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T.S. Vatseba,
L.K. Sokolova [*]***,***
M.D. Tronko [*]***,***
I.K. Churpiy,
M.O. Vatseba,
V.V. Derpak

THE IMPACT OF OBESITY ON THE DEVELOPMENT OF CERTAIN CANCERS IN PATIENTS WITH TYPE 2 DIABETES. MECHANISMS OF ASSOCIATION

Ivano-Frankivsk National Medical University
Halytska str., 2, Ivano-Frankivsk, 76018, Ukraine
SI «V.P. Komisarenko Institute of Endocrinology and Metabolism, NAMN of Ukraine» [*]
Vyshhorodska, 69, Kyiv, 04114, Ukraine
Івано-Франківський національний медичний університет
(ректор – д. мед. н., проф. М.М. Рожко)
вул. Галицька, 2, Івано-Франківськ, 76018, Україна
ДУ «Інститут ендокринології та обміну речовин ім. В.П. Комісаренка НАМН України» [*]
(дир. – чл.-кор. НАН України, академік НАМН України, проф. М.Д. Тронько)
вул. Вишгородська, 69, Київ, 04114, Україна
e-mail: tamara.vatseba@gmail.com

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Abstract. The impact of obesity on the development of certain cancers in patients with type 2 diabetes. Mechanisms of association. Vatseba T.S., Sokolova L.K., Tronko M.D., Churpiy I.K., Vatseba M.O., Derpak V.V. *The aim of the study was to investigate the effect of obesity on the development of cancer of certain localizations in patients with type 2 diabetes mellitus (T2D) and to explain the association mechanisms of obesity in diabetes and cancer. The study included retrospective analysis of first time diagnosed cancer cases in patients with T2D in 2012-2016 in Ivano-Frankivsk region. Analysis of the data was carried out using Statistica 12.0 (StatSoft Inc., USA) program. The data are presented in the tables as M±SD (M± standard deviation). Differences between the studied parameters were determined using the ANOVA- test, taking into account the Bonferroni correction. The relationship between the studied data was evaluated using the criterion of chi-square with Yates correction (χ^2). The odds ratio (OR), 95% confidence interval, the positive and negative predictive value were calculated to determine the association between two events. The differences were considered significant at $p<0.05$. According to the results, 533 cases of the first time diagnosed cancer were detected in patients with T2D. It was found that obesity is inherent in women with breast, uterine, ovarian and colorectal cancer; for men with prostate cancer and with colorectal cancer. According to the criterion of χ^2, the effect of obesity on the incidence of breast cancer in women ($x^2=8.46$; $p<0.05$), and prostate cancer ($x^2=7.02$; $p<0.05$) and colorectal cancer ($x^2=7.94$; $p<0.05$) in men was proven. OR revealed an increased risk of breast cancer in women [OR=2.06; 95% CI (1.28-3.29); $p<0.05$], and prostate cancer [OR=2.94; 95% CI (1.37-6.32); $p<0.05$] and colorectal cancer [OR=2.87; 95% CI (1.42-5.82); $p<0.05$] in men associated with obesity. Thus, among patients with T2D, obesity increases the risk of breast cancer in women, prostate cancer and colorectal cancer in men. The mechanisms of association of obesity and cancer in patients with T2D are hyperglycemia, hyperinsulinemia, cytokine imbalance, hyperestrogenism (in estrogen-dependent cancer), and intestinal dysbiosis (in colorectal cancer).*

Реферат. Вплив ожиріння на розвиток певних видів раку у хворих на цукровий діабет 2 типу. Механізми асоціації. Вацеба Т.С., Соколова Л.К., Тронько М.Д., Чурпій І.К., Вацеба М.О., Дерпак В.В. *Метою дослідження було вивчити вплив ожиріння на розвиток раку певних локалізацій у пацієнтів з цукровим діабетом (ЦД) 2 типу та пояснити механізми асоціації ожиріння та онкологічних захворювань у хворих з діабетом. Дослідження включало ретроспективний аналіз медичних карт хворих на ЦД 2 типу, жителів Івано-Франківської області, з уперше діагностованими онкологічними захворюваннями впродовж 2012-2016 років. Для аналізу даних використовували програму Statistica 12.0 (StatSoft Inc., США). Дані представлені в таблицях у вигляді M±SD (M± стандартне відхилення). Відмінності між досліджуваними показниками визначали за допомогою тесту ANOVA, з урахуванням поправки Бонферроні. Взаємозв'язок між досліджуваними даними оцінювали за критерієм хі-квадрат з корекцією Йєтса (χ^2). Коефіцієнт шансів (OR), 95% довірчий інтервал, позитивне та негативне прогностичне значення були розраховані для визначення асоціації між явищами. Відмінності вважалися достовірними при $p<0,05$. Виявлено 533 випадки вперше діагностованих*

онкологічних захворювань у пацієнтів з ЦД 2 типу. Встановлено, що ожиріння притаманне жінкам з раком молочної залози, тіла матки, яєчників і товстого кишечнику, для чоловіків – зі злоякісними новоутвореннями передміхурової залози та колоректальним раком. За критерієм χ^2 виявлений вплив ожиріння на частоту злоякісних пухлин молочної залози в жінок (x^2=8,46; p<0,05), раку передміхурової залози (x^2=7,02; p<0,05) та колоректального раку (x^2=7,94; p<0,05) у чоловіків. За методом відношення шансів у хворих на ЦД 2 типу виявлений асоційований з ожирінням підвищений ризик раку молочної залози в жінок [OR=2,06; 95% CI (1,28-3,29); p<0,05], передміхурової залози [OR=2,94; 95% CI (1,37-6,32); p<0,05] та колоректальної локалізації [OR=2,87; 95% CI (1,42-5,82); p<0,05] у чоловіків. Таким чином, у хворих на ЦД 2 типу із ожирінням виявлений підвищений ризик раку молочної залози в жінок, простати та колоректального раку в чоловіків. Механізмами асоціації ожиріння та раку у хворих на ЦД 2 типу є гіперглікемія, гіперінсулінемія, дисбаланс цитокінів, гіперестрогенія (при естроген-залежних пухлинах) та дисбіоз кишечнику (при колоректальному раку).

Effective treatment of patients with diabetes mellitus (DM) and oncological diseases (OD) remains a priority of scientific and practical medicine. As of 2019, 463 million patients with diabetes have been identified worldwide [8]. Given the rate of spread, experts from the World Health Organization (WHO) estimate that the number of patients with diabetes will increase to 625 million by 2040 [22].

Along with the increase in the incidence of diabetes, a progressive increase in the frequency of OD is noted [6]. According to the National Cancer Institute in Ukraine, for the last ten years, the number of patients with malignant neoplasms has increased by 25%. According to the data of the cancer registry in Ukraine in 2017, a statistically significant increase in general morbidity in men by 1.6% and in women – by 1.2% was registered [16].

Recent studies prove an increased risk of cancer in patients with type 2 diabetes (T2D) [9]. Pathogenetic factors of diabetes (hyperglycemia, hyperinsulinemia, obesity, cytokine imbalance, oxidative stress) are recognized as potential factors of oncogenesis [17]. Dysmetabolic disorders change the activity of intracellular regulatory systems-signalling pathways that, in addition to metabolism, control the processes of cell apoptosis and survival.

Obesity is an important pathogenetic factor of T2D, which significantly increases risk of cancer. The understanding of the mechanisms of the association of T2D, obesity with cancer is important for the prevention and treatment of both diseases.

The research is aimed to study the effects of obesity on the development of cancer of certain localizations in patients with T2D and to explain the association mechanisms of obesity, cancer and diabetes.

MATERIALS AND METHODS OF RESEARCH

The study was conducted following the guidelines of the Declaration of Helsinki (1975) and its revised version of 1983. The study included the selection and analysis of clinical records of patients with T2D (inpatient and outpatient), who were first diagnosed with cancer in 2012-2016 in Ivano-Frankivsk region of Ukraine. The bases of the retrospective epidemiological study were: Precarpathian Clinical Oncology Center, Ivano-Frankivsk Regional Clinical Hospital and medical institutions in the Ivano-Frankivsk region.

Selection of persons was carried out in accordance with the requirements for epidemiological studies [3]. The results of scientific research and own data were used to explain the mechanisms of association of obesity in diabetes with cancer.

Analysis of the data was carried out using Statistica 12.0 program [14]. The data are presented in the tables as M±SD (M± standard deviation). Differences between the studied parameters were determined using the test One-way ANOVA, taking into account the Bonferroni correction. The relationship between the study data was investigated by Yates-corrected chi-square ($\chi 2$). The odds ratio (OR), 95% confidence interval, the positive and negative predictive values were calculated to determine the risk of predicted events. The differences were considered significant at $p<0.05$ [1, 7].

RESULTS AND DISCUSSION

The results of scientific studies prove the high incidence of different types of cancer in obese patients with T2D at age over 60 [2, 9]. It was proved that aging and carcinogenesis are interrelated [12]. The prevalence of cancer in older people can be associated with the processes of cellular aging. Aging, on the one hand, is a process of protection against cancer, but on the other hand, the age is recognized to be a major risk factor for cancer.

There is a theory that the genes that are responsible for protection against cancer exhaust their useful effects during the reproductive age and are not effective enough in the elderly. DNA damage is a major factor that triggers oncogenesis. Reactive oxygen species and oxidative stress in diabetes are endogenous factors of DNA damage. The physiological response to DNA damage is manifested in the activation of cascades of specific kinases and genes that ultimately affect the cell cycle, either slowing it down (to allow time to repair the damage) or, if repair is not possible, leading to apoptosis of

altered cells. In old age, the system of maintenance and restoration of genetic stability weakens that contributes to the survival of damaged cells, which acquire additional properties: the ability to survive in uncomfortable conditions and to avoid apoptosis [23].

The association between obesity and cancer in diabetes is explained by a change in the regulation of metabolic processes and apoptosis at the level of intracellular signaling pathways. The predisposition of patients with T2D with obesity to cancer is connected with insulin resistance, secondary hyperinsulinemia, increasing bioavailability of IGF-1. In hyperinsulinemia, insulin cross-reacts with IGF-1 receptors (IGF-1R) and, conversely, IGF-1 with insulin receptors (IR). The effect of insulin and IGF-1 is accomplished through the stimulation of the PI3K/Akt/mTOR and MAPK/mTOR signalling pathways, which are involved in metabolism control and in oncogenesis [13, 18].

Obesity is recogized to be potent factor of cancer of reproductive organs through the influence of dysmetabolic and dyshormonal disorders. Excessive conversion of androgen precursors into oestradiol in adipose tissue causes hyperestrogenemia, a major factor in oncogenesis at these localizations. Prolonged hyperestrogenemia and progesterone deficiency contribute to the development of endometrial cancer. Oestradiol not only accelerates cell proliferation and inhibits apoptosis, but also stimulates local IGF-1 synthesis. Recent studies have shown the ability of insulin and IGF-1 to stimulate endometrial proliferation directly, even without the involvement of oestrogens. Synergistic proliferative effect of IGF-1 and oestrogen has been demonstrated. In addition, increased levels of sex hormones in patients with obesity are due to a decrease in levels of sex hormone-binding globulin (SHBG) due to hyperinsulinemia. Peripheral oestrogen synthesis in adipose tissue is predominant exactly in postmenopausal women with obesity [20]. Scientific studies have proved the mitogenic and mutagenic effects of oestrogens that cause direct or indirect DNA damage, inducing genetic instability and mutations in normal and neoplastic cells of the mammary gland [21].

The effect of obesity on the development of the prostate and colorectal cancer probably has a different explanation than in the case of the organs of the reproductive system. The effects of cytokine imbalance and oxidative stress can be the mechanisms of carcinogenesis. Due to obesity, the increasing of adipocyte size leads to insufficient vascularization of adipose tissue, hypoxia, infiltration of the tissue by macrophages and lymphocytes, which produce many cytokines with pro-inflammatory effects, including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), IL-8, IL-18, and others. Each of these factors influences the malignant transformation and progression of cancer [19].

It is proved that hypogonadism, caused by hyperestrogenemia, is inherent for obese men, it reduces the pro-oncogenic effects of testosterone on the cells of prostate. However, the results of a recent study of Céline Lavalette et al. have shown an increased risk of prostate cancer in men with a waist circumference >94.0 cm [(OR=1.20, 95% CI (0.92-1.56)] [4]. In study Francesca Cirillo and co-authors presented data on the dysregulation of microRNAs as potential molecular link between the metabolic changes associated with obesity and the development of colorectal cancer [11].

An additional factor of oncogenesis in colorectal cancer is intestinal dysbiosis, a change in the gut microbiota that is involved in the metabolism of proteins, poly- and oligosaccharides, in endogenous synthesis and in the recirculation of macro- and micronutrients and signaling molecules. Obesity affects the interaction of the microflora with the host, increases intestinal permeability, leads to the leakage of lipopolysaccharides from the gram-negative intestinal bacteria, which promote the development of low-level inflammation and carcinogenesis. These lipopolysaccharides activate the nuclear factor (NF-κB) of the large intestine epitheliocytes, which controls the expression of genes of the immune response, apoptosis, and cell cycle. Gram-positive bacteria, whose amount is low in DM can suppress NF-κB due to their butyrate-producing properties.

Butyrate is one of the short-chain fatty acids (SCFAs) with the prominent anti-inflammatory abilities. The additional value of SCFAs is due to their ability to regulate intestinal motility, facilitating the elimination of products of metabolism, toxins, and carcinogens. The change of qualitative composition of the gut microbiota and the content of SCFAs causes increased concentration of bacterial endotoxins, which leads to the metabolic endotoxicity and to the chronic systemic inflammation [10].

In addition, current studies prove the crucial role of the gut microbiota in the formation of the correct immunological response and immunological response of the body to epigenetic external and internal influences [15]. That is, both diabetes and obesity negatively affect the oncoprotective function of the gut microbiota.

Chronic hyperglycemia, a major manifestation of diabetes, is also a strong factor in oncogenesis in T2D, regardless of BMI. Due to oxidative stress oxidation of intracellular structures takes place, causing DNA damage and changes in genetic control and regulation of cellular apoptosis and survival. In obese patients with insulin resistance, hyperglycemia

stimulates additional insulin production, which contributes to both hyperinsulinemia and obesity and prooncogenic effects associated with them [5].

Based on the results of the medical records, 533 first diagnosed OD cases were detected in patients with T2D in the period of 2012-2016.

According to the results of the study in patients with T2D, different types of cancer were identified. Most often breast, uterine, pancreatic, skin, and colorectal cancer were diagnosed (Table 1).

Table 1

Spectrum and incidence of cancer of different localizations in patients with T2D

Type of cancer	Amount of patients (n=533)	Incidence (%)
Breast cancer	**126**	**23.64**
Colorectal cancer	**72**	**13.51**
Uterine cancer	**65**	**12.20**
Pancreatic cancer	**52**	**9.76**
Skin cancer	**44**	**8.26**
Gastric cancer	**34**	**6.38**
Prostate cancer	**34**	**6.38**
Lung cancer	**18**	**3.38**
Kidney cancer	**12**	**2.25**
Ovarian cancer	**11**	**2.06**
Laryngeal cancer	**10**	**1.88**
Bladder cancer	**9**	**1.69**
Cancer of other localizations: thyroid gland, biliary tract, female external genital organs (EGO), sinuses, soft tissues, parotid glands, oropharynx, salivary glands, oesophagus, adrenal glands, urinary tract, small intestine, male EGO, lymphoma, bone sarcoma	**46**	**8.63 (<1.5% each of the cancers in particular)**

Note. % – for all patients with cancer and type 2 diabetes.

Age characteristics and body mass index (BMI) of patients with T2D with the most common types of cancer were determined. According to data of Table 2, cancer is most often diagnosed in patients over 60 years of age.

Using Bonferoni correction, it was found that BMI of women with cancer of the pancreas was lower than in women with breast, uterine, ovarian, and colorectal cancer ($p<0.05$). In women with gastric cancer, BMI was lower than in those with breast cancer ($p<0.05$). In men with prostate cancer and colorectal cancer BMI was higher than in patients with skin ($p<0.05$), lung ($p<0.05$) and pancreatic cancer ($p<0.05$), in men with colorectal cancer BMI was also higher than in patients with gastric cancer ($p<0.05$) (Table 2).

Table 2

Age characteristics and BMI of patients with T2D and cancer

Localizations of cancer	Age (M±SD)	BMI (M±SD)
Breast cancer females (n=126)	**62.50±8.31[b,e]**	**32.03±4.01[d,f]**
Colorectal cancer	**67.72±8.09[l]**	**30.70± 4,33[d,e,f,h]**
males (n=41)	**64.50±6.45 [a,c,i,j]**	**30.74±3,66 [d]**
females (n=31)		
Uterine cancer (n=65)	**60.25±7.84[b,d,e]**	**30.94±4.02 [d]**
Pancreatic cancer	**67.21±8.36**	**27.18±3.82[b]**
males (n=28)	**67.04±7,32[a,c,j]**	**26.96±3.22[a,b,c,j]**
females (n=24)		
Skin cancer	**67.56±8.66 [h]**	**26.57±5.36[b,g]**
males (n=25)	**74.10±6.67 [a,c,h,i,j]**	**28.37±3.82**
females (n=19)		
Gastric cancer	**63.04±8.31 [l]**	**27.30±4.33[b]**
males (n=23)	**63.70±9.38**	**27.03±3.01[a]**
females (n=11)		
Prostate cancer (n=34)	**65.62±6.32 [l]**	**30.56±3.87[d,e,h]**
Lung cancer	**60.57± 6.11[e,l]**	**25.37±3.15[b,g]**
males (n=14)	**59.25±2.87 [e]**	**29.50±5.41**
females (n=4)		
Kidney cancer	**64.29±6.45**	**29.09±2.93**
males (n=7)	**55.00±5.57[b, e]**	**27.44±4.07**
females (n=5)		
Laryngeal cancer males (n=10)	**64.5±6.00**	**26.58±3.63**
Bladder cancer males (n=10)	**75.0±3,57[b,f,g,h]**	**26.92±3.65**
Ovarian cancer (n=11)	**56.09±6.07[b,d,e,]**	**31.77±6.49 [d]**

Notes: - the difference is significant in comparison with indicators of patients with cancer of certain localizations: a – breast cancer; b – colorectal cancer; c – uterine cancer; d – pancreatic cancer; e – skin cancer; f – gastric cancer; g – prostate cancer; h – lung cancer; i – kidney cancer; j – ovarian cancer; k – laryngeal cancer; l – bladder cancer. The difference was evaluated using correction Bonferroni ($p<0.05$).

Among 322 women, 189 were obese and 133 were not obese; among 211 men, 90 were obese and 121 were not obese.

The analysis of differences in the frequency of obesity in patients with T2D with most common localizations of cancer was performed by Yates-corrected χ^2 (Table 3).

According to the results obtained, the effect of obesity on the incidence of breast cancer in women ($x^2=8.46$; $p<0.05$), prostate cancer ($x^2=7.02$; $p<0.05$) and colorectal cancer ($x^2=7.94$; $p<0.05$) in men was proven, but it does not affect the incidence of cancer of the pancreas, skin, lung and stomach ($p<0.05$) (Table 3).

Table 3

Estimation of differences of obesity frequency in patients with T2D and cancer

Type of cancer	With obesity		Without obesity		χ^2	p
	with specif. type of cancer	without specif. type of cancer	with specif. type of cancer	without specif. type of cancer		
Breast cancer	**87**	**102**	**39**	**94**	**8.46**	**p<0.05**
Colorectal cancer	**47**	**232**	**25**	**229**	**5.0**	**p<0.05**
males	**26**	**64**	**15**	**106**	**7.94**	**p<0.001**
females	**21**	**168**	**10**	**123**	**0.78**	**p>0.05**
Uterine cancer	**42**	**147**	**23**	**110**	**0.89**	**p>0.05**
Pancreatic cancer	**13**	**266**	**39**	**215**	**16.08**	**p<0.001**
males	**5**	**85**	**23**	**98**	**6.99**	**p<0.05**
females	**8**	**181**	**16**	**117**	**5.80**	**p<0.05**
Skin cancer	**14**	**265**	**30**	**224**	**7.23**	**p<0.05**
males	**8**	**82**	**17**	**104**	**0.87**	**p>0.05**
females	**6**	**183**	**13**	**120**	**4.99**	**p<0.05**
Gastric cancer	**10**	**269**	**24**	**230**	**6.71**	**p<0.05**
males	**9**	**81**	**14**	**107**	**6,21**	**p<0.05**
females	**1**	**188**	**10**	**123**	**9,54**	**p<0.05**
Prostate cancer	**22**	**68**	**12**	**109**	**7.02**	**p<0.05**
Lung cancer	**3**	**276**	**15**	**239**	**8.08**	**p<0.05**
males	**1**	**89**	**13**	**108**	**6.25**	**p<0.05**
females	**2**	**187**	**2**	**131**	**0.02**	**p>0.05**
Kidney cancer	**5**	**274**	**7**	**247**	**0.21**	**p>0.05**
males	**4**	**86**	**3**	**118**	**0.16**	**p>0.05**
females	**1**	**188**	**4**	**129**	**1.73**	**p>0.05**
Ovarian cancer	**6**	**183**	**5**	**128**	**0.001**	**p>0.05**
Laryngeal cancer, males	**4**	**86**	**6**	**115**	**0.02**	**p>0.05**
Bladder cancer, males	**3**	**87**	**6**	**115**	**0.05**	**p>0.05**

Notes: results are presented as χ^2 test for assessment of significance of the relationship between the categorical variables, p – p value for the evaluation of the significance of the relation between two groups.

Considering the higher frequency of obesity in patients with breast cancer, prostate cancer and colorectal cancer, the risk of this malignant neoplasms (associated with obesity) was evaluated using the statistical method of the Odds ratio (Table 4).

Table 4

Assessment of cancer risk associated with obesity in patients with T2D

Type of cancer	With obesity		Without obesity		OR	95% CI	p
	with specif. type of cancer	without specif. type of cancer	with specif. type of cancer	without specif. type of cancer			
Breast cancer (females)	87	102	39	94	2.06	1.28-3.29	p<0.05
Prostate cancer (males)	22	68	12	109	2.94	1.37-6.32	p<0.05
Colorectal cancer (males)	26	64	15	106	2.87	1.42-5.82	p<0.05
Colorectal cancer (females)	21	168	10	123	1.54	0.70-3.38	p>0.05

Notes: OR – Odds ratio; 95% CI - 95% confidence interval.

OR revealed an associated with obesity increased risk of breast cancer in women [OR=2.06; 95% CI (1.28-3.29); p<0.05], prostate cancer [OR=2.94; 95% CI (1.37-6.32); p<0.05] and colorectal cancer [OR=2.87; 95% CI (1.42-5.82); p<0.05] in men (Table 4).

The results of our study proved the prevalence of cancer in elderly patients, as well as the association of obesity with the development of cancer in some localizations.

The results of our study coincide with the data of other scientific studies.

Patients with T2D with obesity require screening to identify mentioned forms of cancer. Normalization of BMI is one of the methods of cancer prevention in patients with T2D.

CONCLUSIONS

1. Among patients with type 2 diabetes, obesity increases the risk of breast cancer in women, prostate cancer and colorectal cancer in men.

2. The mechanisms of association of obesity in diabetes with cancer are hyperglycemia, hyperinsulinemia, cytokine imbalance, hyperestrogenism (in estrogen-dependent cancer), and intestinal dysbiosis (in colorectal cancer).

Further scientific research will be directed to the study of the effect of anti-diabetic drugs of different groups on the development of oncological diseases.

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REFERENCES

1. Antonomonov MYu. [Mathematical processing and analysis of biomedical data]. Kyiv; 2017;578. Russian.

2. Vatseba TS, Sokolova LK. [Pathogenetic mechanisms of oncogenesis on the background of diabetes mellitus and analysis of oncological morbidity of patients with diabetes mellitus in the Carpathian region]. Endocrinology. 2018;2(23):128-37. Ukrainian. Available from: http://nbuv.gov.ua/UJRN/enkrl_2018_23_2_6.

3. Lekhan VM, Voronenko YuV, Maksymenko OP, Zyukov OL, Hubar IO. [Epidemiological methods for studying non-infectious diseases]. Dnipropetrovsk; 2004;184. Ukrainian.

4. Lavalette C, Trétarre B, Rebillard X, et al. Abdominal obesity and prostate cancer risk: epidemiological evidence from the EPICAP study. Oncotarget. 2018;9(77):34485-94.
doi: https://doi.org/10.18632/oncotarget.26128

5. Marín-Aguilar F, Pavillard LE, Giampieri F, et al. Adenosine Monophosphate (AMP)-Activated Protein Kinase: A New Target for Nutraceutical Compounds. Int J Mol Sci. 2017;18(2):288.
doi: https://doi.org/10.3390/ijms18020288

6. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):359-86.
doi: https://doi.org/10.1002/ijc.29210

7. Eroğlu O, Yuksel S. Statistical Method Selection İn Medical Research. Experimental biology. 2019;29:364-71. doi: https://doi.org/10.26449/sssj.1219

8. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels; 2019. p. 176.

9. Oberaigner W, Ebenbichler C, Oberaigner K, et al. Increased cancer incidence risk in type 2 diabetes mellitus: results from a cohort study in Tyrol/Austria. BMC Public Health. 2014;14:1058. doi: https://doi.org/10.1186/1471-2458-14-1058

10. McNabney SM, Henagan TM. Short Chain Fatty Acids in the Colon and Peripheral Tissues: A Focus on Butyrate, Colon Cancer, Obesity and Insulin Resistance. Nutrients. 2017;9(12):1348.
doi: https://doi.org/10.3390/nu9121348

11. Cirillo F, Catellani C, Sartori C, et al. Obesity, Insulin Resistance, and Colorectal Cancer: Could miRNA Dysregulation Play A Role? Int J Mol Sci. 2019;20(12):2922. doi: https://doi.org/10.3390/ijms20122922

12. Pilleron S, Sarfati D, Janssen-Heijnen M, et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study. Int J Cancer. 2019;144(1):49-58. doi: https://doi.org/10.1002/ijc.31664

13. Poloz Y, Stambolic V. Obesity and cancer, a case for insulin signaling. Cell Death Dis. 2015;6(12):e2037. doi: https://doi.org/10.1038/cddis.2015.381

14. STATISTICA (data analysis software system), version 12. StatSoft, Inc. USA: Tulsa; 2014. Available from: https://www.statsoft.com

15. Rajagopala SV, Vashee S, Oldfield LM, et al. The Human Microbiome and Cancer. Cancer Prev Res. 2017;10(4):226-34.
doi: https://doi.org/10.1158/1940-6207.CAPR-16-0249

16. Ukrainian cancer registry statistics, 2017. "Cancer in Ukraine", 2017-2018, Bulletin of national cancer registry of Ukraine. 2017;20.
Available from: http://www.ncru.inf.ua

17. Vatseba TS. Influence of pathogenetic factors of type 2 diabetes on activation of PI3K/AkT/mTOR pathway and on the development of endometrial and breast cancer. Regulatory Mechanisms in Biosystems. 2019;10(3):295-99. doi: https://doi.org/10.15421/021945

18. Vatseba TS, Sokolova LK, Pushkarev VV, et al. Activation of the PI3K/Akt/mTOR/p70S6K1 signaling cascade in the mononuclear cells of peripheral blood: association with insulin and insulin-like growth factor levels in the blood of patients with cancer and diabetes. Cytology and Genetics. 2019;53:489-493. doi: https://doi.org/10.3103/S0095452719060112

19. Wu Y, Liu Y, Dong Y, Vadgama J. Diabetes-associated dysregulated cytokines and cancer. Integr Cancer Sci Ther. 2016;3(1):370-8. doi: https://doi.org/10.15761/ICST.1000173

20. Yang X, Wang J. The Role of Metabolic Syndrome in Endometrial Cancer: A Review. Front Oncol. 2019;9:744, doi: https://doi.org/10.3389/fonc.2019.00744

21. Yasuda MT, Sakakibara H, Shimoi K. Estrogen and stress-induced DNA damage in breast cancer and chemoprevention with dietary flavonoid. Genes Environ. 2017;39:10. doi: https://doi.org/10.1186/s41021-016-0071-7

22. Zimmet PZ. Diabetes and its drivers: the largest epidemic in human history? Clin Diabetes Endocrinol. 2017;3(1). doi: https://doi.org/10.1186/s40842-016-0039-3

23. Zinger A, Cho WC, Ben-Yehuda A. Cancer and Aging – the Inflammatory Connection. Aging Dis. 2017;8(5):611-27.
doi: https://doi.org/10.14336/AD.2016.1230

СПИСОК ЛІТЕРАТУРИ

1. Антомонов М. Ю. Математическая обработка и анализ медико-биологических данных. Киев. 2017. 578 с.

2. Вацеба Т. С., Соколова Л. К. Патогенетичні механізми онкогенезу на тлі цукрового діабету та аналіз онкологічної захворюваності пацієнтів із цукровим діабетом у Прикарпатському регіоні. *Ендокринологія*. 2018. Т. 23, № 2. С. 128-137. URL: http://nbuv.gov.ua/UJRN/enkrl_2018_23_2_6

3. Епідеміологічні методи вивчення неінфекційних захворювань / В. М. Лехан та ін. Дніпропетровськ. 2004.184 с.

4. Abdominal obesity and prostate cancer risk: epidemiological evidence from the EPICAP study / C. Lavalette et al. *Oncotarget*. 2018. Vol. 77, No. 9. P. 34485-34494. DOI: https://doi.org/10.18632/oncotarget.26128

5. Adenosine Monophosphate (AMP)-Activated Protein Kinase: A New Target for Nutraceutical Compounds / F. Marín-Aguilar et al. *Inter. journal of molecular sciences*. 2017. Vol. 18, No. 2. P. 288. DOI: https://doi.org/10.3390/ijms18020288

6. Cancer incidence and mortality worldwide: sources, methods, and major patterns in GLOBOCAN 2012 / J. Ferlay et al. *Inter. journal of cancer*. 2015. Vol. 136, No. 5. P. 359-86. DOI: https://doi.org/10.1002/ijc.29210

7. Eroğlu O., Yuksel S. Statistical method selection in medical research. *Experimental biology*. 2019. Vol. 29. P. 364-371. DOI: https://doi.org/10.26449/sssj.1219

8. International Diabetes Federation. IDF Diabetes Atlas. 9th ed / Brussels, 2019. 176 p.

9. Increased cancer incidence risk in type 2 diabetes mellitus: results from a cohort study in Tyrol, Austria / W. Oberaigner et al. *BMC Public Health*. 2014. No. 14. P. 1058.
DOI: https://doi.org/10.1186/1471-2458-14-1058.

10. McNabney S. M., Henagan T. M. Short Chain Fatty Acids in the Colon and Peripheral Tissues: A Focus on Butyrate, Colon Cancer, Obesity and Insulin Resistance. *Nutrients*. 2017. Vol. 9. No. 12. P. 1348. DOI: https://doi.org/10.3390/nu9121348

11. Obesity, Insulin Resistance, and Colorectal Cancer: Could miRNA Dysregulation Play A Role? / F. Cirillo et al. *Inter. journal of molecular sciences*. 2019. Vol. 20, No. 12. P. 2922.
DOI: https://doi.org/10.3390/ijms20122922

12. Pilleron S., Sarfati D., Janssen-Heijnen M. Global cancer incidence in older adults, 2012 and 2035: A population-based study. *Int J Cancer*. 2019. Vol. 144, No. 1. P. 49-58. DOI: https://doi.org/10.1002/ijc.31664

13. Poloz Y., Stambolic V. Obesity and cancer, a case for insulin signaling. *Cell Death Dis*. 2015. 31 Dec. (Vol. 12, No. 6). P. e2037.2015.
DOI: https://doi.org/10.1038/cddis.2015.381

14. STATISTICA (data analysis software system), version 12. StatSoft, Inc. USA: Tulsa, 2014. Available from: https://www.statsoft.com.

15. The Human Microbiome and Cancer / S. V. Rajagopala et al. *Cancer prevention research* (Philadelphia, Pa.) 2017. Vol. 10, No. 4. P. 226-234. DOI: https://doi.org/10.1158/1940-6207.CAPR-16-0249

16. Ukrainian cancer registry statistics, 2017. "Cancer in Ukraine", 2017-2018. *Bulletin of national cancer registry of Ukraine.* 2017. No. 20.
URL: http://www.ncru.inf.ua

17. Vatseba T. S. Influence of pathogenetic factors of type 2 diabetes on activation of PI3K/AkT/mTOR pathway and on the development of endometrial and breast cancer. *Regulatory Mechanisms in Biosystems*. 2019. Vol. 10, No. 3. P. 295-299.
DOI: https://doi.org/10.15421/021945

18. Vatseba T. S., Sokolova L. K., Pushkarev V. V. Activation of the PI3K/Akt/mTOR/p70S6K1 signaling cascade in the mononuclear cells of peripheral blood: association with insulin and insulin-like growth factor levels in the blood of patients with cancer and diabetes. *Cytology and Genetics.* 2019.Vol.53, No. 6. P. 489-493. DOI: https://doi.org/10.3103/S0095452719060112

19. Wu Y., Liu Y., Dong Y., Vadgama J. Diabetes-associated dysregulated cytokines, and cancer. *Integ. cancer science and therapeutics*. 2016. Vol. 3. P. 370-378. DOI: https://doi.org/10.15761/ICST.1000173

20. Yang X., Wang J. The Role of Metabolic Syndrome in Endometrial Cancer: A Review. *Frontiers in oncology.* 2019. No. 9. P. 744.
DOI: https://doi.org/10.3389/fonc.2019.00744

21. Yasuda M. T., Sakakibara H., Shimoi K. Estrogen and stress-induced DNA damage in breast cancer and chemoprevention with dietary flavonoid. *Genes Environ*. 2017. No. 39. P. 10.
DOI: https://doi.org/10.1186/s41021-016-0071-7

22. Zimmet P. Z. Diabetes and its drivers: the largest epidemic in human history? *Clinical Diabetes and Endocrinology.* 2017. Vol. 3, No. 1.
DOI: https://doi.org/10.1186/s40842-016-0039-3

23. Zinger A., Cho W. C., Ben-Yehuda A. Cancer and Aging – the Inflammatory Connection. *Aging and disease*. 2017. Vol. 8, No. 5. P. 611-627.
DOI: https://doi.org/10.14336/AD.2016.1230

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