался метахронно, сочетался как первая опухоль с раком молочной железы в 1 (14,3%) случае, раком тела матки в 2 (28,5%) случаях и раком яичников в 1 (14,3%) случае, как вторая опухоль сочетался также с раком тела матки в 2 (28,5%) случаях и раком яичников в 1 (14,3%) случае. Оценка факторов риска позволила обобщить ряд факторов, наиболее часто встречающихся у пациенток с гормонально-зависимыми формами первично-множественного рака: это ожирение, сахарный диабет, нерегулярный менструальный цикл, пролиферативные заболевания молочных желёз в анамнезе, приём тиреоидных препаратов, гиперпластические процессы матки и гипотиреоз.

Заключение. Понимание особенностей развития и течения гормонозависимых полинеоплазий органов женской репродуктивной системы позволит выработать тактику диспансерного наблюдения женщин, прошедших лечение первичной опухоли и находящихся в группе риска по развитию второй опухоли гормонозависимых органов, с целью профилактики не только рецидива заболевания, но и прогнозирования, а также своевременного выявления второй опухоли.

Ключевые слова: первично-множественный рак; рак молочной железы; рак эндометрия; рак яичников; рак щитовидной железы; гормонозависимые полинеоплазии.

Как цитировать:
Клюкина Л.А., Соснова Е.А., Ищенко А.А., Давыдов М.М. Феномен гормонозависимых полинеоплазий органов женской репродуктивной системы // Архив акушерства и гинекологии им. В.Ф. Снегирёва. 2023. Т. 10, № 1. С. 25-37. doi: 10.17816/2313-8726-2023-10-1-25-37

Рукопись получена: 12.11.2022 **Рукопись одобрена:** 07.12.2022 **Опубликована:** 17.03.2023

BACKGROUND

The problem of primary multiple malignant neoplasms (primary multiple cancer, or PMC) is becoming increasingly relevant globally because of a significant increase in the efficiency of treatment of the first neoplasm and, consequently, an increase in life expectancy, use of high-resolution examination methods, and application of various treatment methods, such as chemotherapy and radiation therapy, which contribute to the emergence of second tumors and improve the quality of recording of these tumors in connection with the creation of cancer registries [1]. Currently, according to official data, PMC is considered a common oncological pathology. In 2021, 58,217 primary multiple tumors were detected for the first time in Russia, which accounted for 10.0% of all newly diagnosed malignant neoplasms (for comparison, 9.5% in 2020, 9.3% in 2019, and 5.4% in 2018) [2].

The term "polyneoplasia or primary multiple malignant tumors" implies the presence in one patient of several independent malignant neoplasms, located in isolation and not metastases [3]. According to observations, a diagnosis of cancer increases the risk of developing a new malignant tumor by 20% [3]. The description by Abu Ali Ibn Sina (Avicenna) of a clinical case of bilateral lesions of the mammary glands was considered the first case of PMC, and in 1973, American doctor J. Pearson made the first description of a patient with PMC of the breast and uterus. It was Avicenna who first suggested that bilateral breast cancer (BC) could be caused by tumors arising independently from each other or metastasis. Over the past centuries, the study of PMC has achieved certain results, from the routine description of the development of several tumors in one patient to the study of the most characteristic combinations of tumors, identifying the causes and pathogenetic aspects of different variants of polyneoplasia. In Russia, in accordance with the generally accepted criteria of N.N. Petrov [4], tumors that have undoubted signs of malignancy, located in isolation, and the possibility of metastasis of the same tumor are excluded are considered primary multiple, i.e. the primacy of all tumor diseases in a patient must be proven. According to the pathogenetic principle, it is customary to distinguish the following:

1) hormone-related polyneoplasia (a combination of breast and endometrial cancer caused by prolonged hyperestrogenism);

2) radiation-induced polyneoplasia (rectal cancer that developed after radiation treatment of cervical cancer;

3) virus-dependent polyneoplasia (squamous cell cancer of the cervix, vulva, and vagina associated with infection with the herpes virus);

4) alcohol/diet dependence, nicotine dependence, genetically determined, and some others.

An important aspect is the time of occurrence of several tumors in one patient; therefore, according to the classification of I.F. Zisman and G.D. Kirichenko (1978), polyneoplasias can be metachronous, synchronous, metachronous–synchronous, and synchronous–metachronous polyneoplasias. Neoplasms are considered synchronous if a second malignant neoplasm is diagnosed <6 months after the detection of the first tumor. Tumors diagnosed with a time interval of ⩾6 months are considered metachronous. Synchronous and metachronous tumors are divided into multicentric multiple tumors in one organ, systemic tumors and tumors of paired organs, and nonsystemic multiple tumors of various organs [5].

The lack of data on primary multiple tumors in official sources by nosological groups, steady increase in the incidence of malignant polyneoplasia among women, and need for timely diagnosis of new tumor foci have become the basis for increased interest in this problem in oncology. In this regard, this study aimed to analyze the incidence, risk factors, and clinical characteristics of polyneoplasia of the female reproductive system for 2010–2021.

MATERIALS AND METHODS

Using a continuous sampling method, this study was a retrospective analysis of the medical records of 147 female patients with a verified diagnosis of polyneoplasia of the female reproductive system organs, who were treated at the National Medical Research Center "Treatment and Rehabilitation Center" of the Ministry of Health of Russia and the University Clinical Hospital No. 4 of the I.M. Sechenov First Moscow State Medical University for 2010–2021. This number accounted for 3.6% (147/4016) of all newly verified neoplasms of the female reproductive system. The study included data from female patients with two or more verified tumors and one of them was located in the organs of the female reproductive system. When processing the material, the sequence of tumor occurrence was established according to the classification of I.F. Zisman and G.D. Kirichenko (1978).

The incidence of PMC of the female reproductive system organs was distributed with the PMC of the breast of 2.2% (64/2942); PMC rates of the endometrium, ovaries, and uterine cervix were 6% (28/473), 5.7% (19/348), and 2.6% (5/193), respectively.

This study was performed as part of a dissertation and was approved by the local ethics committee of the I.M. Sechenov First Moscow State Medical University (extract from the LEC protocol dated 02/11/2021, No. 03-21). All study participants signed the necessary documents and provided voluntary informed consent to participate in the study and publish the data obtained.

RESULTS

The results of the data from female patients with PMC of the female reproductive system are presented in Table 1.

Among 147 cases of PMC, metachronous tumors predominated (*n*=101, or 68.7%), and synchronous tumors were identified in 46 (31.3%) cases. The average age of the patients at the time of diagnosis was 62 years.

Table 1. Distribution of primary multiple malignant tumors by organ

Localization of the first tumor	Total number of patients, *n* (%)	Localization of the second tumor, *n*									
		Mammary gland	Uterine body	Ovaries	Uterine cervix	Large intestine	Thyroid gland	Skin	Kidneys	Bladder	Vulva
Mammary gland	64 (100)	27	4	4	–	4	–	–	1	1	–
Uterine body	28 (100)	10	–	2	–	3	2	–	1	1	–
Ovaries	19 (100)	5	3	–	–	1	1	–	–	–	–
Uterine cervix	5 (100)	1	1	–	–	1	–	–	–	–	1
Vulva	3 (100)	–	–	–	1	–	–	–	–	–	–
Large intestine	16 (100)	3	2	1	–	–	–	–	–	–	1
Thyroid gland	7 (100)	1	2	1	–	–	–	–	–	–	–
Skin	3 (100)	2	–	1	–	–	–	–	–	–	–
Lungs	2 (100)	1	1	–	–	–	–	–	–	–	–

According to the data presented, bilateral BC and BC in combination with uterine body cancer (UBC) represented the largest share among polyneoplasias. BC was more often the first tumor and was combined with cancer of the other mammary gland in 27 (42.1%) cases, with uterine cancer in 4 (6.25%), ovarian cancer (OC) in 4 (6.25%), colon cancer (CC) in 4 (6.25%), and thyroid cancer (TC) in 1 (1.5%). The average interval for the occurrence of a second tumor with metachronous development was 12 years. Compared with CC, UBC, OC, and TC also developed more often as first tumors.

OC with metachronous development was combined with BC in 5 (26.3%) of the 19 cases and with uterine cancer in 3 (16.2%). A metachronous combination with TC was noted in 2 (10.5%) women. The average interval for the occurrence of a second tumor with metachronous development was 7 years.

Uterine cancer was more often combined with BC in 10 (35.7%) cases, with OC in 2 (7.1%) cases, and with TC in 2 (7.1%) cases. Another 3 (11.1%) cases were recorded along with CC. The average interval for the occurrence of a second tumor with metachronous development was 10 years. Simultaneously, uterine cancer was combined with OC in 1 (3.6%) patient and BC in 2 (7.1%) patients. According to the histological structure, endometrioid adenocarcinoma, pathogenetic variant I of high and moderate degrees of differentiation, was identified in 20 (71.4%) patients, and only in 8 (28.5%) women, uterine cancer corresponded to pathogenetic variant II (Table 2).

Few polyneoplasia cases were recorded with cancer localized in the cervix and vulva (*n*=5 (3.4%) and 3 (2%), respectively). As part of polyneoplasia, cervical cancer was more often the first tumor (*n*=4, or 80%), was synchronously combined with uterine cancer in 1 (20%) case, and metachronously combined with BC, CC, and vulvar cancer in 1 (20%) each case. According to the histological structure, cervical cancer in all cases was represented by squamous cell nonkeratinizing cancer associated with human papillomavirus (HPV). The average interval for the occurrence of a second tumor with metachronous development was 8 years.

In contrast to the above localizations, vulvar cancer was more often a second tumor (in 2, or 67% cases), and in all cases, it was metachronously combined with cervical cancer (in 2, or 67% cases) and CC (in 1, or 33.3%). The histological structure was consistent with that of squamous cell carcinoma.

Considering the important influence of the thyroid gland on the reproductive function of women, TC had characteristics as part of polyneoplasia. According to our study, TC was registered in 7 (5.6%) cases; in all cases, it developed metachronously and was the first tumor combined with BC in 1 (14.3%) case, uterine cancer in 2 (28.5%), and OC in 1 (14.3%). As a second tumor, it was also combined with uterine cancer in 2 (28.5%) cases and OC in 1 (14.3%). The average interval for the occurrence of a second tumor with metachronous development was 7 years. The histological structure was consistent with papillary and follicular carcinomas.

Table 2. Combination of pathogenetic types of uterine body cancer with breast and ovarian cancer in the composition of polyneoplasias

Pathogenetic type of uterine body cancer	Number of patients		Breast cancer (carcinoma)	Ovarian cancer (carcinoma)
	n	%		
Type I	356	75.2	11	4
Type II	117	24.7	3	1
Total	473	100%	14	5

DOI: https://doi.org/10.17816/2313-8726-2023-10-1-25-37

Table 3. Risk factors for polyineoplasia in the female reproductive organs

Localization of polyneo-plasias, *n* (%)	Risk factors															
	BMI 25–30 kg/m^2	BMI >30 kg/m^2	Pregnancy	Childbirth	Infertility	Irregular menstrual cycle	Diabetes mellitus	Fibrocystic mastopathy	Uterine fibroids	Hyperplastic processes of the endometrium	Late menopause	Ovarian cysts	Colon polyps	Pathology of the thyroid gland and hypothyroidism	Intake of COC for 3 years and longer	Intake of MHT for 3 years or longer
BC and BC, *n* = 27 (100%)	11	8	25	19	2	7	1	5	7	4	–	4	1	6	4	3
BC and UBC, *n* = 14 (100%)	3	9	13	10	1	3	5	4	3	4	–	5	–	3	3	1
BC and OC, *n* = 9 (100%)	6	1	9	7	–	3	–	2	2	4	–	3	–	1	2	2
BC and CC, *n* = 7 (100%)	2	4	7	7	–	1	1	1	3	2	–	1	3	2	1	–
BC and TC, *n* = 1 (100%)	–	1	1	1	–	1	–	1	1	–	–	–	–		1	–
UBC and OC, *n* = 5 (100%)	2	1	4	2	1	2	–	–	2	2	–	2	–	1	1	2
UBC and CC, *n* = 5 (100%)	1	2	5	4	–	–	–	1	1	2	–	–	1	1	2	–
UBC and TC, *n* = 4 (100%)	1	2	3	3	1	2	1	–	2	3	–	2	–	3	3	2
OC and TC, *n* = 2 (100%)	1	–	2	1	–	2	–	2	1	2	–	1	–	1	1	–
OC and CC, *n* = 2 (100%)	1	1	2	2	–	1	–	–	–	2	–	1	1	–	–	1

Note. BC, breast cancer; BMI, body mass index; CC, colon cancer; COCs, combined oral contraceptives; MHT, menopausal hormone therapy; OC, ovarian cancer; TC, thyroid cancer; UBC, uterine body cancer.

Considering the polyetiological nature of polyneoplasias, studying the risk factors for polyneoplasia of female reproductive organs according to their location was considered important; the results are presented in Table 3. In this study, many cases of polyneoplasia with damage to female reproductive organs are associated with metabolic disorders, irregular menstrual cycles, and previous proliferative processes in organs affected by cancer. However, the small sample of cases only suggests a possible relationship.

DISCUSSION

In the analysis of various combinations of polyneoplasia of the organs of the female reproductive system, 51.7% of them were classified as hormone-dependent, which is of the greatest clinical interest. Hormone-dependent polyneoplasia is considered a polyetiological problem primarily because it is based on metabolic disorders with hyperestrogenism and the state of chronic anovulation. Researchers stated that estrogens have a genotoxic effect, which enhances proliferative activity in the tissues of the mammary gland, uterus, ovaries, and colon.

As the incidence of BC increases, the incidence of BC associated with malignant neoplasms of other organs also increases. BC and OC are genetically determined and associated with *BRCA1* and *BRCA2* mutations. The lifetime risk for women with *BRCA1* mutations is approximately 72% for BC (95% confidence interval (CI) 65–79%) and 44% for OC (95% CI 36–53%). Corresponding estimates for *BRCA2* are 69% (95% CI 61–77%) and 17% (95% CI 11–25%) [6]. However, synchronous or metachronous BC and OC tumors have also been verified in the absence of mutations in these genes, which suggests the development of polyneoplasia in response to simultaneous exposure to hormones and carcinogens [7]. To explain the presence of multiple similar cancers in female genital organs, the theory of the "secondary Müller system" was proposed [8]. According to this theory, the epithelium of the cervix, fallopian tubes, ovaries, and peritoneal surfaces

respond simultaneously to a carcinogenic stimulus [8]. Risk factors in this case were hyperestrogenic conditions such as obesity, perimenopause, chronic anovulation, polycystic ovary syndrome, estrogen-producing ovarian tumors, and uncontrolled estrogen replacement therapy [9]. This suggests that hormonal estrogenic effects may be responsible for the development of these concurrent cancers [9]. However, most studies analyzed a small number of patients; therefore, these predictors of tumor development and recurrence have not yet been clearly established [9]. According to T.N. Popova (2002), obesity is registered in 66.3% of patients with malignant neoplasms of the female reproductive system, that is, excess weight up to 10 kg is noted in 24.2% of women, up to 20 kg in 25.8%, and excess weight >20 kg in 33% of the patients. Vascular pathology, which accompanies obesity, was detected in 64.8% of the patients, and type 2 diabetes mellitus was noted in 17.7% of women with cancer of the female reproductive organs. According to S.Ya. Maksimov, in patients with BC, the relative risk (RRs) of uterine cancer were 9.0, 2.4, 2.2, and 3.6 in years 1, 5, 10, and 15, respectively [10].

The greatest pathogenetic similarity in the syndrome of hormone-dependent primary multiple tumors was noted for BC and UBC. Among 2,157 patients with uterine cancer, polyneoplasia was verified in 297 (13.8%) cases, and BC ranked first (32.3% in relation to PMC) [10]. According to S.Ya. Maksimov, in patients with UBC, the RRs of BC were 13.6, 5.3, 3.9, and 3.0 in years 1, 5, 10, and 15, respectively [10]. The researchers suggested that in patients with both BC and UBC, the risk of a second tumor is implemented to a greater extent in year 1, i.e. due to synchronous polyneoplasia. In these patients, typical severe reproductive and metabolic disorders were identified. Moreover, the predominance of hormone-dependent type I UBC (according to Ya.V. Bokhman's classification) and adrenal and involution types of BC (according to V.F. Semiglazov's classification) was noted [10]. Similar characteristics of uterine cancer as part of polyneoplasia were noted in the study by S.A. Bekhterova et al. (2018), who reported that PMC of the endometrium more often progressed metachronously according to pathogenetic variant I, was the first tumor, and was more often combined with hormone-dependent tumors of other localizations, OC and BC, in both synchronous and metachronous development [11]. The results of previously published studies are also consistent with the results of our study.

Diagnosis of polyneoplasia with OC is a difficult task because the tumor is asymptomatic for quite a long time and is often (up to 70% of cases) detected at stages III and IV. Therefore, among polyneoplasias, OC is more often detected as a synchronous or second tumor. Synchronous primary endometrial and OC is considered the most common combination [12]. This is confirmed by studies conducted by Russian authors. In their work, P.Z. Koutalia et al. [13] reported that in polyneoplasia, OC was most often combined with tumors of the breast (*n*=102; 38.63%), uterine body (*n*=79; 30%), colon (*n*=21; 7.81%), and cervix (*n*=19; 7.22%). In another large study, among 1992 patients with primary OC, polyneoplasia was morphologically verified in 191 (9.6%) patients. Most often, OC as part of polyneoplasia was combined with adenocarcinomas of the endometrium (38.7%), breast (35.1%), and colon (4.7%) [10]. S.A. Bekhterova et al. analyzed the incidence and combinations of polyneoplasia of the female reproductive system and showed that OC was most often synchronously combined with UBC (*n*=40; 67.8%), BC (*n*=7; 11.86%), and cervical cancer (*n*=6; 10.16%) and rarely with sigmoid CC (*n*=2; 3.38%). Metachronously, OC was more often combined with BC (*n*=18; 58.06%) and cervical cancer (*n*=4; 12.9%) [14].

HPV is significant in the occurrence of squamous cell carcinoma of the cervix (cervical cancer). Cervical adenocarcinoma represents a special histological variant; although both morphological types of cervical cancer have common risk factors, their contribution to pathogenesis is different. Thus, in cervical adenocarcinoma, obesity and metabolic disorders significantly contribute to pathogenesis compared with squamous cell carcinoma. Risk factors for the development of cervical adenocarcinoma include long-term (>10–12 years) use of combined oral contraceptives [15].

The analysis of polyneoplasia of cervical adenocarcinoma revealed cases of metachronous combination with BC. The incidence of metachronous cervical cancer ranges from 0.82% to 1.33% [16].

In patients with HPV, tamoxifen therapy increases the expression of high oncogenic HPV type 16 and 18 and oncoproteins E6 and E7 in cervical cancer cells [17]. R. Watrowski et al. observed a case of the development of papillary serous adenocarcinoma of the cervix following the intake of tamoxifen [18]. The development of endometrioid adenocarcinoma of the cervix after 6 months of tamoxifen therapy for invasive ductal carcinoma of the breast was also described by Nalini Sharma et al. (2017) [19]. HPV infection also plays a certain role in BC development, as reported in several studies [20–21]. E.M. Hennig et al. reported the presence of HPV type 16 DNA in breast and cervical tissues of patients with BC diagnosed with severe cervical intraepithelial neoplasia [21]. Although the routes of infection and transmission are not yet known, there is a possibility of HPV infection spreading to various organs and tissues with subsequent development of carcinoma.

Each factor characterizing metabolic, genetic, and reproductive disorders does not increase the risk of developing multiple primary tumors. The combination of various disorders in homeostasis creates a real risk for the development of polyneoplasia in the female reproductive organs. Given the small number of cases in our study, our results must be confirmed in larger cohorts, with preferential prospective follow-up.

Colon cancer

Many studies revealed that CC and cancer of the female reproductive organs represent a common combination.

However, researchers have reported that with the combination of CC and cancer of the female reproductive organs, we should not suggest only the hormonal mechanism of tumor development. Thus, according to the research by Yu.G. Payanidi et al., metachronous polyneoplasia of the uterine body and colon; in 84.0% of cases, CC was detected, which developed after UBC radiation therapy with an interval of ⩾8 years. Molecular genetic studies have shown that congenital defects in the DNA unpaired base repair system (*MSH2, MLH1,* and *MSH6*) were noted in 37% of female patients with PMC of the reproductive system and colon [22].

S.Ya. Maksimov suggested a pathogenetic polymorphism of cancer arising in various parts of the colon. According to the results, among the monitored 2,072 primary patients with CC, multiple organ primary tumors were identified in 164 (7.9%) women [10]. In 89.1%, CC was associated with adenocarcinomas of the uterus, ovaries, and breast. Metabolic disorders were more common when uterine cancer and BC was combined with colon carcinoma (81.8%). Moreover, 65.8% of its combinations accounted for the hormone-dependent type of uterine cancer and only 34.2% accounted for the autonomous type (p <0.05). In patients with rectal cancer as a part of polyneoplasia, the ratios of I (hormone-dependent) and II (autonomous) types of UBC were 40% and 60% (p <0.05), respectively.

Based on these results, the term "hormone-dependent" could apply only to tumors of the middle intestine.

Thyroid cancer

The onset of thyroid dysfunction occurs during the fertile period in women, leading to the disruption of menstrual function, folliculogenesis, and ovulation and is one of the main causes of miscarriage and infertility [23]. These disorders occur for several reasons. First, the reduced levels of triiodothyronine (T_3) and thyroxine (T_4) lead to a decrease in the production of sex steroid-binding globulin, resulting in an increase in the level of free androgen fractions and the concentration of 5α-dihydrotestosterone, a decrease in the secretion of estradiol, and an increase in the production of luteinizing hormone (LH), while the ratio of LH and follicle-stimulating hormone is disrupted, which induces anovulation [24]. Second, hypothyroidism is a common cause of secondary hyperprolactinemia because a decreased level of thyroid hormones leads to excess production of thyrotropin-releasing hormone (through a feedback mechanism), which causes an increase in the secretion of both thyroid-stimulating hormone (TSH) and prolactin [25].

Thyroid dysfunction leads to dyshormonal diseases of the mammary glands and has an equally significant effect on the proliferative, hyperplastic processes of the endometrium, for example, with the development of endometrial cancer of pathogenetic variant I [26]. In relation to OC and thyroid hormones, T_3 promotes the expression of inflammation-related genes, including cyclooxygenase-2 and matrix metalloproteinase-9, both of which may play a key role in tumor invasion or angiogenesis [27]. In a preclinical study, both T_3 and T_4 inhibited the transcription of genes involved in tumor suppression, growth differentiation factor 15 (GDF-15), insulin-like growth factor binding protein 6, cell cycle, and p21 and p16 proteins, thereby affecting the proliferation and survival of OC cells [28]. Excessive influence of thyroid hormones on the ovaries can lead to increased proliferation and invasiveness of ovarian tumors, thereby affecting the survival of patients with OC. Thyroid hormones regulate nucleic acid synthesis in lymphoid cells. Hypothyroidism can influence carcinogenesis through metabolic disorders, leading to hypercholesteremia, inhibition of lipolysis, which causes dysfunction of macrophages and cellular immunity, and metabolic immunosuppression. Thus, assessing the incidence and risk of TC along with polyneoplasias, which are characterized by a tendency to increase frequency and a long latent period, and by general stages of pathogenesis and risk factors appears important.

The incidence of PMC affecting the thyroid gland ranges from 5.4 to 20%, whereas many researchers note that in primary multiple malignant neoplasms along with TC, tumors of the female reproductive system significantly predominate [29]. According to most studies, extrathyroid tumors in patients with polyneoplasia are most often localized in the mammary glands [29]. Currently, etiological factors such as imbalance of thyroid hormones, iodine consumption patterns in the tissues of the mammary glands and thyroid gland, folic acid metabolism, imbalance of female sex hormones, and the thoroughly studied problem of overweight and obesity are being actively investigated.

The transmembrane protein sodium–iodine symporter (NIS) is involved in the uptake of iodide in the follicular cells of the thyroid gland and in the cells of the lactating mammary gland [30]. Iodine oxidation in the alveolar cells of the mammary gland occurs with the participation of lactoperoxidase, which is similar in structure to peroxidase in the thyroid gland. The NIS protein is predominantly expressed in the intracellular space, whereas in lactating mammary glands, NIS is located on the basolateral membrane [31]. Therefore, the researchers hypothesized that mislocalization of the NIS protein could lead to a discrepancy between the level of NIS expression and the noted radioactive iodine uptake. More than 40 years ago, BC tissue was found to absorb radioactive iodine; however, no absorption occurs in the cells of the nonlactating mammary gland [32]. Results from a retrospective single-center study in Portugal suggest that the risk of developing a second primary cancer is increased after radioiodine therapy, particularly at activity >200 mCi [33].

According to endocrinological studies, iodine deficiency can stimulate the secretion of gonadotropins, leading to a hyperestrogenic state, with relatively high production of estrone and estradiol and a relatively low ratio of estriol to estrone and estradiol. This change in the endocrine condition may increase the risk of BC [34]. However, excess iodide intake is also unfavorable for BC development because it

stimulates the transcriptional activity of estrogen receptor alpha (ER-α) [35].

According to many authors, the highest risk of BC is registered in hyperthyroidism, particularly in female patients with toxic nodular goiter [36]. Moreover, the risk of BC increases with increasing blood levels of thyroxine (a marker of the severity of hyperthyroidism) [37]. In addition, thyroxine is a proliferative factor for BC cells in vitro and can stimulate nuclear estrogen receptor alpha-dependent proliferation of BC cells bearing this receptor [38]. However, according to one study, the risk of BC varied depending on the treatment status of hyperthyroidism, with the risk of BC in female patients receiving treatment for hyperthyroidism being 38% higher than that in women without thyroid dysfunction [39]. Among postmenopausal women, the association between T_4 and BC risk was also stronger in women who are obese and had higher blood estrogen concentrations than in normal-weight women [40].

At present, the results of studying the effect of hypothyroidism on carcinogenesis cannot be called unambiguous because this condition can contribute to carcinogenesis, and growing tumors cause inhibition of thyroid function, which promotes tumor transformation of the organ through a negative feedback mechanism. An assessment of the interaction between hypothyroidism and BC shows opposite results; according to most studies, no increase was noted in the risk of developing BC with reduced thyroid function [41]. In a large cohort of postmenopausal women, the reduction in BC risk associated with hypothyroidism disappeared in women who received menopausal hormone therapy (MHT) for any period. Sh. Yuan et al. [42] revealed that high TSH levels and hypothyroidism were associated with a decreased risk of BC (mainly ER-positive tumors) and TC, whereas hyperthyroidism and elevated free thyroxine levels were associated with a higher risk of BC (mainly ER-positive tumors).

Certain results were obtained when studying the metabolism of folates during carcinogenesis. T. Zara-Lopes et al. revealed that changes in the methylenetetrahydrofolate reductase (*MTHFR*) gene, which is involved in folate metabolism (*C677T*), are significantly associated with an increased incidence of TC and BC [43].

The relationship between obesity and an increased risk of cancer has been known for many years; weight gain and obesity cause approximately 20% of all malignant neoplasms, and BC and TC are no exceptions [44]. Although the correlation between obesity and BC is quite known, the correlation with TC is a less studied problem. H.Y. Shin et al. conducted a large-scale case–control study and suggested that middle-aged people who are prone to gaining excess weight have a higher risk of developing papillary TC [45]. A study conducted in France also confirmed this hypothesis. In a study by F. Clavel-Chapelon et al., a significant direct relationship was identified between the risk of developing TC and BMI, particularly in women who gained weight from menarche to adulthood [46].

According to the results of Russian researchers, endometrial cancer and OC rank second and third, respectively, in the structure of polyneoplasias with damage to the thyroid gland [47, 48]. According to A.F. Romanchishen et al., TC was combined with BC in 28.8% (30/104) of cases, endometrial cancer in 18.3% (19/104), and OC in 13.5% (14/104) [47]. Concomitant endocrine metabolic disorders (obesity and type 2 diabetes mellitus), which represent undoubted risk factors for carcinomas, occurred in more than half of the patients with polyneoplasia of hormone-dependent organs [47]. The metabolic status of women with polyneoplasia of these localizations was characterized by hyperlipidemia. The authors concluded that the incidence of endometrial and ovarian carcinomas in patients with TC exceeds that in the population, which is facilitated by a decrease in the level of thyroid hormones [47]. Similar results were obtained by Z.A. Afanasyeva et al, who reported that a combination of TC with mammary gland carcinomas was established in 17 out of 73 (23.2%) patients and that with endometrial carcinoma was registered in 5 (6.8%) cases [29].

Several authors, when studying polyneoplasia with damage to the thyroid gland, discovered an equally interesting fact that in patients with polyneoplasia of the colon and rectum, the risk of TC was significantly higher [48–49].

Therefore, normal thyroid gland activity can be a factor in antitumor protection. Therefore thyroid hormone therapy is increasingly used in complex treatments and prevention of carcinogenesis of the organs of the female reproductive system.

CONCLUSION

Thus, given the increasing incidence of detection of PMC, particularly cancer of the female reproductive system organs, and insufficient knowledge of the problem, further research in this field becomes an extremely urgent task. The main aims currently are prediction, timely diagnostics and treatment, and prevention of the development of second tumors. What, first, can be achieved by a detailed study of risk factors for the possible occurrence of tumors of other localizations, which will enable the formation of risk groups for the development of polyneoplasia, to establish the most typical localizations and timing of the occurrence of second tumors? Timely detection of a second tumor at an earlier stage determines further prognosis. Therefore, closer clinical monitoring of women from high-risk groups for the development of polyneoplasia, integration of available diagnostic tests, and correction of risk factors are necessary regular activities throughout a woman's life. Dispensary follow-up performed in this light should aim not only at preventing disease relapse but also at early diagnosis of the second tumor, which is most often localized in the organs of the same system as the first tumor.

DOI: https://doi.org/10.17816/2313-8726-2023-10-1-25-37

ДОПОЛНИТЕЛЬНО

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.
Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.
Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.
Этическое утверждение. Исследование выполнялось в рамках диссертационной работы Л.А. Клюкиной и его проведение согласовано с локальным этическим комитетом Первого Московского государственного медицинского университета им. И.М. Сеченова (выписка из протокола ЛЭК от 11.02.2021 г. № 03-21).
Информированное согласие на публикацию. Все пациентки, участвовавшие в исследовании, подписали необходимые документы о добровольном информированном согласии на участие в исследовании и публикацию их медицинских данных.

ADDITIONAL INFO

Author's contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.
Funding source. This study was not supported by any external sources of funding.
Competing interests. The authors declares that there are no obvious and potential conflicts of interest associated with the publication of this article.
Ethics approval. The study was carried out within the framework of L.A. Klyukina's dissertation work and its conduct was coordinated with the Local Ethics Committee of the I.M. Sechenov First Moscow State Medical University (extract from the LEC Protocol No. 03-21 dated 02/11/2021).
Consent for publication. All the patients who participated in the study signed the necessary documents on voluntary informed consent to participate in the study and the publication of their medical data.

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