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ORIGINAL ARTICLE

PROGNOSTIC MODEL OF SKIN CANCER RISK ASSESSMENT

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ABSTRACT

Introduction: Early detection of people at risk of skin cancer will reduce the incidence of disease, lower the cost of health technologies and decrease anxiety level in patients.
The aim of the work is to create a prognostic model for identifying people at increased risk of skin cancer development.
Material and methods: We used the results of our previous research on identifying risk factors in patients with actinic keratosis (AK), squamous cell carcinoma in situ (SCCis) and cutaneous squamous cell carcinoma (cSCC), who were under dynamic observation at the State Institution of Science "Research and Practical Centre of Preventive and Clinical Medicine" State Administrative Department (hereinafter SIS) in 2014-2017.
Results: The prognostic model is valid, AUC = 0.97 (95% CI 0.96 – 0.99) showing a significant association of the risk of skin cancer development with the following factors: patient's age, sunburns, using skin sunscreens, exposure to the sun in recent times, exposure to radiological materials, drug administration (antiarrhythmic drugs, antihypertensive medications, hormonal contraceptives, antibiotics), burdened family history (melanoma, squamous cell cancer). Model sensitivity was 95.1% (95% CI 91.6% - 97.4%), specificity – 88.5% (95% CI 84.6% - 91.8%).
Conclusions: The developed and analysed mathematical risk prediction system made it possible to identify 11 factors which are significantly associated with risk of skin cancer development. The prognostic model might be offered for specialists in taking decision at the stage of primary and secondary prevention of skin cancer.

KEY WORDS: prognostic model, risk factors, skin cancer, primary and secondary prevention

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INTRODUCTION

Understanding of the most appropriate way to identify people at high risk of skin cancer development can help improve prevention strategy and therapeutic approach [1]. In the international clinical protocols it is recommended to identify risk factors (RF) of skin cancer and to conduct dynamic observation of people at high risk of cancer development [2].

In most countries with predominantly people of European ethnicity, the incidence of non-melanoma skin cancer (NMSC) has increased over the last decade [3]. A recent systematic review of scientific literature has shown that the annual rate of progression of single actinic keratosis (AK) as a predictor of NMSC to an invasive form of squamous cell carcinoma of the skin (cSCC) ranges from 0% to 0.53% per year, but this data is incomplete [4]. At the same time, annual regression rates of single AK range from 15% to 63%, with a relapse rate of 15% -53% [5].

Rational reasoning for screening and follow-up of people at high risk of NMSC is based on the evidence that early diagnosis reduces the incidence of the disease [6], lowers medical costs [7] and decreases anxiety level in patients [8]. Significant role in the development of NMSC according to different authors play the excessive sun exposure [9], the use of drugs that increase skin sensitization to UVI [10], the genetic predisposition to cancer [11,12], the influence of chemical carcinogens [13,14] etc.

The detection of individuals with RF of skin cancer development is a part of primary and secondary prevention [15]. However, at present, there are no unified techniques for primary and secondary care physicians that could be used to effectively identify people at high risk of skin cancer development [16].

THE AIM

The aim of the research is to create a prognostic model for identifying people at increased risk of skin cancer development, which will provide timely dynamic observation of this category of people, as well as early detection of subclinical forms of skin cancer.

MATERIALS AND METHODS

We used the results of our previous research on identifying risk factors in 244 patients with actinic keratosis (AK), squamous cell carcinoma in situ (SCCis) and cutaneous squamous cell carcinoma (cSCC), who were under dynamic observation at the State Institution of

Table I. The results of the analysis of one-factor logistic regression models for pathology risk prediction

Factor		Coefficient of the model equation, b±m	Significance level, p	OR (95% CI)	AUC (95% CI)
Sex	female	Reference			0.56 (0.52–0.60)
	male	0.51±0.17	0.003	1.7 (1.2–2.3)	
Age	under 65	Reference			0.76 (0.72–0.79)
	65-69	0.91±0.27	0.001	2.5 (1.5–4.2)	
	70-74	0.38±0.29	0.19	–	
	>75	2.61±0.26	<0.001	13.6 (8.2–22.8)	
1. How often did you get sunburns of the skin (especially in childhood or adolescence)?		0.99±0.10	<0.001	2.7 (2.2–3.3)	0.77 (0.73–0.80)
2. Do you use skin sunscreens in the sun?		–1.57±0.16	<0.001	0.21 (0.15–0.29)	0.76 (0.72–0.79)
3. Have you spent much time in the sun recently?		–0.95±0.18	<0.001	0.39 (0.27–0.55)	0.61 (0.57–0.65)
4. Have you had long-term exposure to radioactive materials?		1.26±0.43	0.003	3.5 (1.5–8.1)	0.53 (0.49–0.57)
5. Have you had long-term exposure to toxic chemicals?		–2.39±1.04	0.02	0.09 (0.01–0.70)	0.52 (0.48–0.56)
6. How often do you traumatize benign neoplasms of the skin, such as naevus?		–0.35±0.10	0.001	0.70 (0.57–0.86)	0.57 (0.53–0.61)
7. What medicines do you often use?					
7.1 antiarrhythmic_drugs		–1.86±0.22	<0.001	0.16 (0.10–0.24)	0.68 (0.64–0.72)
7.2 antihypertensive_medications		–1.06±0.18	<0.001	0.35 (0.25–0.49)	0.63 (0.59–0.67)
7. hormonal_contraceptives		0.22±0.30	0.46	–	–
7.4 other_ hormonal_agents		–0.60±0.41	0.14	–	–
7.5 antibiotics		–1.53±0.28	<0.001	0.22 (0.13–0.37)	0.60 (0.56–0.64)
7.6 cytostatic_agents		0.81±0.52	0.12	–	–
7.7 immune_adjuvants		0.63±0.59	0.29	–	–
7.8 other		–0.49±0.44	0.26	–	–
8. Fitzpatrick phototype					
photo-type	1	Reference			0.55 (0.51–0.59)
	2	–0.52±0.22	0.02	0.59 (0.39–0.90)	
	3	–0.29±0.27	0.29	–	
9. Have any of your close relatives (father/mother, brother/sister, aunt/uncle) had skin cancer? Namely:					
9.1 melanoma=»Y»		2.12±0.77	0.006	8.3 (1.8–37.4)	0.52 (0.48–0.56)
9.2 basalioma=»Y»		0.87±0.26	0.001	2.4 (1.4–3.9)	0.55 (0.51–0.59)
9.3 squamous_cell_ skin_cancer=»Y»		1.62±0.51	0.002	5.1 (1.9–13.8)	0.53 (0.49–0.57)

Science "Research and Practical Centre of Preventive and Clinical Medicine" State Administrative Department (hereinafter SIS) in 2014-2017. There was also carried out medical and social survey of 323 residents of Kyiv city and Kyiv region with no signs of oncological pathology. To identify RF, the method of building and analyzing the logistic regression models was used. In the course of the analysis, the presence of AK, SCCis, cSCC in patient was considered as a dependent variable Y. As the risk factors, the analysis was carried out for such variables as sex, patient's age and 9 items of the developed questionnaire: the presence of burns in childhood and adolescence, skin phototype, the possible use of skin sunscreens, the possible long-term exposure to radioactive or toxic chemicals, traumatization of benign neoplasms of the skin, the use of drugs that have photosensibilizing effect on the skin and cases of skin cancer among close relatives. Each RF was appraised by points [17]. Statistical processing was

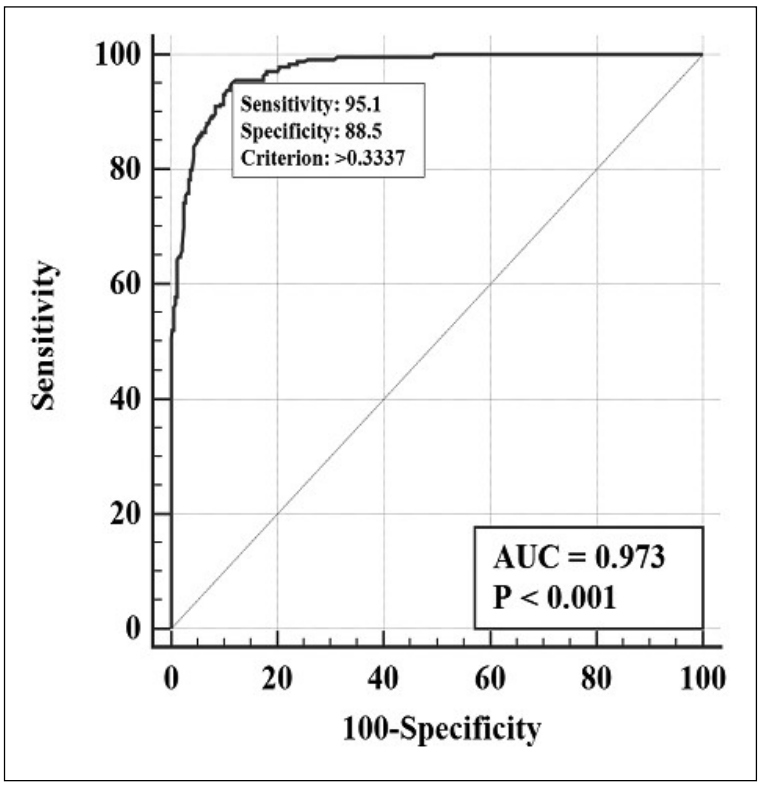

Figure 1. ROC-curve of the 11-factor model for the pathology risk prediction.

carried out using MedCalc v.18.11.3 (MedCalc Software Inc., Broekstraat, Belgium, 1993–2019).

RESULTS AND DISCUSSION

The survey involved 323 residents of Kyiv city and Kyiv region with no signs of oncological pathology of the skin, 157 men and 166 women among them. There was the following age distribution of respondents: 60-64 years – 42.4% (male – 40.8%, female – 44%), 65-69years – 24.1% (male – 20.4%, female – 22.3%), 70-74 years – 24.2% (male – 22.9%, female – 25.3%), 75 years and over – 12% (male – 15.9%, female – 8.4%).

A total of 244 patients with AK, SCCis, cSCC was also surveyed, including 103 patients with AK (62 men, 41 women), 59 patients with SCCis (32 men, 27 women), 60 patients with cSCC (38 men, 22 women) and 22 patients with combined course of AK, SCCis, cSCC (17 men, 5 women). There was the following age distribution: 35-39 years – 0.8%, 40-44 years – 1.2%, 50-54 years – 0.4%, 55-59 years – 4.1 % (male – 4.02%, female – 4.2%), 60-64 years – 8.2% (male – 6.04%, female – 11.6%), 65-69 years – 18.1% (male – 18.8%, female – 16.8%), 70-74 years – 11.9% (male – 10.7%, female – 13.7%), 75 years and over – 55.3% (male – 58.4%, female – 50.5%).

Among 323 residents of Kyiv city and Kyiv region with no signs of oncological pathology of the skin, there prevailed the following RF of skin cancer: skin phototype 2 – 52.4%, excessive sun exposure – 42% (male – 41.3%, female – 42.5%), exposure to radioactive materials – 3% (male – 4%, female – 1%) and toxic chemicals – 4.1% (male – 4.3%, female – 3.8%), the use of drugs with photosensibilizing action – 20.02% (male – 20.3%, female – 19.7%), traumatization of benign neoplasms of the skin – 23.5% (male – 19%, female – 27.8%), inheritance of basal cell carcinoma – 8.5% (male – 8.1%, female – 8.9%), squamous cell carcinoma – 1.5% (male – 1.08%, female – 1.92%).

Among 244 respondents with AK, SCCis, cSCC there prevailed the following RF of skin cancer: skin phototype 2 – 60.9%, excessive sun exposure – 58.6% (male – 64.4%, female – 49.5%), exposure to radioactive materials – 8.2% (male – 12.1%, female – 2.1%), traumatization of benign neoplasms of the skin – 46.7% (male – 47.0%, female – 46.3%), the use of drugs with photosensibilizing action – 47.5% (male – 42.3%, female – 55.8%), inheritance of basal cell carcinoma – 18.03% (male – 18.1%, female – 17.9%), squamous cell carcinoma – 7.4% (male – 6.7%, female – 8.4%).

The analysis involved the results of the survey of 567 patients, of which 323 patients had no signs of the pathology (Y = 0) and 244 were diagnosed with AK, SCC, SCCI (Y = 1).

At the first stage, one-factor logistic models for the pathology risk prediction were constructed and analysed. Table I presents the results of one-factor regression models.

The analysis showed a weak association (area under ROC-curve AUC = 0.56 (95% CI 0.52-0.60)) between risk of pathology and patient's sex; thus among men the risk increases (p = 0.003), OR = 1.7 (95% CI 1.2 – 2.3) compared to women. There was found a moderate association (area under ROC-curve AUC = 0.76 (95% CI 0.72–0.79)) between risk of pathology and patients' age of 65-69 years

Table II. The results of the analysis of 11-factor logistic regression model for pathology risk prediction

No.	Factor		Coefficient of the model equation, b±m	Significance level, p	OR (95% CI)	AUC (95% CI)
1	Age	under 65		Reference		0.97 (0.96–0.99)
		65-69	0.79±0.48	0.10	–	
		70-74	–0.29±0.56	0.60	–	
		>75	2.98±0.53	<0.001	19.7 (7.0–56)	
2	How often did you get sunburns of the skin (especially in childhood or adolescence)?		1.50±0.18	<0.001	4.5 (3.2–6.4)	
3	Do you use skin sunscreens in the sun?		–2.39±0.32	<0.001	0.09 (0.05–0.17)	
4	Have you spent much time in the sun recently?		–0.98±0.39	0.01	0.37 (0.17–0.81)	
5	Have you had long-term exposure to radioactive materials?		1.56±0.80	0.05	4.7 (1.0–22.9)	
6	What medicines do you often use?					
6.1	antiarrhythmic_drugs		–2.43±0.42	<0.001	0.09 (0.04–0.20)	
6.2	antihypertensive_medications		–2.65±0.42	<0.001	0.07 (0.03–0.16)	
6.3	hormonal_contraceptives		4.41±0.76	<0.001	82.6 (18.5–369)	
6.4	antibiotics		–1.81±0.60	0.003	0.16 (0.05–0.53)	
7	Have any of your close relatives (father/mother, brother/sister, aunt/uncle) had skin cancer? Namely					
7.1	melanoma=»Y»		1.89±1.04	0.07	6.6 (0.9–50.6)	
7.2	squamous_cell_skin_cancer =»Y»		1.67±0.98	0.09	5.4 (0.8–36.2)	

(p=0.001), OR=2.5 (95% CI 1.5–4.2) and 75 years and over (p=0.001), OR=13.6 (95% CI 8.2–22.8) compared to under 65 years. The analysis also showed a moderate association (area under ROC-curve AUC = 0.77 (95% CI 0.73–0.80) and AUC = 0.76 (95% CI 0.72–0.79)) between risk of pathology and sunburns of the skin (p=0.001), OR=2.7 (95% CI 2.2-3.3) and non-use of skin sunscreens (p=0.001), OR=0.21 (95% CI 0.15-0.29).

Such factors as "exposure to the sun in recent times" and "traumatization of benign neoplasms of the skin" had weak association (AUC = 0.61 (95% CI 0.57-0.65) and AUC = 0.57 (95% CI 0.53-0.61) respectively) with risk of pathology (p=0.001), OR=0.39 (95% CI 0.27-0.55) and (p=0.001), OR=0.70 (95% CI 0.57-0.86) respectively. The analysis also showed a weak correlation (AUC = 0.53 (95% CI 0.49–0.57) and AUC = 0.52 (95% CI 0.48–0.56)) between risk of pathology and a long-term exposure to radioactive materials (p=0.003), OR=3.5 (95% CI 1.5-8.1) and toxic chemicals (p=0.02), OR=0.09 (95% CI 0.01-0.70).

A weak relationship between the pathology (AUC = 0.52 (95% CI 0.48-0.56), AUC = 0.55 (95% CI 0.51-0.59) and AUC = 0.53 (95% CI 0.49-0.57) respectively) and hereditary factor of melanoma (p=0.006), OR=8.3 (95% CI 1.8-37.4), basal cell carcinoma (p=0.001), OR=2.4 (95% CI 1.4-3.9) and squamous cell carcinoma (p=0.002), OR=5.1 (95% CI 1.9-13.8) was detected.

At the second stage of the analysis, a minimum set of factors which were significantly associated with the risk of pathology was selected. Multi-factor logistic regression models were used for the analysis, the stepwise method (enter variable if p<0.1 and remove variable if p>0.2) was used for selection. As a result, 11 factors were selected, namely: patient's age, sunburns, the use of skin sunscreens, exposure to the sun in recent times, exposure to radioactive materials, the use of drugs (antiarrhythmic drugs, antihypertensive medications, hormonal contraceptives, antibiotics), burdened family history (melanoma, squamous cell cancer). Based on the set of signs, the 11-factor logistic regression model for the pathology risk prediction was built. Figure 1 presents ROC-curve of the model.

The prognostic model is valid, AUC = 0.97 (95% CI 0.96 – 0.99) showing a significant association of the risk of skin cancer development with the following factors: patient's age, sunburns, using sun-protection preparations, exposure to the sun in recent times, exposure to radioactive materials, drug administration (antiarrhythmic drugs, antihypertensive medications, hormonal contraceptives, antibiotics), burdened family history (melanoma, squamous cell cancer). Table II presents the results of the 11-factors regression model.

The analysis showed a weak relationship between risk of the pathology with patient's age; thus at the age of 75 and over the risk increases (p<0.001), OR = 19.7 (95% CI 7.0 - 56) compared to patients under 65 years (on

adjustment of other risk factors). There was also found an increase ($p<0.001$) of the pathology risk at higher frequency of sunburns (OR = 4.5 (95% CI 3.2 – 6.4) for each frequency rise in the questionnaire (on adjustment of other risk factors), non-use of skin sunscreens (OR = 0.09 (95% CI 0.05 – 0.17) for each frequency rise in the questionnaire (on adjustment of other risk factors)) and exposure to the sun in recent times (OR = 0.37 (95% CI 0.17 – 0.81) for each frequency rise in the questionnaire (on adjustment of other risk factors)).

On the basis of a strong correlation between 11 selected factors with the risk of skin pathology (AK, SCCis. cSCC) there can be proposed a system for the pathology risk prediction; when choosing the optimal threshold for decision-making, the sensitivity of the model was 95.1% (95% CI 91.6% - 97.4%), the specificity – 88.5% (95% CI 84.6% - 91.8%).

For practical use, the 11-factor logistic regression model for pathology risk prediction was implemented in Excel spreadsheet (Risk.xls file).

To perform counts, enter the patient information into appropriate cell of the table and press the ENTER key.

Here are some examples of the 11-factor logistic regression model.

Example 1. A 72-year-old patient with frequent sunburns in history, did not use skin sunscreens, has not been in the sun recently, has not used photosensitizing drugs and is not hereditary tainted. It was found that the risk of skin pathology was high and amounted to 0.951 (risk of pathology development). The patient was diagnosed with actinic keratosis.

Example 2. A 76-year-old patient, sometimes had sunburns and did not use skin sunscreens, has not been in the sun recently, but had a long-term exposure to radioactive materials, did not use photosensitizing drugs and is not hereditary tainted. It was found that the risk of skin pathology was high and amounted to 0.998 (risk of pathology development). The patient was diagnosed with combined pathology of the skin – actinic keratosis and squamous cell skin cancer in-situ.

Example 3. A 64-year-old patient often had sunburns, hardly ever used skin sunscreens, has not been in the sun recently, but had a long-term exposure to radioactive materials, takes antiarrhythmic and antihypertensive drugs and is not hereditary tainted. It was found that there was no risk of skin pathology as it was 0.066 (favourable prognosis). The patient was not diagnosed with the studied skin pathology.

Example 4. A 70-year-old patient sometimes had sunburns, hardly ever used skin sunscreens, has not been in the sun recently, did not have exposure to radioactive materials, takes antiarrhythmic and antihypertensive drugs, has family history of squamous cell skin cancer. It was found that there was no risk of skin pathology as it was 0.059 (favourable prognosis). The patient was not diagnosed with the studied skin pathology.

Example 5. A 56-year-old patient often had sunburns, hardly ever used sun sunscreens, has not been in the sun recently, did not have exposure to radioactive materials, did not use photosensitizing drugs and is not hereditary tainted. It was found that the risk of skin pathology was high and amounted to 0.705 (risk of pathology development). The patient was diagnosed with cutaneous squamous cell carcinoma.

CONCLUSIONS

The developed and analyzed mathematical risk prediction system made it possible to identify 11 factors which are significantly associated (AUC = 0.97 95% CI 0.96 – 0.99) with risk of skin cancer development. The prognostic model might be offered for specialists in taking decision at the stage of primary and secondary prevention of skin cancer.

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Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

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ORAL HEALTH ABNORMALITIES IN CHILDREN BORN WITH MACROSOMIA ESTABLISHED DURING MIXED DENTITION PERIOD

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ABSTRACT

Introduction: The prevalence of soft tissue and hard tooth tissuediseases in the oral cavity and the morphofunctional disorders of craniofacial complex, require attention ofspecialistsin various branches of medicine. Scientists began to pay attention to metabolic and other violations that have occurred in the fetal development and led to the occurrence of certain changes in the dental status of the child.

The aim of thisresearch is to study the features of the dental health condition in the children of Northeast of Ukraine, who were born with macrosomia during the period of mixed dentition. The study takes into account intrauterine body length growth acceleration, intrauterine obesity or well-balanced acceleration of both the body weight and length gain.

Materials and methods: Thirty 6.5–11-year-old children with fetal macrosomia were examined (MainGroup). A Comparison Group was comprised of sixteen children, whose weight-height parameters at birth were normal (fetal normosomia). All children in the Main group were split into four subgroups in accordance with weight-height parameters at birth using the V. I. Grischenko and his co-authors' harmonious coefficient. The evaluation of the hygiene status of the oral cavity, the dental caries intensity evaluation, and the quantitative analysis of minor salivary gland secretion have been performed. The prevalence of dentoalveolar abnormalities was evaluated.

Results: The highest values of caries intensity were recorded in macrosomic-at-birth children born with harmonious (well-balanced) intrauterine development, with intrauterine obesity and increased body length, or with intrauterine obesity and an average body length. Macrosomic children have reduced number of minor salivary glands per unit area in comparison with the normosomic-at-birth children. The saliva secretion of minor salivary glands in macrosomic children is reliably, by 16,5% on average, reduced. Children born with fetal macrosomia have long narrow faces and high palates more frequently than normosomic-at-birth children. Children born macrosomic have a significantly higher percentage (100% versus 73%)of dentoalveolar abnormalitiesin comparison with the normosomic-at-birth children.

Conclusions: The processes causing fetal macrosomia have a great impact on the dental status of children in the period of mixed dentition.

KEY WORDS: fetal macrosomia; caries; minor salivary glands; malocclusion

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INTRODUCTION

The prevalence of soft tissue and hard tooth tissuediseases in the oral cavity and the morphofunctional disorders of craniofacial complex, require attention ofspecialistsin various branches of medicine. Changes in the structure of hard and connective tooth tissue and impaired blood supply caused by metabolic disorders have been already investigated. Thepernicious influence of obesity, diabetes mellitus, and metabolic syndrome on the hard tooth tissue and mucous membrane condition in the oral cavity have been described in several papers [1, 2, 3].

Nevertheless, only a few dentists pay attention to the birth weight of the baby, when parents are consulting the dentist to find out what is causing child's one or the other dental problem. That is, the dentist has information about the current state of health, and the data on the course of the fetal period, as a rule, are lost eventually and are not taken into account in analyzing the causes and characteristics of the current dental status of the child. Over the years, scientists began to pay attention to metabolic and other violations that have occurred in the fetal development and led to the occurrence of certain changes in the dental status of the child [4, 5].

One of the variations in intrauterine metabolic disorders is fetal macrosomia, or a large birth weight. The fetal macrosomiameans that the birth weight of a full-term newborn is greater than or equal to 4,000 g [6]. In recent decades, researchers from different countries have found out high caries intensity in children and adolescents,which were born with fetal macrosomia [7, 8].

The investigations we have conducted in previous years have also revealed the presence of a large number of soft tissueabnormalitiesin the oral cavity, the features in the timing of desiduous teeth eruption, hypoplastic changes in minor salivary glands, the high intensity of desiduous teeth caries in pre-school age children which were born macrosomic, as compared tothe children whose weight-height parameters at birth were normal [9].

THE AIM

The aim of this investigation is to study the features of the dental state condition of the children born macrosomicin the Northeast of Ukraineduring the period of mixed dentition. The study takes into account an intrauterine accelerated increase in the body length; intrauterine obesity,