DOI 10.26724/2079-8334-2019-2-68-30-34
UDC 618.19+616-006+616-056.36+616.379-008.64

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BREAST CANCER IN WOMEN WITH DIABETES MELLITUS TYPE 2

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Prevalence of breast cancer in the women with diabetes mellitus type 2 and the effect of hypoglycemic therapy on the frequency of the cancer and survival rates were studied. A significantly higher risk of breast cancer was detected in the women with type 2 diabetes mellitus [OR = 3.30; 95% CI (2.59-4.22) p<0.001]. Obesity and decompensation of diabetes are the factors of oncogenesis in patients with type 2 diabetes. The influence different types of hypoglycemic therapy on the frequency and survival rate of patients with breast cancer has not been proven. The higher risk of death from breast cancer to 5 years in people with diabetes mellitus type 2 compared with the patients without diabetes was revealed [OR = 4.80; 95% CI (2.96-7.81) p<0.001].

Key words: diabetes mellitus, cancer risk, breast cancer, survival rate of patients.

The study is a fragment of the research project "Epidemiology of oncological diseases in patients with diabetes mellitus and the effect of antihyperglycemic drugs on oncogenesis markers" (registration number 0117U005263), included into the complex research work of the SHEI «Ivano-Frankivsk National Medical University» - "Pathogenetic mechanisms of development of changes in organs of the respiratory, endocrine, nervous systems in the modeled pathological conditions and their correction" (registration number 0117U001758).

Over the past decades, diabetes mellitus (DM) remains a priority issue in the health care system of many countries in the world. The social significance of diabetes is determined not only by the prevalence but also by high disability and mortality of the patients.

The results of the studies indicate a growth in the frequency of certain localizations malignant neoplasms (MN) in patients with DM. Currently, a scientific hypothesis about cancer as a possible complication of DM is being studied. Among the suggested mechanisms of association between the above diseases influence of obesity, hyperglycemia, hyperinsulinemia, cytokine imbalance and chronic inflammatory process are considered [8, 9].

Clinical observations indicate a significant prevalence of breast cancer (BC) in the women with DM type 2. The proven factor of oncogenesis with the given localization of cancer is hormonal imbalance. Hyperestrogenism and the increasing amount of estrogens receptor - α (ERα) in the epithelium of the mammary gland (MG) enhances mitotic processes and promotes BC [10].

There are several pathogenetic mechanisms of BC in women with DM type2. The first is associated with obesity and the activation of aromatisation of peripheral androgens, which leads to an increase in the concentration of estrogen in the whole fatty tissue and locally in the MG. The direct relationship between hyperestrogenism and the body mass index (BMI) has been proven in the women during the postmenopausal period. Upon availability hyperestrogenic conditions, proliferative effects are realized by stimulation of the local synthesis of insulin-like growth factor-1 (IGF-1) in the tissues of the glandular organs. The identified increased risk of primary multiple cancer in obese patients: a combination of endometrial cancer, MG, ovaries and colon [1, 14].

The second mechanism of oncogenesis in breast tissue is linked to the previous one and is realized through the hyperinsulinemia, wich associated with malignant cell transformation by genetic mutations against the background of high mitotic activity and inhibition of apoptosis [3,4]. Insulin stimulates the development of neoplasms and tumor progression through insulin receptors (IR) on membranes of healthy and malignant cells. In addition to the direct effect of inflammation, this hormone has a mitogenic effect by stimulating the synthesis of IGF, reducing the IGF binding protein in the liver and activating the IGF receptor (IGF-R), similar to estrogen. Stimulation of IR and IGF-R induces a cascade of phosphorylation reactions of proteins and activation of gene transcription [7, 13]. The expression of IGF in MG in patients with DM is increased due to the decrease in the level of sex hormones bound globulin (SHBG) and contributes to hyperestrogenism. Insulin and IGF-1 are able to stimulate endometrial and MG proliferation directly, without the involvement of estrogens. IGF and estrogens can simultaneously activate the early responses of some oncogenes that regulate cell growth and proliferation [1].

The third mechanism of oncogenesis in patients with DM is related to the effect of adipokins. High levels of leptin, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) promote the development and progression of BC [9]. In contrast to proinflammatory cytokines, adiponectin possesses insulin-sensitizing, anti-tumor and anti-inflammatory properties [11, 15].

Undeniable factor in the potentiation of oncogenesis processes in patients with DM is hyperglycemia, which causes the endocrine (insulin secretion) and progenotoxic (generation of oxygen active forms) effects associated with damage to the mitochondrial apparats. With increasing glycemia, the cell proliferation process is intensified [5].

Thus, hyperglycemia and oxidative stress, hyperinsulinemia, changes in the synthesis and activity of growth factors and cytokines, disorders of steroid production are components of predisposition to tumor`s growth, with subsequent activation of proliferation, weakening of differentiation and apoptosis. Taking into account the considerable prevalence of DM type 2 and increasing oncological morbidity, we have planned scientific study of this issue.

The purpose of the study was to assess the risk and prevalence of breast cancer in in women with diabetes mellitus and to investigate the dependence of cancer incidence and survival rate of patients from the kind of hypoglycemic drug.

Materials and methods. The study was performed on the basis of cancer cases analysis in patients with DM who were treated at the Precarpathian clinical oncology center and in the Ivano-Frankivsk regional clinical hospital in 2012-2017.

Statistical processing of the obtained results was carried out using the STATISTIKA-8 computer software and the package of statistical functions of the "Microsoft Excel" software with a personal computer, using the variation statistics method of analysis. The arithmetic mean value M, the mean error of the arithmetic mean m, the variant number (n), the reliability of the difference between the two arithmetic means «p» determined. The values of $p<0.05$ are considered reliable. The odds ratio (Odds ratio, OR), 95% confidence interval, the positive and negative predictive value were calculated to determine the risk of predicted events.

Results of the study and their discussion. During the 5-years observation period, oncological diseases were first diagnosed in 386 patients with DM. Among them, 367 patients (95.1%) have DM type 2 and 19 persons (4.9%) have DM type 1. Esteblished that cancer of rectum and lymphatic system were prevalented in patients with DM type 1, while cancer of skin, uterus, pancreas, prostate, stomach, lungs, breast cancer and colorectal localization were more often diagnosed in patients with DM type 2.

With the help of the statistical odds ratio method, it was determined that women with DM type 2 have a higher risk of developing breast cancer [OR = 3.30; 95% CI (2.59-4.22); $p<0.001$] and uterus cancer [OR = 2.13; 95% CI (1.54-2.93); $p<0.001$]. Regardless of the gender, an increased risk of pancreas [OR = 4.18; CI (2.86-6.10); $p>0.001$] was determined (table 1). According to the results of our study did not show an increased risk cancer of other localization (table 1).

Table 1

Risk of malignant neoplasms in patients with DM type 2

Cancer localization	Number of patients with DM type 2		Number of patients aged >35 without DM type 2		OR	95% CI	p
	Total	From MN	Total	From MN			
Breast cancer (women)	26918	80	368849	332	3.30	2.59-4.22	<0.001
Uterine cancer (women)	26918	43	368849	277	2.13	1.54-2.94	<0.001
Pancreas cancer	42532	34	658122	126	4.18	2.86-6.10	<0.001
Skin cancer	42532	46	658122	612	1.16	0.86-1.57	>0.05
Colorectal cancer	42532	21	658122	250	1.30	0.83-2.03	>0.05
Gastric cancer	42532	18	658122	226	1.23	0.76-1.99	>0.05
Pulmonary cancer	42532	18	658122	357	0.78	0.49-1.25	>0.05
Prostate cancer (men)	15614	12	289273	233	0.95	0.53-1.70	>0.05

Note: OR – odds ratio; 95% CI – 95% confidence interval.

Our results prove the results of other scientific research about prevalence of reproductive system cancer in women with DM type 2 [10].

It has been established that BC is the most common form of cancer in women with DM type 2, found in 80 patients. Most frequently it was diagnosed in persons aged 60-70 (50.0%), with almost identical frequency at the age of 50-60 and over 70 years (23.7% and 20.0% respectively). In women aged 40-50, breast cancer was detected with frequency of 6.3%. According to anthropometric data established that BC predominantly was diagnosed in obese women (78.7%), 16 persons had overweight (20.0%) and only one person had normal BMI (1.25%).

The obtained results coincide with the results of other studies that reproductive system cancer is common in women with obesity in the postmenstrual period, which is associated with excessive peripheral

activity of aromatase, which leads to local and general hyperestrogenism in the breast tissue. In addition, hyperinsulinemia promotes bioavailability IGF-1and its proliferative effects [1, 5].

Most frequently BC was diagnosed in patients with the duration of DM 5 - 10 years - in 41 women (51.2%), less frequently - up to 5 years of disease - in 17 women (21.3%) and in 12 persons duration of DM was 10-15 years (15.0%). Only 2 cases of cancer (2.5%) were diagnosed in women, who suffer from diabetes over 15 to 20 years. However, with an increase duration of DM more than 20 years, there was a tendency to increase the frequency of BC.

In most cases BC was diagnosed against a background of moderate severity DM - in 68 patients (85.0%). Patients had a mild and severe form of diabetes equally often (7.5%). At the time of the examination, 52 women (65.0%) had decompensation of DM with a level of glycosylated hemoglobin (HbA1c) > 7.5%.

It is known that hyperglycemia contributes to the energy provision of the pathological cancer cell proliferation, but Ferrero's study of Patricia has shown that the predictive value for survival of patients with breast cancer has a level of insulin, a state of insulin sensitivity, but not an HbA1c level [6].

The analysis of hypoglycemic therapy (HGT) in patients with DM and BC was performed during the last 5 years before the cancer diagnosis and after the cancer treatment. It was established that in the vast majority of cases, before the diagnosis of BC, in the HGT, patients used metformin - 53 persons (66.25%), most frequently in combination with sulfonylurea derivatives. It was found practically same frequency of BC in patients at different types of monotherapy: metformin, insulin and diet therapy (13.75%, 12.5% and 13.75% respectively). Overall, 63 patients (78.75%) had received tablets HGT before being diagnosed BC, and 17 patients (21.25%) had been treated with insulin therapy. After the BC treatment, the vast majority of the patients observed continued to take tablets form of hypoglycemic drug (HGD) - 53 persons (66.25%). The number of patients who needed insulin therapy increased to 27 people (33.75%) (table 2).

Table 2

Hypoglycemic therapy for patients with diabetes mellitus and breast cancer

Therapy type	Before cancer diagnosing		After cancer treatment	
	Number of patients (n=80)	Prevalence (%)	Number of patients (n=80)	Prevalence (%)
Metformin (monotherapy)	11	13.75	20	25.0
Metformin + sulfonylurea derivatives	33	41.25	24	30
Metformin + DPP-4 inhibitors	2	2.5	7	8.75
Metformin + glitazones	1	1.25	0	0
Metformin + insulin	6	7.5	17	21.25
Insulin (monotherapy)	10	12.5	10	12.5
Sulfonylurea derivatives (monotherapy)	5	6.25	2	2.5
Insulin + sulfonylurea derivatives	1	1.25	0	0
Diet therapy	11	13.75	0	0

Note: 1. % − in relation to all the breast cancer patients.

The results obtained lead us to a more profound analysis of HGT with the measurement of insulin levels, the main factor of oncogenesis and effective DM treatment.

During the study it was found that in the period of 2012-2017 among the 80 surveyed patients with BC on the DM background, 21 women died. 18 people died (22.5%) within the period up to 3 years, 3 women died (3.75%) up to 5 years and 59 patients (73.75%) have survive for more than 5 years.

Using the odds ratio statistical analysis, it has been proved that patients with BC on the background of DM type 2 have a greater risk of cancer deaths up to 5 years compared with the patients without diabetes (table 3).

Table 3

Risk of death up to 5 years in women with breast cancer on the background of DM type 2

Localization	Number of women with breast cancer and with DM		Number of women with breast cancer without DM		OR	95% CI	p
	Total	Have died	Total	Have died			
Breast cancer	80	21	15094	825	4.80	2.96 7.81	<0.001

Note: OR –odds ratio; 95% CI – 95% confidence interval.

Received results are the same as in research of Lipscombe L. L. and others. They prove that in women with diabetes of 40 percent increases mortality in first 5 years after the diagnostic of cancer that is probably caused by DM [12].

The reliable influence of different groups of hypoglycemic drugs (HGD) on survival rates of patients was not found ($p>0.05$).

Thus, the results of the study performed prove the increase risk of cancer selected localizations in patients with DM type 2. BC is one of the most common forms of cancer in women with uncompensated DM and obesity in the post-menopausal period. The reliable influence different groups of HGD on the incidence of BC was not detected. Almost the same number of cancer cases with different types of monotherapy: insulin, metformin and diet therapy indicate the important role of hyperinsulinemia (exogenous or endogenous) in the process of oncogenesis. The reliable influence of different groups HGD on the survival of patients with BC has not been proven, which may be explained by the preferential use of combined HGT and the necessity of more observations for analysis.

An increase in the cancer deaths risk within the period up to 5 years in patients with DM type 2 prompts the search for pathological mechanisms that aggravate the oncological diseases and may also adversely affect the anticancer therapy efficacy. For women with DM 2 should be performed screening test on the organs of the reproductive system. In future, scheduled to search for probable biochemical markers of oncogenesis in patients with DM and to study the influence of HGD different groups on their activity.

Conclusions

1. Women with DM type 2 have a significantly higher risk of breast cancer.
2. Obesity and decompensation of DM are factors of oncogenesis in the patients with breast cancer.
3. The effects of various types of HGT on the survival of patients with breast cancer have not been proven.
4. Patients with breast cancer on the background of DM type 2 have a higher risk of cancer deaths up to 5 years compared with patients without diabetes.

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Реферати

РАК МОЛОЧНОЇ ЗАЛОЗИ У ЖІНОК З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

Вацеба Т. С., Соколова Л. К.

Досліджено поширеність раку молочної залози у жінок із цукровим діабетом 2 типу та вплив

РАК МОЛОЧНОЙ ЖЕЛЕЗЫ У ЖЕНЩИН С САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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Исследована распространенность рака молочной железы у женщин с сахарным диабетом 2 типа и влияние

цукрознижуючої терапії на частоту раку та виживаності. У жінок з цукровим діабетом 2 типу виявлено підвищений ризик раку молочної залози [OR = 3,30; 95% ДІ (2,59-4,22); p<0,001]. Ожиріння і декомпенсація цукрового діабету є факторами онкогенезу у хворих з діабетом 2 типу. Вплив різних видів гіпоглікемічної терапії на частоту і виживаність хворих на рак молочної залози не доведено. Виявлено більш високий ризик смерті від раку молочної залози до 5 років у жінок з цукровим діабетом 2 типу порівняно з пацієнтами без діабету [OR = 4,80; 95% ДІ (2,96-7,81); p<0,001].

Ключові слова: цукровий діабет, ризик раку, рак молочної залози, виживаність пацієнтів.

Стаття надійшла 2.07.18 р.

гипогликемической терапии на частоту рака и выживаемости. У женщин с сахарным диабетом 2 типа выявлено достоверное повышение риска рака молочной железы [OR = 3,30; 95% ДИ (2,59-4,22); p<0,001]. Ожирение и декомпенсация сахарного диабета являются факторами онкогенеза у больных с диабетом 2 типа. Влияние различных видов гипогликемической терапии на частоту и выживаемость больных раком молочной железы не доказано. Выявлен более высокий риск смерти от рака молочной железы до 5 лет у лиц с сахарным диабетом 2 типа по сравнению с пациентами без диабета [OR = 4,80; 95% ДИ (2,96-7,81); p<0,001].

Ключевые слова: сахарный диабет, риск рака, рак молочной железы, выживаемость пациентов.

Рецензент Геращенко С.Б.

DOI 10.26724/2079-8334-2019-2-68-34-39
УДК: 616127-002-037-073+616.017

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ВИЗНАЧЕННЯ ДІАГНОСТИЧНОЇ І ПРОГНОСТИЧНОЇ РОЛІ ІМУНОЛОГІЧНИХ БІОМАРКЕРІВ У ПАЦІЄНТІВ З МІОКАРДИТОМ

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Метою роботи було встановити діагностичні та прогностичні імунологічні біомаркери порушення структурно-функціонального стану серця та персистенції серцевої недостатності у хворих з міокардитом. Досліджено 70 пацієнтів з гострим міокардитом із серцевою недостатністю II або вище функціонального класу за класифікацією Нью-Йоркської Асоціації серця (NYHA) та зниженою фракцією викиду (ФВ) лівого шлуночка (ЛШ), що складала ≤ 40%. Обстеження проводили в 1-й місяць від дебюту захворювання та через 12 місяців спостереження. Встановлено, що в дебюті захворювання міокардит характеризується наявністю активних запальних змін міокарду, які виявляються при магнітно-резонансній томографії серця і супроводжуються активацією імунопатологічних реакцій клітинного і гуморального типу, синтезом ефекторних Т-лімфоцитів, антиміокардіальних антитіл та прозапальних цитокінів, що обумовлює дилатацію та систолічну дисфункцію ЛШ. Доведено вплив високого вмісту антиміозинових антитіл (≥ 3,0 од. опт.) та антитіл до β_1-адренорецептора (≥ 0,35 од. опт.) в 1-й місяць від дебюту міокардиту на наявність активних запальних змін міокарду (набряку та гіперемії) через 12 місяців спостереження та високої активності сенсибілізованих до тканини міокарду Т-лімфоцитів (≥ 7,0 %) в 1-й місяць від дебюту міокардиту на наявність систолічної дисфункції ЛШ (ФВ ≤40%) через 12 місяців.

Ключові слова: міокардит, імунний статус, антитіла до міокарду, цитокіни, структурно-функціональний стан серця.

Робота є фрагментом НДР «Провести аналіз біомаркерів міокардиту та встановти предиктори його трансформації в дилатаційну кардіоміопатію» (№ держреєстрації 0118U003026).

На сьогоднішній день міокардит багатьма провідними вітчизняними і зарубіжними вченими розглядається як одна з найбільш складних проблем кардіології з точки зору діагностики, прогнозування перебігу та вибору оптимальної тактики лікування. Труднощі діагностики міокардиту обумовлені широким розмаїттям клінічної симптоматики, непередбачуваним перебігом та необхідністю застосування лабораторних і інструментальних методів дослідження, що однак не гарантує встановлення вірного діагнозу. Основним принципом діагностики міокардиту є застосування комплексного підходу, що включає дослідження імунного статусу, електрокардіографію і холтерівське моніторування ЕКГ, ехокардіографію та найсучасніші методики візуалізації серця - магнітно-резонансну томографію або однофотонну чи позитронну емісійну томографію [2, 3, 4, 12].

Тим не менше, слід зауважити, що нові можливості для вдосконалення діагностики та прогнозування перебігу міокардиту відкриваються завдяки останнім дослідженням щодо ролі імунопатологічних реакцій з проявами аутоімунізації, гіперреакції, імуносупресії в організмі хворого як патогенетичної основи запального процесу в міокарді [5, 6, 8]. Тому актуальним є з'ясування зв'язку між аутоімунним ураження серцевого м'язу та прогресуванням структурно-функціональних змін серця, що при несприятливому перебігу захворювання супроводжуються наявністю резистентної серцевої недостатності (СН) та завершуються формуванням фенотипу дилатаційної кардіоміопатії [7, 10, 12].

За кілька останніх десятиліть проведена велика кількість досліджень, які підтверджують провідну роль антиміокардиальних антитіл, імуноглобулінів різних класів, прозапальних і протизапальних цитокінів, реакцій клітинного імунітету та інших біомаркерів в прогресуванні дисфункції серця при міокардиті [2, 13, 14]. При цьому слід відзначити, що визначення рівнів