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CERVICAL CANCER IN THE STATE ENTITIES OF THE RUSSIAN ARCTIC ZONE: A COMPARATIVE ANALYSIS OF INCIDENCE AND MORTALITY IN THE PERIOD FROM 2016 TO 2020

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On the basis of age-standardized and calculated per 100,000 population cervical cancer (CC) incidence and mortality rates, an analysis of the prevailing over 5 years, from 2016 to 2020, is presented. CC data analysis was conducted among nine state entities of Russia, whose territories are wholly or partially located in the Arctic. The calculations carried out using the Friedman's and Wilcoxon's tests, as well as the T-test showed that in these territories there is an unfavorable situation in relation to CC. In most state entities, the CC incidence and its dynamics, as well as the dynamics of CC mortality over five years from 2016 to 2020 show worse results than in Russia as a whole. The most vulnerable to cervical cancer at the present time is the population of Krasnoyarski Krai, Nenetski and Chukotski Autonomous Okrugs. Therefore, these territories especially require the use of new and strengthening of existing measures aimed at the CC prevention, early detection and improvement of treatment.

Keywords: health disparities, human papillomavirus, ethnic groups, indigenous population, North.

Cervical cancer (CC) has still been remaining one of the most common cancer sites among malignant neoplasms (MN) in spite of a screening and an immunization against the human papillomavirus (HPV), as well as the development and implementation of new treatment ways in the health care system. The latest available data reflecting the global cancer statistics - 2020 from the International Agency for Research on Cancer (IARC) of the World Health Organization [1] showed that CC has occupied the top positions in terms of the incidence and mortality amongst all cancer sites. According to its age-standardized incidence rates (ASIRs) CC has ranked, in descending order, to the 5th place in the world including both sexes (13.3 cases per 100,000 populations) and following breast, prostate, lung and colorectal cancers. In the case of women CC has ranked the 4th in the world following breast cancer, colorectal cancer and lung cancer. In terms of the age-standardized mortality rate (ASMR) CC has ranked the 7th (7.3 cases per 100,000 population) worldwide including both sexes following lung, breast, colorectal, liver, stomach, and prostate cancers; and the 3rd place in the case of women following breast and lung cancer [2].

According to the IARC too in Russia in 2020 CC was almost in the same positions – the 6th place (14.1 cases per 100,000 populations) in ASIR including both sexes following breast cancer, prostate cancer, colorectal cancer, lung, and corpus uteri cancer, and the 4th in women following breast cancer, cancer of the corpus uteri and colorectal cancer. In ASMR the CC ranked to 7th place (6.1 cases per 100,000 populations) including both sexes following lung, breast, colorectal, prostate, stomach, and pancreatic cancers, and tied for 3rd place with lung cancer in women following breast cancer and colorectal cancer [2].

The CC incidence (CCI) in Russia in 2020 continues to significantly exceed the level set by the WHO in its global strategy to accelerate the elimination of CC as a public health problem for the period 2020-2030 with the aim to achieve and maintain the CCI at a level of less than 4 cases per 100,000 thousand women per year [3].

Russia is a country with a large population - according to the World Bank in 2020 its population was 144.104 million people. Such a population allowed Russia to take the 9th place among all countries of the world in order to theirs citizens' number [4]. Among the state territorial entities of the upper level (SEs) of the Russian Federation there is a significant variability in population's density, number, ethnic groups, income, educational level and other demographic and social indicators [5]. Therefore, CC disparities among the population in different territories are expected and, moreover, confirmed in studies [6].

Studies on health disparities in different territories make possible to show the residence area of the population, which are in first needs to be organized activities to prevent, early detect and increase effectiveness for certain diseases treatment.

In the Investment Portal of the Arctic Zone of the Russian Federation (AZRF) of the Ministry for the Development of the Russian Far East and Arctic there is the statement saying the AZRF forms a fifth of the federal budget revenues [7]. Also the Document entitled "Foundations of the Russian Federation State Policy in the Arctic for the Period up to 2035", approved by Decree of the President of the Russian Federation No.164 dated March 5, 2020, has the statement saying the prosperity and well-being of people living in the Arctic is one of the main interests of Russia [8].

The current study is devoted to the CCI and CCM status evaluation, which has developed over a period of five years, from 2016 to 2020, among the SEs of the Russian Federation, the settlements of which are fully or partially attributed to the Russian Arctic such as the Arkhangelskaya Oblast (AO), the Murmanskaya Oblast (MO), the republics Karelia (RKa), Komi (RKo) and Sakha (Yakutia) (RSYa), the Krasnoyarski Krai (KK), the Chukotski Autonomous Okrug (ChAO), the Yamalo-Nenetski Autonomous Okrug (YaNAO) and the Nenetski Autonomous Okrug (NAO). The period 2016 – 2020 was chosen because of these 5-years data are available as close as possible to the

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time of this study. Difference analyses of the CCI and CCM as well as changes in the CCI and CCM rates in 2020 compare to 2016 among the SEs and Russia as whole with spotting of SEs with the most CC burden were made.

Materials and methods. For a comparative analysis of the CCI and the CCM, the age-standardized CCI and CCM rates per 100,000 populations (CC ASIRs and CC ASMRs, respectively) were used. These statistical indicators are presented in the books of the Moscow Research Oncological Institute named after P.A.Herzen - a branch of the Federal State Budgetary Institution "National Medical Research Center of Radiology" of the Ministry of Health of Russia, which were published from 2017 to 2022 on the Website for medical and pharmaceutical workers "ONCOLOGY.ru" [9]. In the study the indicators of all nine SEs the settlements of which are fully or partially attributed to the Russian Arctic such as the AO, the ChAO, the YaNAO, the NAO, the MO, the RK, the RKo, the KK, the RSYa as well as all-Russian indicators were included.

Retrospective time period is from 2016 to 2020. Cancer site is cervix; code is C53, according to the international classification of diseases (ICD, International Classification of Disease, ICD, 10th revision, version 2010).

Because the preliminary used the Kolmogorov-Smirnov's test showed that the distribution of mean values of the annual CC ASIRs and ASMRs in all nine selected SEs and in Russia as a whole in the mentioned above time period does not correspond to the normal one ($0.999 \geq p \geq 0.481$ and $1.000 \geq p \geq 0.606$, respectively), for finding differences in the CCI and the CCM across multiple indicators and between them Friedman's two-way rank test and Wilcoxon's signed rank test, respectively, were used.

Since included in the study the CC ASIRs and ASMRs in each year are presented in the above-mentioned books as an mean with its error then to find CC incidence and mortality differences between 2020 and 2016, T –test was used.

Differences have been considered significant at $p<0.05$. If $0.05 \leq p \leq 0.1$ differences have been considered to have a tendency to exist.

Results. The annual CC ASIRs and ASMRs in the period 2016-2020 in all nine SEs of the Russian Arctic and in Russia as a whole are shown in Table 1.

Friedman's test revealed the heterogeneity of the annual CC ASIRs in 2016-2020 in the total observation group in which all nine SEs and Russia as a whole were included ($p=0.010$). The ranking of the annual CC ASIRs of all nine SEs and Russia as a whole in this time period is shown in Figure 1. By continuing to carry out Friedman's test and by excluding one by one indicators of the SEs with minimum ranks from the group, it was found that the maximum CCI, estimated by the annual CC ASIRs in this time period were observed in four SEs - in the NAO, the RSYa, the KK and the AO. In these SEs we had seen the homogeneity of the CC ASIRs ($p=0.323$). The Wilcoxon's test, which is presented in Table 2, showed that the CCI in the NAO, which was assigned the maximum rank in accordance with Friedman's test, tended to exceed that one of three SEs - the MO, the ChAO and the YaNAO; the CCI in the RSYa, which take the 2nd place according to Friedman's test, was significantly higher than ones in four SEs - the MO, the RKa, the ChAO and the YaNAO; the CCI in the KK (the 3rd place) was higher than that in three SEs - significantly higher as compared with in the MO and had a tendency to be higher as compared with one in the ChAO and in the YaNAO; the CCI in the AO (the 4th place) were as close as possible to the CCI in the KK and the RSYa (please, see p values) and exceeded those of two SEs - significantly as opposed to in the MO and had a tendency to exceed that in the ChAO.

Also, using the Wilcoxon's test, it was revealed that the CCI in 2016-2020 in most SEs of the Russian Arctic (55.5% or in five out of nine), such as the AO, the MO, the KK, the RSYa and the NAO, significantly exceeded or had a tendency to exceed the all-Russian level. Only in the ChAO the CCI was lower than the all-Russian one.

In 2020 compared to 2016 estimated by its ASIRs the CCI did not increase in any SEs. On the contrary, in the RKa, the RKo, the RSYa and YaNAO, as well as in Russia as a whole, the CCI has significantly decreased (in all listed cases, $p<0.05$). However, again, in most SEs of the Russian Arctic (55.5% or five out of nine SEs), such as the AO, the MO, the KK, the NAO and the ChAO, in 2020 compared to 2016, neither a CCI significant decrease nor tendency toward it were observed.

Friedman's test of the CC ASMRs in the general observation group in the period 2016-2020 revealed only a tendency to heterogeneity ($p=0.070$). The ranking results can also be seen in Figure 1. As well as in the case of the CCI we continued carry out Friedman's test and excluded the SEs with minimum ranks from the general observation group and it was found that the CC ASMRs in most SEs, with the exception of the YaNAO and Russia as a whole, the CCM in this period of time did not differ in accordance to our chosen significance for p.

The presented in Table 2 results of Wilcoxon's test showed that the CC ASMRs in 2016-2020 in the ChAO assigned the maximum average rank in accordance to Friedman's analysis had a tendency to exceed those ones in the AO and significantly exceeded in the RSYa. Comparing the CC ASMRs in the followed the ChAO the NAO with the ranks of other SEs and Russia as a whole did not reveal either the required significance or a tendency towards differences. However, the CC ASMRs in the NAO had a minimal probability of having differences with the ChAO's and the KK's CC ASMRs (please, see p values). The CC ASMRs in the KK, which shared the second place with the NAO in terms of the average rank, had a tendency to exceed those ones in the AO and significantly exceeded those in the RKa. The CC ASMRs in the RKo, the average rank of which was in a third place (according to Friedman's test), had a tendency to exceed those in the AO (which took 7th place), and at the same time, it's the CC ASMRs were closer to those in the MO (4th place) and the RSYa (5th place) than to the ranks of the ChAO, the NAO and the KK (please see p values). The CC ASMRs in the remaining SEs such as the MO, the RSYa, the RKa and the AO did not have significant pairwise differences with each other when calculating the Wilcoxon's test. Therefore, finally, we believe that the maximum CCM estimated by the CC ASMRs in 2016-2020 were noted in the ChAO, the NAO and the KK. The excess over the all-Russian CCM was noted in three SEs of the Russian Arctic – the ChAO, the KK, and in the RKo (Table 2).

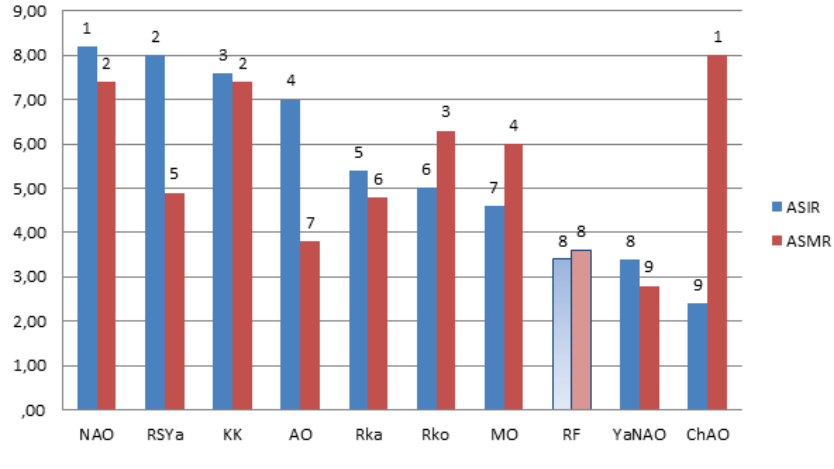
As well as the CCI the CCM, estimated by CC ASMRs, in 2020 in contrast with 2016 did not increase in any of SEs. The CCM in Russia as a whole, in the MO and the RSYa significantly decreased ($p<0.05$), while CCM in the AO had a tendency to decrease ($0.05 \leq p \leq 0.1$). Despite the fact that in this time period in the NAO the CC ASMR decreased by more than 3 times, the difference did not reach either the required significance or a trend towards its presence, as in other SEs, such as the RKa, the RKo, the KK, the ChAO and the YaNAO. That is, in six out of nine SEs (66%), or, if we exclude the NAO from the calculations (because as mentioned above p did not reach the required significance or a trend towards its pres-

Table1

Annual values of CC ASIRs and ASMRs in the SEs of AZRF and in RF in 2016-2020

SE	CC ASIR M (95% CI)				
	2016	2017	2018	2019	2020
RF	15.45 (15.33-15.57)	15.76 (15.64-15.88)	15.80 (15.68-15.92)	15.38 (15.26-15.50)	13.67 (13.55-13.79)
AO	18.32 (16.76-19.88)	17.78 (16.27-19.29)	23.69 (21.91-25.47)	28.85 (26.77-30.93)	15.16 (13.76-16.56)
MO	16.26 (14.63-17.89)	17.73 (15.79-19.67)	20.76 (18.90-22.62)	17.00 (15.26-18.74)	13.57 (12.03-15.11)
RKa	22.58 (20.16-25.00)	19.94 (17.75-22.13)	20.06 (17.92-22.20)	14.64 (12.92-16.36)	13.26 (11.46-15.06)
RKo	17.13 (15.48-18.78)	23.50 (21.54-25.46)	16.77 (15.05-18.49)	17.75 (16.06-19.44)	12.10 (10.68-13.52)
KK	18.90 (17.95-19.85)	21.06 (20.07-22.05)	21.49 (20.50-22.48)	21.03 (20.03-22.03)	19.71 (18.75-20.67)
ChAO	21.30 (13.98-28.62)	13.11 (7.43-18.79)	9.01 (4.02-14.00)	11.28 (5.87-16.69)	11.76 (4.84-18.68)
RSYa	22.85 (20.99-24.71)	20.20 (18.45-21.95)	21.57 (19.76-23.38)	18.38 (16.70-20.06)	16.43 (14.86-18.00)
YaNAO	20.39 (17.90-22.88)	15.96 (13.47-18.45)	12.53 (10.67-14.39)	12.69 (10.86-14.52)	12.21 (10.33-14.09)
NAO	8.01 (2.39-13.63)	29.37 (19.11-39.63)	31.38 (22.15-40.61)	32.50 (22.53-42.47)	25.15(13.42-36.88)
SE	CC ASMR M (95% CI)				
	2016	2017	2018	2019	2020
RF	5.26 (5.19-5.33)	5.18 (5.11-5.25)	5.07 (5.00-5.14)	5.01 (4.94-5.08)	4.84 (4.77-4.91)
AO	7.22 (6.28-8.16)	4.05 (3.39-4.71)	3.81 (3.14-4.48)	5.08 (4.27-5.89)	4.94 (4.20-5.68)
MO	6.83 (5.76-7.90)	7.09 (5.98-8.20)	5.21 (4.34-6.08)	7.35 (6.22-8.48)	3.84 (3.00-4.68)
RKa	5.06 (4.04-6.08)	5.60 (4.56-6.64)	5.56 (4.49-6.63)	4.90 (3.98-5.82)	5.60 (4.56-6.64)
RKo	6.84 (5.84-7.84)	4.89 (4.04-5.74)	5.59 (4.71-6.47)	6.01 (5.05-6.97)	5.35 (4.48-6.22)
KK	6.61 (6.07-7.15)	6.80 (6.25-7.35)	6.40 (5.87-6.93)	6.21 (5.69-6.73)	6.06 (5.53-6.59)
ChAO	19.07 (11.52-26.62)	19.07 (11.52-26.62)	4.78 (1.51-8.05)	5.51 (1.77-9.25)	6.07 (1.95-10.19)
RSYa	6.84 (5.81-7.87)	6.84 (5.81-7.87)	4.61 (3.80-5.42)	5.49 (4.60-6.38)	4.15 (3.38-4.92)
YaNAO	5.64 (4.31-6.97)	4.13 (3.03-5.23)	4.43 (2.94-5.92)	4.03 (2.67-5.39)	5.22 (4.02-6.42)
NAO	0.00 (0.00-0.00)	18.98 (10.37-27.59)	6.53 (2.07-10.99)	9.53 (4.20-14.86)	5.39 (1.72-9.06)

Note: M – mean value, CI - confidence interval. Please, see the explanation of abbreviations in Tables 1-3 and Fig.1 in the text.



Average ranks of the annual CC ASIRs and ASMRs in the SEs of AZRF in 2016-2020

ence), in five out of nine SEs (55.5%) the CCM has not changed, despite the fact that mortality in Russia as a whole has decreased.

Thus, the maximum CCI, estimated by the ASIRs, in the period from 2016 to 2020 among the SEs, the settlements of which belong to the Russian Arctic, was observed in the NAO, the RSYa, the KK and the AO. The excess over the all-Russian level of CCI was noted in the AO, the MO, the KK, the RSYa and the NAO. Despite the decrease in the all-Russian CCI in 2020 as opposed to 2016, neither CCI significant decrease nor a trend towards its presence was recorded in the AO, the MO, the KK, the NAO and the ChAO. The maximum CCM estimated

Table2

The p-values for pairwise differences in the ranks of the CC ASIRs/ASMRs between the SEs of AZRF and Russia as a whole in 2016-2020

	AO	MO	RKa	RKo	KK	ChAO	RSYa	YaNAO	NAO
RF	0.043**/ 0.893	0.080*/ 0.138	0.225/ 0.225	0.138/ 0.080*	0.043**/ 0.043**	0.345/ 0.080*	0.043**/ 0.345	0.686/ 0.223	0.080*/ 0.345
AO	N/A	0.043*/ 0.225	0.686/ 0.686	0.220/ 0.080*	0.893/ 0.080*	0.080*/ 0.080*	0.893/ 0.345	0.138/ 0.686	0.345/ 0.345
MO	0.043**/ 0.225	N/A	0.893/ 0.345	0.893/ 0.893	0.043**/ 0.686	0.225/ 0.225	0.043**/ 0.345	0.225/ 0.225	0.080*/ 0.345
RKa	0.686/ 0.686	0.893/ 0.345	N/A	0.686/ 0.500	0.225/ 0.043**	0.043**/ 0.225	0.043**/ 0.686	0.043**/ 0.138	0.345/ 0.500
RKo	0.220/ 0.080*	0.893/ 0.893	0.686/ 0.500	N/A	0.138/ 0.138	0.138/ 0.345	0.138/ 0.715	0.225/ 0.043**	0.138/ 0.345
KK	0.893/ 0.080*	0.043**/ 0.686	0.225/ 0.043**	0.138/ 0.138	N/A	0.078*/ 0.500	0.686/ 0.225	0.080*/ 0.043**	0.345/ 0.686
ChAO	0.080*/ 0.080*	0.225/ 0.225	0.043**/ 0.225	0.138/ 0.345	0.078*/ 0.500	N/A	0.043**/ 0.043**	0.138/ 0.043**	0.080*/ 0.893
RSYa	0.893/ 0.345	0.043**/ 0.345	0.043**/ 0.686	0.138/ 0.715	0.686/ 0.225	0.043*/ 0.043**	N/A	0.043*/ 0.138	0.500/ 0.345
YaNAO	0.138/ 0.686	0.225/ 0.225	0.043**/ 0.138	0.225/ 0.043**	0.080*/ 0.043**	0.138/ 0.043**	0.043**/ 0.138	N/A	0.080*/ 0.345
HAO	0.345/ 0.345	0.080*/ 0.345	0.345/ 0.500	0.138/ 0.345	0.345/ 0.686	0.080*/ 0.893	0.500/ 0.345	0.080*/ 0.345	N/A

Note. *- differences have been considered to have a tendency to exist, **- differences have been considered significant, N/A- not applicable.

by CC ASMRs, in the period from 2016 to 2020 was in the ChAO, the NAO and the KK, and their CCM also exceeded the all-Russian one. In the RKa, the RKo, the KK, the ChAO, the YaNAO and the NAO in 2020 as opposed to 2016 the CCM had not changed despite a decreasing the all-Russian one.

In each SE a parameter estimated by the CC ASIRs and ASMRs indicating an unfavorable situation in relation to CC there is. However, it is necessary to identify the most vulnerable SEs, which in first needs to be organized activities to prevent, early detect and increase effectiveness of CC treatment. Therefore, a summary table was compiled (Table 3), in which we present the summarized results of this study. In accordance with the results, the most unfavorable situation in relation to CC in the period 2016-2020 based on the annual CC ASIRs and ASMRs were developed in the KK, the NAO and the ChAO.

This is partially confirmed by a study based on the analysis of CCI in the same SEs group but including a longer time period - from 2011 to 2019 (9 years). An unfavorable situation regarding to CC was revealed in the same territories [10].

Stand to take into consideration that all three SEs such as the KK, the NAO and the ChAO in which the most unfavorable situation in relation to CC was revealed are located in the eastern part of the Arctic zone of Russia. Also, the territories of two of these three SEs – the NAO and the ChAO belong to the Russian Arctic completely and are characterized by ethnic diversity.

Conclusion. Based on the CC ASIRs and ASMRs in 2016-2020 in SEs, the settlements of which are fully or partially assigned to the Russian Arctic, and on all-Russian ones it can be argued that they all have an unfavorable situation with regard to CC. Therefore, in these SEs it is necessary to apply new and strengthen existing activities aimed at prevention, early detection and increasing the effectiveness of treatment. In most SEs the CCI and its changes, as well as the CCM changes, over five years from 2016 to 2020 a worse situation than in all Russia has showed. The most CC burden the populations of the KK, the NAO and the ChAO at the present time have.

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Table3

The sum of the calculated CCI and the CCM indicators ranks in SEs of AZRF in 2016-2020

Indicator	AO	MO	RKa	RKo	KK	ChAO	RSYa	YaNAO	NAO
Max CCI	1				1		1		1
The change in CCI in 2020 compare to 2016			-1	-1			-1	-1	
Max CCM					1	1			1
The change in CCM in 2020 compare to 2016	-0.5	-1					-1		
The sum	**0.5**	**-1**	**-1**	**-1**	**2**	**1**	**-1**	**-1**	**2**

Note. 1 - the presence of the indicator, 0.5 – the tendency towards the presence of the indicator. In the lines "The change in ..." negative values correspond to a decrease in the CCI or CCM.

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A VERIFIED CASE OF THE PRESENCE OF ACTIVE BROWN ADIPOSE TISSUE IN AN INDIGENOUS INHABITANT OF THE ARCTIC REGION OF YAKUTIA

A case of verification of active brown adipose tissue in a 40-year-old patient, a professional hunter resident of the Arctic ulus of Yakutia, is described. Real brown adipose tissue was found in samples of adipose tissue from the paranephral fiber. Adipose tissue samples showed high immunoreactivity to the activity marker of this tissue - mitochondrial protein UCP1.

Keywords: brown adipose tissue, cold, histology, immunohistochemistry, UCP1.

Introduction. Yakutia is one of the largest regions of the Russian Federation with a predominance of extremely low temperatures throughout the year. More than 40% of the territory of our republic is located beyond the Arctic Circle and belongs to the Arctic zone.

The extreme conditions of the Arctic have an impact on the adaptive potential, affect the functional state of the human body and its working capacity, the level of health and the duration of active life.

The exploration and development of the Arctic is one of the priorities of Russia's state policy. The life support and economic potential of the country are essentially determined by the health of the population. Research aimed at ensuring the health of the Arctic population is becoming especially relevant in modern conditions.

The first description of brown adipose tissue dates back to 1551, when Gessner described this tissue in a book on anatomy as "nec pinguitudo nec caro", which means "neither fat nor flesh" [1]. However, as a thermogenic organ necessary for mammalian thermoregulation, it was recognized only less than half a century ago [2]. During the second half of the XX century and the beginning of the XXI, it was believed that it is present only in newborns and disappears after a year [2,3]. Although some indirect data had previously led several authors to assume its presence [1,4-9], and only with the advent of positron emission tomography with 18-fluorodeoxyglucose (PET-FDG), a functional imaging method evaluating areas of increased metabolic activity, began to be used more often in the observation of certain types of cancer, brown adipose tissue was It was found in at least one subgroup of the adult human population [2,10-14]. This discovery aroused great interest among researchers in this field and the hypothesis that the presence or absence of brown adipose tissue may be the cause of such common metabolic diseases as obesity and type 2 diabetes, as well as probably a potential therapeutic target, since excess energy is spent through non-contractile thermogenesis.

However, despite the presence of many indirect signs of activation of brown adipose tissue in adult residents of regions with extremely cold climates, up to now the fact has not been confirmed by histomorphological verification of brown adipose tissue.

In this article we describe a case of a verified fact of the presence of metabolically active brown adipose tissue in an indigenous inhabitant of the Arctic ulus of Yakutia.

Material and methods of research. Histological studies were carried out on the basis of the pathoanatomical Department of t Republican Hospital № 1 of the National Medical Center and the Faculty of Human and Animal Anatomy of the Polytechnic University del Marche (Ancona, Italy). The work was carried out within the framework of international cooperation between the Yakutsk Scientific Center for Complex Medical Problems (Yakutsk) and the Polytechnic University of del Marche (Ancona, Italy).

The patient received samples of adipose tissue from paranephral tissue taken from the area surrounding the renal artery after nephrectomy for urolithiasis.

Patient R., male, 40 years old, height 168 cm, slim build, was born and lives in Srednekolymsky ulus (Arctic zone of Yakutia), professional hunter-cadre officer, nationality Evenk. He spent a significant part of his working time outdoors and was exposed to significant exposure to cold.

Ethics Committee. The study was approved by the local Committee on Biomedical Ethics of the Yakut Scientific Center of Complex Medical Problems(Protocol No. 46 of May 24, 2018).

Histology. The collected samples were fixed by immersion in 4% paraformaldehyde in 0.1 M phosphate buffer (FB), pH 7.4. After thorough washing in FB, the samples were dehydrated in a graduated series of ethanol, purified in xylene and waxed. Serial paraffin sections with a thickness of 3-4 microns were obtained from each sample. The samples were stained with hematoxylin and eosin to assess morphology. All studies were carried

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