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THE INFLUENCE OF DIABETES-ASSOCIATED FACTORS OF ONCOGENESIS ON THE RISK OF BREAST AND ENDOMETRIAL CANCER AND ON THE SURVIVAL OF WOMEN WITH THIS CANCER

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Summary

Introduction. Patients with type 2 diabetes mellitus (T2D) have an increased risk of cancer of different localizations. Identification and correction of diabetes-associated factors of oncogenesis can be important in cancer prevention.
The aim of the study. To investigate the influence of diabetes-associated factors of oncogenesis on the formation of the risk of breast cancer (BC) and endometrial cancer (EC), as well as on the survival of women with the indicated localization of cancer, and to develop a method of calculating the predicted risk of BC and EC in women with T2D.
Materials and methods. The study includes the results of a retrospective epidemiological analysis of cancer cases in patients, residents of Ivano-Frankivsk region with T2D during 2012-2016, with an analysis of 5-year survival of patients. Statistical processing of the results was conducted using STATISTIKA-12 (StatSoft Inc., USA). The impact of the pathogenetic factors of T2D on the development of BC and EC was evaluated through multifactorial analysis and ROC-analysis in the Medcalc v.19.1.6 program. The coefficient of predicted cancer risk was determined using mathematical modelling and a logistic regression equation. Kaplan-Meier cumulative survival analysis and Cox-Mantel Test were used to assess patient survival.
Results. BC and EC were most often diagnosed in women of postmenopausal age, with obesity, with a duration of T2D > 5 years, on combined antidiabetic therapy. Among women with BC, who take secretagogues 67 % had obesity and 24 % were overweight, with EC – 54 % and 27 % respectively. A new method to calculate the predicted risk of BC and EC (Y) in women with T2D has been introduced. The accuracy of the mathematical model for calculating the Y index is 76.24 %. It was proved that coefficient Y increases in women with obesity ($p<0.001$), duration of T2D > 5 years ($p<0.001$), on combined therapy with non-secretagogues and secretagogues ($p<0.05$). It was found that T2D increases the risk of death within 1 year in women with both types of cancer ($p<0.05$). A worse 5-year survival rate was found in women with EC stage I treated with drugs that increase blood insulin levels ($p<0.05$), as well as in women with EC stage II with HbA1c > 8.0 % ($p<0.05$).
Conclusions. Obesity, duration of diabetes > 5 years, and use of secretagogues in obesity increase the risk of breast and endometrial cancer in women with T2D. The use of antidiabetic drugs that contribute to iatrogenic hyperinsulinemia may negatively affect survival in obese women with breast and endometrial cancer, both by increasing the risk of cardiovascular events and by hyperactivating insulin signaling. Decompensation of diabetes reduces the 5-year survival of patients with breast cancer and endometrial cancer. Detection of a predicted high-grade cancer risk ($p = 0.7-1.0$) may be an indication for correction of factors of oncogenesis and cancer screening in women with T2D.

Keywords: **diabetes, predicted cancer risk, breast cancer, endometrial cancer, patient survival**

INTRODUCTION

Diabetes mellitus (DM), along with cancer and cardiovascular diseases, remains one of the main causes of mortality worldwide. As of 2021, there are 537 million people with diabetes registered in the world, the absolute majority of whom (526 million) are people with type 2 diabetes (T2D) (98 %). WHO experts predict an increase in the number of diabetes patients to 647 million people by 2030, to 783 million by 2045 [1].

Along with the increase in the number of patients with DM, a progressive increase in the frequency of malignant diseases (MD) has been proven. In 2020, 19.3 million new cases of cancer were registered in the world. By 2040, the number of cancer patients is expected to increase to 28.4 million cases, a 47 % increase from 2020, with a greater increase in developing countries [2]. The high level of chronic emotional stress in Ukraine has a significant impact on the occurrence and severity of DM [3].

Numerous studies have proven the significant prevalence of MD and the increased risk of cancer of various localizations in patients with DM [4]. The vast majority of studies concern patients with T2D. Dysmetabolic disorders that cause dysregulatory effects at the level of intracellular signaling pathways are studied as factors of oncogenesis in DM [5].

Breast cancer (BC) and endometrial cancer (EC) are among the most common forms of cancer in women. According to the 2020 World Cancer Registry, the share of BC among all cancer cases in women was 24.5 % (2 million 254 thousand), and uterine cancer was 5.0 % (460 thousand). Mortality from BC among women who died because of cancer in 2020 was 15.5 % (682 thousand) and from uterine cancer about 2.5 % (110 thousand) [2]. In Ukraine in 2020, the part of BC among all cancer cases in women was 21.5 %, and uterine cancer was 10.0 % [6].

Taking into account the increasing prevalence of diabetes, as well as the proven susceptibility to cancer in people with diabetes, it is reasonable to state that the increase in cancer incidence may be due to the proportion of people with diabetes. The study of diabetes-associated factors of oncogenesis and methods of their correction can be one of the significant methods of primary cancer prevention.

THE AIM OF THE STUDY

To investigate the influence of diabetes-associated factors of oncogenesis on the formation of the risk of breast cancer (BC) and endometrial cancer (EC), as well as on the survival of women with the indicated localization of cancer, and to develop a method of calculating the predicted risk of BC and EC in women with T2D.

MATERIALS AND METHODS

The selection of patients with T2D among women with MNS of the breasts and corpus uteri was conducted based on the analysis of data from the RCR on the accounting of concomitant diseases. The study involved the examination and analysis of archived documents, including medical records of patients of the Carpathian Oncology Center, the Ivano-Frankivsk Regional Clinical Hospital, and medical institutions of the Ivano-Frankivsk region for the period 2012-2016.

Official information on the number of patients with T2D was obtained from the state statistical reporting form No. 12 «Report on diseases registered in patients living in the service area of a medical and preventive institution». Information on the clinical characteristics of patients with diabetes, data on the course and antidiabetic therapy (ADT) was obtained on request from endocrinologists of medical institutions in the Ivano-Frankivsk region. The sixth edition of the TNM classification of American Joint Committee on Cancer was used to characterize the tumors.

Statistical processing of the results was carried out with the computer program STATISTIKA-12 (StatSoft Inc., USA) using the package of statistical functions of the program «Microsoft Excel» and variation statistical analysis. Numerical data are given in the form of arithmetic mean value M, standard deviation SD, and number of variants n. Body mass index (BMI) is determined by the formula: BMI = weight, kg/(height, m^2). The degree of obesity was assessed according to the WHO classification (1997).

A quantitative and statistical evaluation of the data was carried out. The predicted risk of cancer was determined using the method of multifactorial analysis, mathematical modeling and the logistic regression equation. ROC analysis was performed using the Medcalc v.19.1.6 program. For the analysis of patient survival, the Kaplan-Meier and Cox-Mantel cumulative survival estimation methods were used.

The work is a fragment of the complex scientific research work of the Ivano-Frankivsk National Medical University: «Scientific substantiation and improvement of diagnosis and treatment of endocrinopathies based on the study of priority etiopathogenetic factors and comorbid conditions» (2019-2024, state registration number 0120U105103).

RESULTS

According to the results of the epidemiological analysis, in women with T2D, an increased risk of BC (OR=1.31; 95 % CI 1.10-1.58; $p<0.05$) and EC (OR=1.38; 95 % CI 1.07-1.78; $p<0.05$)) was found [7]. Most often, BC and EC were diagnosed in women aged 60-70. The frequency of BC in women of this age was 51.59 %, and EC was 56.92 %. The average age of women with T2D who were first diagnosed with BC was 62.50±8.31 years, and EC was 60.25±7.84 years (table 1).

Table 1

Clinical characteristics and HbA1c level in women with type 2 diabetes with newly diagnosed breast and uterine cancer (M±SD)

Cancer localization	Average age, years	BMI, кg/m^2	Duration of T2D, years	HbA1c, %
Breast cancer	62.50±8.31	32.03±4.01	8.14±5.92	8.18±1.15
Endometrial cancer	60.25±7.84	30.94±4.02	7.14±3.93	8.44±1.15

Notes: 1. BMI – body mass index, T2D – type 2 diabetes, HbA1c – glycosylated hemoglobin

Most women with both cancer sites were obese. Among women with BC, 69.05 % were obese, with EC – 64.65 %. The average BMI of women with BC was 32.03±4.01 kg/m2, with MNS of the uterus 30.94±4.02 kg/m2 (table 1). Statistical analysis using the odds ratio method proved a significant influence of obesity on the risk of BC (OR=2.06; 95 % CI 1.28-3.29; $p<0.05$) [7]. Most often MNS of both localizations were diagnosed in patients with diabetes lasting more than five years. The average duration of T2D before diagnosis of BC was 8.14±5.92 years, EC – 7.14±3.93 years. At the time of cancer detection, the absolute majority of patients had decompensated T2D (table 1).

The scheme of ADT, which was received by women with T2D before the diagnosis of cancer was studied. It was found that before the detection of cancer of both localization, women with T2D most often received combined therapy (medication without effect on insulin synthesis or secretion + stimulators of insulin secretion or synthesis (sulfonylurea derivatives (SUD) and gliptins)). This therapy received 57 women (45.24 %) with BC and 25 women (38.46 %) with EC. At the same time, the widespread use of secretagogues in the ADT of women, particularly those with obesity, attracted attention. Among 126 patients diagnosed with BC, secretagogues were taken by 75 women (59.5 %), 50 of which (67.0 %) were obese, and 18 (24.0 %) were overweight (table 2). Among 65 patients with detected EC, secretagogues were taken by 37 women (56.9 %), 20 of them (54.0 %) were obese, and 10 women (27 %) were overweight (table 2).

Table 2

Frequency use of SUD by women with type 2 diabetes before cancer diagnosis, according to their body weight

Cancer localization	The number of women who were treated with SUD	The number of women with obesity	The number of overweight women	The number of women with normal BMI
Breast cancer	75	50 (67.0 %)	18 (24.0 %)	7 (9.0 %)
Endometrial cancer	37	20 (54.0 %)	10 (27.0 %)	7 (19.0 %)

Notes: 1. % is a percentage of the total number of persons in the specified category. 2. SUD – sulfonylurea derivatives, BMI – body mass index

Using multifactorial data analysis method of mathematical modelling and logistic regression equation were developed to calculate the predicted risk of cancer (PCR) of the breasts and endometrium in women with T2D. The equation includes indicators whose impact was studied in the study (age, BMI, duration of DM, ADT scheme, HbA1c), as well as numerical coefficients determined by the analytical program in accordance with the significance of the influence of factors. Determination of the predicted risk of breast cancer and endometrial cancer includes three stages.

1) Calculation of the coefficient of PCR: $Y = 0.005 \times \text{age} + 0.15 \times \text{HbA1c} + 0.33 \times \text{BMI} + 0.17 \times \text{duration of diabetes} + 0.38 \times \text{therapy (1-6)} - 14.9$.

2) Transformation (normalization) of the coefficient of PCR (Y) using the logistic transformation formula: $p = 1/(1+2.71\text{^}(-Y))$.

3) Assessment of PCR: p = 0.1-0.3 the risk is low, p = 0.4-0.6 – medium, p = 0.7-1.0 – the risk is high.

The accuracy of the mathematical model for calculating the Y index (according to the ROC analysis) is 76.24 %. Belonging to group 0 – «no risk of cancer» is determined by the model with an accuracy of 80.18 % and belonging to group 1 – «high risk of cancer» – with an accuracy of 71.43 %, the area under the curve AUC=0.853 (0.796-0.899), $\chi2=80.4$, $p<0.001$. The model has a high predictive power (AUC=0.853) compared to the diagonal (AUC=0.5), which proves the high reliability of the assessment of the probability of the development of MNS depending on the independent indicators included in the model. According to the data of ROC analysis, it was established that BMI ($p<0.001$), duration of T2D ($p<0.001$) and ADT scheme ($p<0.05$) had the greatest significance in the calculation of the PCR of breasts and endometrium.

The influence of pathogenetic factors of T2D on the survival of women with cancer was studied. During the first year from the moment of cancer detection, among 1580 women with BC without T2D 122 patients died, among 126 women with T2D 18 patients died. Among 774 women with EC without T2D 80 people died within 1 year, among 65 women with EC with T2D 13 people died. Statistical analysis using the odds ratio method revealed an increased risk of death by 1 year in women with T2D with BC (OR=1.99; 95 % CI 1.17-3.29; $p<0.05$) and EC (OR=2.17; 95 % CI 1.13-4.16; $p<0.05$) compared to women without diabetes.

Statistical analysis of the cumulative survival of patients by Kaplan-Meier using the log-rank test (Mantel-Cox test) confirmed the inverse dependence of survival on the stage of cancer in women with BC ($p<0.01$) and with EC ($p <0.01$).

Differences in the survival of women with the same stage of cancer were studied. The significance of the influence of the investigated parameters was assessed (age, BMI, duration of diabetes, ADT scheme, HbA1c). The criterion for the distribution of ADT types was the ability of medications to increase the level of insulin in the blood: therapy 1 – drugs that do not increase the level of insulin in the blood (metformin, glitazones, gliflozin), therapy 2 – drugs that increase the level of insulin in the blood (SUD, gliptins, insulin medications), therapy 3 – a combination of drugs (therapy 1 + therapy 2).

According to the obtained data, no significant influence of the studied parameters on the survival of women with BC of certain stages was found ($p>0.05$). Women with EC stage 1 on therapy 2 had shorter survival compared to women on therapy 1 (C=2.50; $p<0.05$) and on therapy 3 (C=2.65; $p<0.05$) (fig. 1). Women with EC stage II with HbA1c level >8.0 % had shorter survival compared to women with HbA1c level <8.0 % (C=1.92; $p<0.05$) (fig. 2).

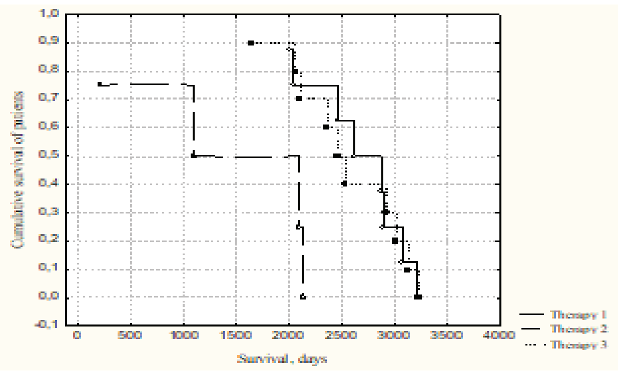

Figure 1. Dependence of women survival with endometrial cancer stage I on the type of antidiabetic therapy (p<0.05)

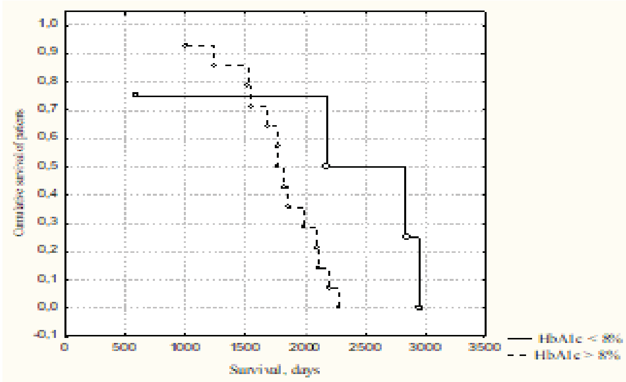

Figure 2. Dependence of women survival with endometrial cancer stage II on HbA1c level (p<0.05)

DISCUSSION

According to the results of the study, it was established that the factors that significantly affect the formation of cancer risk in women with T2D are obesity, the duration of T2D for more than 5 years, and the combination of secretagogues and insulin sensitizers such as ADT (in obese women). The results are consistent with data from other studies in which obesity in T2D is defined as a favourable background for the development of cancer due to a combination of dysmetabolic and dyshormonal influences. Metabolic changes due to obesity, such as insulin resistance (IR) and hyperinsulinemia, lead to dyshormonal changes that contribute to the development of cancers of reproductive organs.

With visceral obesity, IR causes secondary hyperinsulinemia, which plays an important role in oncogenesis. Due to the structural similarity, insulin (only in excessive concentration) has the property of competitively binding to insulin-like growth factor-1 (IGF-1) receptors, increasing bioavailability, and enhancing the anabolic and antiapoptotic effects of IGF-1 [8].

The role of obesity is particularly significant in the oncogenesis of estrogen-dependent forms of cancer: breast cancer, cancer of the endometrium, and ovaries. In obese people hyperestrogenemia, caused by excessive conversion of androgens into estrogens in subcutaneous adipose tissue, the percentage of androstenedione that is converted to estrone increases ten times. An excess of estrogen provokes the development of BC and EC [9, 10]. According to the results of our study, BC and EC were most often diagnosed in postmenopausal women. It is at this age that peripheral synthesis of estrogens prevails in women. Hyperinsulinemia also contributes to hyperestrogenemia. Excess insulin reduces the content of sex hormone-binding globulin. Hyperestrogenemia inhibits apoptosis, stimulates cell proliferation, and the local synthesis of IGF-1. The synergism of IGF-1 and estrogens in the induction of cell proliferation has been revealed [11].

Another factor in oncogenesis associated with obesity in T2D is cytokine imbalance. Leptin and IL-6 can stimulate the local synthesis of estrogens in adipose tissue, and activate ERα, contributing to the proliferative effects of estrogens [12]. The negative effect of a low level of adiponectin (ADP) has been proven. In particular, decrease the ability of ADP to activate adenosine monophosphate protein kinase (AMPK), to reduce lipolysis and oxidative stress (OS) [13]. OS is a main DNA-damaging (oncogenic) factor in diabetes capable of causing gene mutations [14].

In our study, the direct dependence of the risk of BC and EC on the duration of T2D was proven. It is obvious that as the duration of diabetes increases, the pro-oncogenic effect of metabolic and hormonal disorders increases too, and age-dependent mechanisms of antitumor protection are suppressed. Ageing processes, T2D and oncological processes are interrelated. DM increases the prerequisites for premature ageing, including immunocompetent cells. Senescent cells have the ability to form a special microenvironment favourable for proliferation [15]. Therefore, at an older age, apoptosis of «damaged» cells may not occur or may be ineffective [16]. Therefore, the correction of metabolic disorders in patients with DM, as well as in patients with prediabetes, reduces the conditions for the development of MNS.

According to the results of our study, the factor that significantly affects the indicator of the coefficient of the PCR is the choice of ADT. In particular, the most frequent therapy was the combination of secretagogues with non-secretagogues. The choice of such ADT is fully justified by the duration and severity of the disease. The advisability of prescribing metformin to obese T2D patients is beyond doubt, taking into consideration the effects of the drug on BMI and IR. However, the frequent use of secretagogues in obese women (used by more than 50 % of women) can contribute to hyperinsulinemia, which increases the risk of BC and EC [17]. Some studies prove the negative effect of SUD on the risk of cancer due to hyperinsulinemia [18]. According to other studies, this effect is debatable [19]. SUDs are still widely used in the treatment of patients with T2D due to their availability and powerful hypoglycemic effect. However, potential oncogenesis-related mechanisms of action of ADT are important to consider in each case.

Using the results of multifactorial analysis, a logistic regression equation was developed, which can be used in clinical practice to estimate the predicted risk of BC and EC. For women with T2D with a level of p-index > 0.7, we can recommend correction of diabetes-dependent factors of oncogenesis (BMI, HbA1c level, ADT scheme), as well as screening for BC and EC.

It was found that T2D increases the risk of mortality up to 1 year in patients with BC and EC. The results of many studies prove the negative impact of DM on patient survival rates and mortality from MNS [20, 21].

Our study revealed a negative effect of decompensation of DM and drugs that increase blood insulin levels on the survival of women with EC. Such an effect may be related to the course of diabetes, as well as to the effect of chronic hyperglycemia and possible iatrogenic hyperinsulinemia in obese postmenopausal women. This proves the importance of selecting an effective ADT aimed at preventing cardiovascular events and cancer-related complications.

CONCLUSIONS

1. Obesity, duration of diabetes > 5 years, and use of secretagogues in obesity increase the risk of breast and endometrial cancer in women with T2D.

2. The use of antidiabetic drugs that contribute to iatrogenic hyperinsulinemia may negatively affect survival in obese women with breast and endometrial cancer, both by increasing the risk of cardiovascular events and by hyperactivating insulin signaling.

3. Decompensation of diabetes reduces the 5-year survival of patients with breast cancer and endometrial cancer.

4. Detection of a predicted high-grade cancer risk ($p = 0.7$-1.0) may be an indication for correction of factors of oncogenesis and cancer screening in women with T2D.

Prospects for further research. In the future, we plan to investigate the effect of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on the survival of patients with cancer diagnosed on the background of T2D.

COMPLIANCE WITH ETHICAL REQUIREMENTS

Ethical approval was obtained from the Bioethics Committe of the Ivano-Frankivsk National Medical University (protocol No. 3, dated February 17, 2020). The study was conducted in accordance with the recommendations of the Ethics Committees for Biomedical Research, Ukrainian Health Legislation and the Declaration of Helsinki of 2000, European Community Directive 86/609 On Human Participation in Biomedical Research.

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The authors declare no conflict of interest regarding this article. No external funding was provided for this study. Acknowledgements: none.

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Резюме

ВПЛИВ ДІАБЕТ-АСОЦІОВАНИХ ЧИННИКІВ ОНКОГЕНЕЗУ НА РИЗИК РАКУ МОЛОЧНОЇ ЗАЛОЗИ І ТІЛА МАТКИ ТА НА ВИЖИВАНІСТЬ ЖІНОК ІЗ ВКАЗАНИМИ ЛОКАЛІЗАЦІЯМИ РАКУ

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Вступ. Хворі на цукровий діабет 2 типу (ЦД2) мають підвищений ризик раку різних локалізацій. Виявлення і корекція діабет-асоційованих чинників онкогенезу можуть бути важливими в профілактиці раку.
Мета. Дослідити вплив діабет-асоційованих чинників онкогенезу на формування ризику раку молочної залози (МЗ) і раку ендометрія (РЕ) та на виживаність жінок із вказаними типами раку, а також розробити спосіб розрахунку прогнозованого ризику раку МЗ і РЕ у жінок з ЦД2.
Матеріали та методи. В роботі використано результати ретроспективного епідеміологічного аналізу випадків раку у хворих з ЦД2, жителів Івано-Франківської області, впродовж 2012-2016 рр., з аналізом 5-річного виживання пацієнтів. Статистичну обробку результатів проведено в програмі STATISTIKA-12 (StatSoft Inc., США). Вплив патогенетичних чинників ЦД2 на розвиток раку МЗ і РЕ оцінювали за допомогою багатофакторного аналізу та ROC-аналізу, в програмі Medcalc v.19.1.6. Коефіцієнт прогнозованого ризику раку визначено за допомогою математичного моделювання і рівняння логістичної регресії. Для оцінки виживання пацієнтів використано аналіз кумулятивного виживання Каплана-Майєра і Cox-Mantel Test.
Результати. Рак МЗ і РЕ найчастіше діагностували у жінок постменопаузального віку, з ожирінням, тривалістю ЦД2 > 5 років, на комбінованій цукрознижувальній терапії. Серед жінок з раком МЗ, які приймали секретагоги, 67 % мали ожиріння, 24 % мали надлишкову вагу, серед жінок з РЕ – 54 % і 27 % відповідно. Розроблено новий спосіб розрахунку коефіцієнта прогнозованого ризику раку МЗ і РЕ (Y) у жінок із ЦД2. Точність математичної моделі розрахунку індекса Y складає 76,24 %. Доведено, що показник коефіцієнта Y зростає в жінок з ожирінням ($p<0,001$), з тривалістю ЦД > 5 років ($p<0,001$), на комбінованій терапії несекретагогами з секретагогами ($p<0,05$). Виявлено, що ЦД2 підвищує ризик смерті до 1-го року жінок з обома типами раку ($p<0,05$). Гірше 5-річне виживання виявлено у жінок з РЕ I стадії на терапії ліками, які підвищують рівень інсуліну крові ($p<0,05$), а також у жінок з РЕ II стадії з HbA1c > 8,0 % ($p<0,05$).
Висновки. Ожиріння, тривалість діабету > 5 років і використання секретагогів при ожирінні підвищують ризик раку молочної залози та ендометрія у жінок із ЦД2. Застосування антидіабетичних препаратів, які сприяють ятрогенній гіперінсулінемії може негативно вплинути на виживання жінок з ожирінням з раком молочної залози і з раком ендометрія, як через збільшення ризику серцево-судинних подій, так і через гіперактивацію інсулінового сигналінгу. Декомпенсація ЦД знижує 5-річне виживанння хворих з раком молочної залози і з раком ендометрія. Виявлення прогнозованого ризику раку високого ступеню ($p = 0,7-1,0$) може бути показом для корекції чинників онкогенезу та скринінгу раку у жінок із ЦД2.

Ключові слова: **цукровий діабет, прогнозований ризик раку, рак молочної залози, рак ендометрію, виживаність пацієнтів**