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ANALYSIS OF THE CERVICAL CANCER INCIDENCE IN THE ARCTIC ZONE OF THE RUSSIAN FEDERATION TO IDENTIFY REGIONS IN FIRST NEED OF ITS PREVENTION

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To identify the territories of the Arctic in which urgent measures are needed for the cervical cancer prevention, including vaccination, a comparative analysis of cervical cancer incidence (CCI) was carried out among Arkhangelskaya and Murmanskaya Oblasts, republics Karelia, Komi, Sakha (Yakutia), Krasnoyarski Krai, Chukotski, Yamalo-Nenetski and Nenetski Autonomous Okrugs and Russia as a whole. The annual rates of CCI per 100 thousand populations, standardized by age, were analyzed. Multiple and paired rank analyzes, as well as the calculation of annual changes from baseline in CCI, showed that cervical cancer prevention is an important task in these state entities, and the population of the Nenetski Autonomous Okrug, which is characterized by a significant proportion of indigenous people and ethnic minorities, needs it most urgently.

Keywords. HPV, vaccination, immunization, ethnic groups, indigenous population, North.

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Introduction. Development and availability of a vaccine against human papillomavirus (HPV) has provided an exceptional opportunity for the prevention of HPV-associated cancers, such as cervical cancer, oropharyngeal, anal, vaginal, vulvar and penile cancer [1].

28 countries in the WHO European Region have added HPV vaccination to their routine immunization schedules [2], as the United States and Canada have [1,3].

In its global strategy for the period 2020-2030 the WHO recognized it is extremely important to include immunization against HPV in the National Health Programs of all countries of the world

to accelerate the cervical cancer elimination. To eliminate cervical cancer the WHO emphasizes that all countries must achieve and maintain cervical cancer incidence at a rate of less than 4 cases per 100,000 women per year. Among the measures to eliminate cervical cancer the WHO notes the roadmap of complete vaccination of 90% of girls by the age of 15 years in all countries by 2030 [4].

In the Russian National Immunization Schedule named “Russian national preventive vaccinations and the vaccinations by epidemic indicators calendar” immunization against HPV has not yet been included. The Ministry of Health of the Russian Federation approved Order

No. 125n of March 21, 2014 [5]. At the same time, in the Russian Federation (RF), in the structure of cancer incidence and mortality, cervical cancer has a significant proportion. For example, in 2020 in the RF cervical cancer incidence and mortality took the 4th place in the structure of all cancer sites in women, and cervical cancer incidence had the rate 14.1 cases per 100 thousand populations that are significantly higher than the target rate set by the WHO [6].

If immunization against HPV becomes affordable to the most of Russian citizens and will be included in the Russian National Immunization Schedule or other administrative health programs, for instance, in any Zonal and Regional Health-Saving Programs, then at the start there may be a lack of vaccines. So, it is necessary to indicate territories where they should be delivered first. For this, in our opinion, it is necessary to determine territories with the highest rates of cervical cancer incidence and mortality, as well as a statistical correlation between them in their increasing. In accordance with these criteria we found in our previous research study that among State Entities located in Siberia, the Kemerovskaya Oblast, the Republic Buryatia and especially the Tyva Republic are in first need of cervical cancer prevention. These state entities have a high proportion of indigenous peoples and ethnic minorities [7,8].

The aim. Some regions of the Russian Arctic also have a significant proportion of indigenous peoples and ethnic minorities. Therefore, in this study, the goal was set - to find out whether a large vulnera-

bility to cervical cancer is also typical for multiethnic territories of the Arctic, and to find out which State Entities, whose settlements are attributed to the land territories of the Arctic zone of the Russian Federation (AZRF), are in first need to carry out preventive measures in relation to cervical cancer, including immunization against HPV. AZRF includes settlements of Arkhangelskaya Oblast (AO), Murmanskaya Oblast (MO), republics Karelia (RKa), Komi (RKO) and Sakha (Yakutia) (RSYa), as well as Krasnoyarski Krai (KK), Chukotski Autonomous Okrug (ChAO), Yamalo-Nenetski Autonomous Okrug (YaNAO) and Nenetski Autonomous Okrug (NAO) [9]. Objectives of the research study were to compare cervical cancer incidence (CCI) rates of these SEs with the all-Russian, and also to conduct analysis to identify SE(s) with the most negative situation in terms of the highest CCI rates and the highest values of the CCI increase from baseline.

Materials and methods. The CCI rates were extracted from 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. The books issued from 2012 to 2020 on the Website for medical and pharmaceutical workers "ONCOLOGY.ru". The CCI rates per 100 thousand populations which were standardized in accordance with the world distribution of the population by age (age-standardized incidence rate, ASIR) were used for the comparative assessment [10].

The CC ASIRs of the AO, the ChAO,

the YaNAO, the NAO, the MO, the RKa, the RKO, the KK, the RSYa and the RF were analyzed in this research study. The retrospective time period was from 2011 to 2019, as the CCI data in the YaNAO have become available since 2011.

The cancer site is the cervix uteri (C53).

As the CC ASIRs did not have a normal distribution to identify differences in more than two SE's multiple ordinal data Friedman's two-way rank analysis was used. To identify differences between data of SEs Wilcoxon rank test was used. To identify paired differences in mean values T-test was used.

The values of the annual CCI changes from baseline (ABCi) were calculated as the ratio of the difference between the annual CC ASIRi (i - [2017; 2019]) and the CC ASIR in 2016 (ASIRo) to the value of the CC ASIR in 2016, which was taken as the baseline:

$CCI\ ABCi = (CC\ ASIRi - CCI\ ASIRo) / CC\ ASIRo;$

The values of the CC ASIR in 2016 were taken as the baseline, since only in this year separate data on CCI in the AO and the NAO became available. Until 2015 such data were presented together and so taken into account together too.

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

Results. The CC ASIRs in the AO, the MO, the RKa, the RKO, the KK, the ChAO, the RSYa, the YaNAO, the NAO and Russia as a whole in the period 2011-2019 are presented in Table 1. As in the books the CCI data in the YaNAO

Table 1

Annual values of CC ASIRs in SEs whose settlements belong to the land territories of AZRF, in the period 2011-2019

Год	RF		AO with NAO		AO		MO		RKa		RKO		KK		ChAO		RSYa		YaNAO		NAO	
	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка	Значение	Ошибка
2011	13,70	0,12	15,52	1,41			11,01	1,37	35,67	3,00	17,16	1,74	14,94	0,88	22,14	9,06	16,68	1,70	15,27	2,01		
2012	13,90	0,12	15,90	1,43			10,33	1,32	24,61	2,49	15,71	1,62	16,10	0,91	36,99	11,80	16,58	1,69	17,83	2,85		
2013	14,17	0,12	16,15	1,42			11,21	1,44	22,72	2,39	17,41	1,70	17,29	0,94	24,86	9,42	20,30	1,84	11,41	1,76		
2014	14,47	0,12	18,89	1,56			17,15	1,76	24,57	2,46	16,53	1,65	19,73	1,00	20,91	7,47	19,59	1,83	15,26	2,35		
2015	15,01	0,12	17,84	1,53			19,80	1,92	22,90	2,43	16,48	1,69	20,62	1,03	22,90	8,13	19,20	1,79	22,88	3,06		
2016	15,45	0,12			18,32	1,63	16,26	1,70	22,58	2,52	17,13	1,72	18,90	0,99	21,30	7,62	22,85	1,94	20,39	2,59	8,01	5,85
2017	15,76	0,13			17,78	1,57	17,73	2,02	19,94	2,28	23,50	2,04	21,06	1,03	13,11	5,92	20,20	1,82	15,96	2,59	29,37	10,69
2018	15,80	0,12			23,69	1,85	20,76	1,94	20,06	2,23	16,77	1,79	21,49	1,03	9,01	5,20	21,57	1,89	12,53	1,94	31,38	9,61
2019	15,38	0,12			28,85	2,17	17,00	1,81	14,64	1,79	17,75	1,76	21,03	1,04	11,28	5,64	18,38	1,75	12,69	1,91	32,50	10,39

Note: See the explanation of abbreviations in Tables 1-2 and Fig.1-2 in the text

became available since 2011, and the AO and the NAO data were presented together until 2015 - their division occurred only in 2016, so we identified 2 time periods for conducting comparative analysis. The first observation period was 2011-2015 when the CCI data in the AO and the NAO was taken together and the period 2016-2019 that have separated data from the AO and the NAO.

Friedman's two-way rank analysis during the observation period 2011-2015 revealed the heterogeneity of the CC ASIRs among all SEs ($p = 0.000$), while in the period 2016-2019 there was only a tendency to have the heterogeneity ($p = 0.065$). But, when we excluded 2016 from the studied time period, so the period changed to 2017-2019, the analysis revealed the CC ASIRs heterogeneity with the required significance ($p = 0.006$). Therefore, as a result, the period 2017-2019 was highlighted for comparative analysis.

The CC ASIRs average ranks of SEs whose settlements belong to the land territories of the AZRF during these time periods are shown in Figure 1.

Multiple and paired rank analyzes allowed us to identify SEs, with the maximum CCI rates in the period 2011-2015, and that were the ChAO and the RKa. No differences in their CC ASIRs were revealed ($p = 0.715$). The CC ASIRs in the ChAO and in the RKa exceeded the CC ASIRs in the AO with NAO, the MO, the RKo, the KK, the ChAO, the RSYa, and the YaNAO ($p = 0.043$ of the rank analysis in pairs of listed SEs with ChAO; $p = 0.043$ in pairs of listed SEs with the RKa).

In the period 2017-2019 the maximum CCI rates in a group of all SEs were found in a subgroup contained the AO, the NAO, the RKo, the KK and the RSYa, their CC ASIRs were homogeneous ($p = 0.155$ of multiple rank analysis). As a result of the CC ASIRs paired rank analysis no differences were recorded in this subgroup either (p did not reach the required significance in any CC ASIRs pair of these SEs). However, it should be noted that the CCI rates in the NAO was near to have the tendency to be maximum in the group ($p = 0.109$ of the CC ASIRs rank analysis in pairs of rest eight SEs with NAO), while the CCI rates in the AO, the RKo, the KK and the RSYa exceeded with the same significance a fewer number of SEs: the CCI rates in the KK and the RSYa exceeded the rates of four SEs such as the MO, the RKa, the ChAO and the YaNAO, whereas the CCI rates in the AO have exceeded the rates of three SEs such as the MO, the ChAO and the YaNAO, while the CCI rates in the RKo

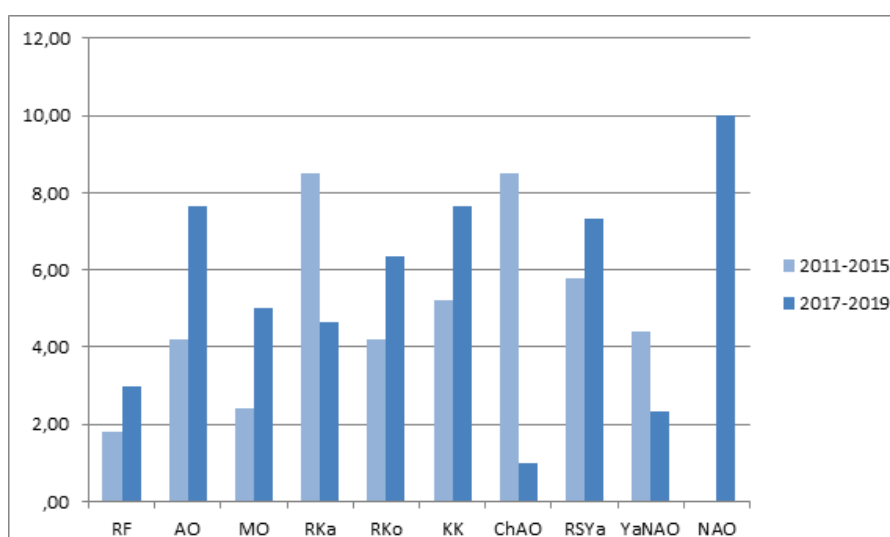


Fig 1. CC ASIRs average ranks of SEs whose settlements belong to the land territories of the AZRF

have exceeded the rates of two SEs such as the ChAO and the YaNAO.

In 2011-2015 in six territories out of eight - in the AO with NAO, the RKa, the RKo, KK, ChAO and the RSYa, the CC ASIRs exceeded all-Russian ($p = 0.043$ of the CC ASIRs rank analysis in all pairs of these territories with the RF). The CC ASIRs of the MO and the YaNAO did not have significant differences with the all-Russian ($p = 0.686$ of the rank analysis in pair MO-RF and $p = 0.225$ in pair YaNAO-RF).

In 2017-2019 in six SEs out of nine - in the AO, the NAO, the MO, the RKo, the KK and the RSYa the CC ASIRs were near to have the tendency to exceed the all-Russian ($p = 0.109$ of the CC ASIRs rank analysis in all pairs of these SEs

with RF). The CC ASIRs in the ChAO was near to have the tendency to be lower than the all-Russian ($p = 0.109$ of the paired rank analysis), while the CC ASIRs in the RKa and the YaNAO did not have significant difference from the all-Russian ($p = 0.285$ of the CC ASIRs rank analysis of these SEs paired with the RF).

Thus in five SEs out of nine - in the AO, the NAO, the RKo, the KK and the RSYa, in 2011-2015 the CCI rates significantly exceeded the all-Russian, and exceeding has continued about as the tendency in 2017-2019. The CCI rates in 2011-2015 in the ChAO and the RKa being the highest among SEs selected for this study had exceeded significantly the all-Russian, but in 2017-2019 "gave up" its previous positions and did not differ

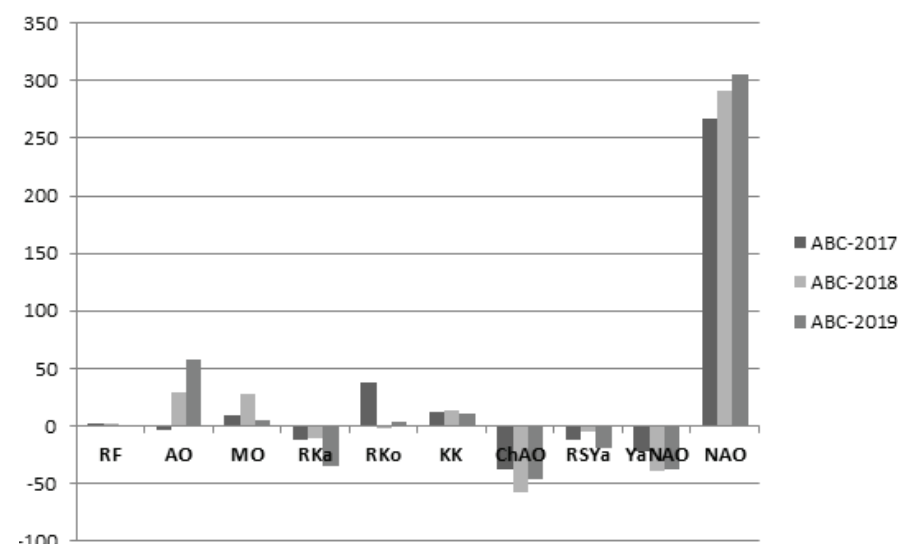


Fig 2. The expressed in percentage CCI ABCs in SEs whose settlements belong to the land territories of AZRF, in the period 2017-2019 versus to 2016

Table 2

The sum of the analyzed data on CCI in SEs whose settlements belong to the land territories of the AZRF, 2011-2019

	AO	MO	PKa	PKo	KK	ChAO	RSYa	YaNAO	NAO
The maximum CC ASIR	1		1	1	1	1	1		1.5
CCI ABCs	2		-1	1	0.5		-0.5	-2	2.5
The maximum increase of CCI from baseline									1
The sum	3	0	0	2	1.5	1	0.5	-2	5

from the all-Russian. The CCI rates in the MO and the YaNAO did not differ significantly from the all-Russian in 2011-2015 and in 2017-2019.

The CCI ABCs expressed in percentage in SEs whose settlements belong to the land territories of AZRF, in the period 2017-2019 versus to 2016 are graphically presented in Figure 2.

The highest value of the CCI ABCs revealed in the NAO, there were the tendency to increase by 3.7 times in 2017 ($0.05 < p \leq 0.1$ associated with T-test when we calculated differences in the CC ASIRs in this year compared to 2016) and significant increase by 4 times in 2018 and 2019 ($p < 0.05$ associated with T-test). The increase by 1.3 times and 1.6 times recorded in the AO in 2018 and 2019 respectively ($p < 0.05$ associated with T-test) and in the RKo - by 1.4 times in 2017 ($p < 0.05$ associated with T-test). In the KK the tendency to increase by 1.13 times in 2018 were ($0.05 < p \leq 0.1$ associated with T-test).

The maximum values of the CCI decrease from baseline was noted in the YaNAO – by 1.6 times in 2018 and 2019 and in the RKa – by 1.5 times in 2019 ($p < 0.05$ associated with T-test in all cases mentioned above). Also, a tendency to decrease in the CCI rates by 1.2 times was identified in the RSYa in 2019 ($0.05 < p \leq 0.1$ associated with T-test). In the ChAO, despite the fact that the values of the CCI decrease from baseline were essential, and this values from year to year have been steadily decreasing – by 1.6 times in 2017, 1.9 times in 2018 and 2.4 times in 2019, the p value (associated with T-test) did not reach either significance neither having the tendency when differences in CC ASIRs in this years were calculated, y ($p > 0.1$ associated with T-test).

In the rest of the years and in other SEs included in the study no changes in CCI from baseline were revealed.

In order to get a picture, we have compiled Table 2, which reflected the analyzed data. In it, we assigned 1 point to the presence of analyzed data, 0.5 point to the tendency towards its presence, and 0 to its absence. In the "CCI ABCs" column, 1 point corresponds to every year when the CCI rate had the increase from baseline, 0.5 points – to every year when the CCI rate had the tendency to the increase from baseline and the negative values correspond to the decrease from baseline. And as a result, among SEs, the whose settlements belong to the land territories of the Russian Arctic, the maximum final score reflecting the current situation regarding to CCI as the

most negative was assigned to the NAO, whose population have a significant proportion of indigenous people and ethnic minorities.

Conclusion. Our research study showed that for the population of SEs, whose settlements are attributed to the land territories of the Russian Arctic, as well as for the population of SEs, located in Siberia, the implementation of preventive measures against cervical cancer, including immunization against HPV, is an important task. CCI in 2011-2019 in all highlighted in this study SEs exceeded or was comparable with the all-Russian which in turn significantly exceeded the target rate established by the WHO - 4 cases per 100 thousand women per year. In addition, in five SEs – in the AO, the NAO, the RKo, the KK and the RSYa in 2011-2015 rates of CCI significantly exceeded the all-Russian with the tendency to exceeding in the period 2017-2019.

The most unfavorable situation in relation to CCI was revealed in the NAO, which is a home for a significant number of indigenous peoples and ethnic minorities. Of course, in order to get a clearer picture for taking measures to prevent CC including immunization against HPV and for CC early detection in these territories further analysis is needed, especially, of CC mortality, and this will be our next research study.

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