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DISPARITIES OF CERVICAL CANCER AND MORTALITY INDICES IN THE REPUBLICS LOCATED IN SIBERIA AND ALL OVER RUSSIA IN THE PERIOD FROM 2007 TO 2019

The article presents a research of disparities in cervical cancer incidence (CCI) and mortality (CCM) in the period 2007 - 2019 among the republics Altai (RA), Buryatia (RB), Tyva (RT), Khakassia (RKh), Sakha (Yakutia) (RSYa) and Russia as a whole. In this period the CCI in the republics was significantly higher than in Russia as a whole, the highest CCI was in RT, while the lowest was in the RSYa and the increase of CCI in the republics exceeded such in Russia as a whole. In this period CCM in the republics, except of RSYa, was also significantly higher than in Russia as a whole, and the highest CCM was in RB, while the lowest was in RSYa. CCM in 2019 compared to 2007 significantly increased in RT and decreased in RA. CCI and CCM have a statistical relationship in RB. Obtained results confirm the expediency to carry out vaccination against HPV in the republics first of all.

Key words: human papilloma virus (HPV), vaccination, Altai, Buryatia, Tyva, Khakassia, Sakha, Yakutia.

Introduction. Cervical cancer (CC) is a fourth most frequent cancer among women worldwide. Now more than 300,000 women have been dying from it annually. CC burdens more in low- and middle-income countries where public healthcare services are restricted [1].

In Russia CC has significant rate in the structure of cancer incidence among women too. So, in 2019 CC incidence (CCI) percentage rate (5%) took up fifth place after breast cancer incidence (21.2%), skin cancer (15.2%, with melanoma – 17.2%), uterine cancer (7.8%), colon cancer (7.3%) [2].

Also the CC mortality (CCM) rate was significant at the structure of women's cancer mortality; in 2019 this rate was on a 9-th place (4.7%), after mortality from breast cancer (15.9%), colon cancer (9.7%), stomach cancer (8.3%), pancreatic cancer (7.3%), tracheal, bronchial and lung cancers (7.1%), cancer of lymphoid and hematopoietic tissues (6.1%),rectal cancer (5.8%), ovarian cancer (5.5%) and uterine cancer (5.0%) [2].

There are significant disparities in CCI and CCM among countries [3] and different territories of the same country [4,5,6], including the territories of Russia [7,8].

To design optimal approaches to CC preventive vaccination scientific research of CC territorial, ethnic and gender disparities are needed [9,10].

Basically all cases of CC are caused by infection of the Human Papilloma Virus (HPV). A study of an archival biological samples related to prior to vaccination against HPV period (1993-2005) showed that HPV DNA was found out in 90.6% cases of CC and also in 98.8% cases of CC in situ [10].

Research in this scientific area in Russia including in Siberia are few in number. Possibly it may be related that vaccination against HPV is not included in the national vaccination calendar and the vaccination by epidemic indications approved by Order of Ministry of Health of the Russian Federation, March 21, 2014, N 125n.

Meanwhile on the 73-rd session of World Health Assembly, in May 2020, countries- members of World Health Organization approved the resolutions to develop world public health including the global strategy of WHO to accelerate CC elimination as a problem of public health. In this strategy a main attention in the period 2020-2030 is paid to prevent CC by the vaccination against HPV along with screening and treatment precancerous lesions and management of patients with CC invasive forms, including palliative care [1].

The research realized in USA showed that the vaccination against HPV can avoid not only invasive CC (prevent 66.2% cases) but other cancer sites associated with HPV, - anal cancer (79.4%), oropharyngeal cancer (60.2%), vaginal cancer (55.1%), penile cancer (47.9%) and vulvar cancer (48.6%). The 9-valent vaccine, which additionally targets HPV 31/33/45/52/58, can prevent an additional 4.2% to 18.3% of the above sites cancer [11].

In our previous studies, we found disparities in CCM among national-state entities (NSEs) located in Siberia - in the republics Altai (RA), Buryatia (RB), Tyva (RT), Khakassia (RKh), Sakha (Yakutia) (RSYa) in the period from 2007 to 2018. It was shown that during this period according to the values of annual age-standardized rates per 100 thousand of the population the lowest CCM was observed in RSYa [7,8], the highest in RB [8]. For the majority of peoples inhabiting these NSEs, the fact of genetic relationship has been established [12].

The aim of this study was to establish the disparities of CCI and CCM in the period from 2007 to 2019 among RA, RB, RT, RKh, RSYa and Russia as a whole. The following tasks were set: to compare the rates of CCI and CCM in NSEs with the rates in Russia as a whole; to identify NSEs with the highest and lowest rates of CCI and CCM; to establish the changes of NSEs' and Russia's CCI and CCM in 2019 in comparison to 2007; to identify NSEs with a statisti-

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cal relationship between CCI and CCM.

Materials and Methods. To establish the disparities of CCI and CCM, the data of national medical cancer statistics from 2007 to 2019 were used. This data is annually published in the books of the P. Hertsen Moscow Oncology Research Institute - a branch of the Federal State Budgetary Institution "National Medical Research Radiological Center" of the Ministry of Health of the Russian Federation from 2008 to 2020, which can be found on the website for medical and pharmaceutical workers "ONCOLOGY.ru" [13].

The CCI and CCM were estimated according to CCI age-standardized rates (ASIR) and to CCM age-standardized rates (ASMR) per 100 thousand. In the above-mentioned books to standardize by the age the world standard for the age distribution of the population was used. The period used in this study was from 2007 to 2019, state formations - RA, RB, RT, RKh, RSYa and Russia as a whole, cite - the cervix (C53).

Since the annual ASIRs and ASMRs did not have a normal distribution, to identify differences in the total (multiple) sample Friedman's analysis of variance by ranks was used. To identify paired differences the Wilcoxon signed ranks test was used. The $p < 0.05$ was chosen as a significance level.

The t-test was used to determine if CC ASIRs and ASMRs in 2019 and 2007 are equal. The $p < 0.05$ was chosen as a significance level of inequality (difference).

To identify the statistical relationship between the annual values of CC ASIR and ASMR, the Spearman correlation coefficient (r) was calculated using the formula for small sample sizes. The Chan scale was used to assess the strength of statistical relationship [14], r were considered significant at $p < 0.05$.

Results and discussion. The annual values of CC ASIR from 2007 to 2019 in RA, RB, RT, RKh, RSYa and in Russia as a whole are presented in Table 1. An analysis of their distribution revealed their heterogeneity (p=0.000).

The average ranks of the annual values of CC ASIR from 2007 to 2019 in RA, RB, RT, RKh, RSYa and in Russia as a whole are shown in Figure 1. Based on these ranks the highest CC ASIRs in this period were in RT, the lowest were in RSYa. At the same time CCI in Russia as a whole was significantly lower than in all NSEs: in comparison with RT - 5.01 times (p=0.001), with RB - 4.14 times (p=0.001), with RKh by 3.01 times (p=0.001), with RA by 2.73 times (p=0.002), with RSYa by 2.34 times (p=0.002).

Analysis of CCI changes in 2019 compared to 2007 showed that CCI increased significantly in RB - by 1.75 times (p=0.000), in RT - by 1.68 times (p=0.002) and in Russia as a whole - by 1.23 times (p=0.000), in RKh and RSYa the increase in incidence also exceeded the all-Russian rate - by 1.4 and 1.31 times respectively and approached to the level of significance we have selected (p=0.052 and p=0.070, respectively). In RA with a visible decrease in the value of CC ASIR in 2019 compared to 2007 (1.55 times), the difference of these indicators did not reach the level of significance (p=0.108). The CC ASIR values in 2017 and 2019 in the republics located in Siberia and in Russia as a whole are graphically presented in Figure 2.

Analysis of the CC ASMRs distribution from 2007 to 2019 in RA, RB, RT, RKh, RSYa and in Russia as a whole also revealed heterogeneity of these indicators (p=0.000). The annual values of the indicators are presented in Table 2.

The average ranks of the annual CC ASMRs from 2007 to 2019 in RA, RB, RT, RKh, and RSYa and in Russia as a whole are shown in Figure 1. According to the ranks the highest CCM in this period was in RB, the lowest was in RSYa. At the same time, CCM in Russia as a whole was also lower than in all NSEs: in comparison with RB by 3.74 times (p=0.001),

Table 1

Annual values of CC ASIRs in the republics located in Siberia and RF as a whole

Year	RA		RB		RT		Rkh		RSYa		RF	
	Value	Error	Value	Error	Value	Error	Value	Error	Value	Error	Value	Error
2007	22.55	3.91	22.83	1.98	30.49	4.34	15.79	2.14	14.07	1.62	12.48	0.11
2008	18.6	3.77	22.9	1.98	27.54	3.98	14.04	1.99	17.21	1.74	12.84	0.11
2009	27.03	4.83	18.66	1.75	17.45	3.12	16.36	2.09	17.44	1.72	13.4	0.12
2010	14.15	3.45	15.57	1.62	20.66	3.54	16.97	2.11	13.36	1.52	13.71	0.12
2011	18.56	3.88	21.09	1.86	27.94	4.11	22	2.47	16.68	1.7	13.7	0.12
2012	18.97	3.87	18.86	1.76	20.2	3.43	20.15	2.34	16.58	1.69	13.9	0.12
2013	22.43	4.16	31.27	2.27	24.07	3.66	20.55	2.37	20.3	1.84	14.17	0.12
2014	16.46	3.35	27.83	2.1	30.97	4.15	26.57	2.69	19.59	1.83	14.47	0.12
2015	21.86	4.04	29.91	2.2	35.4	4.48	17.2	2.12	19.2	1.79	15.01	0.12
2016	16.75	3.71	30.03	2.25	43.88	4.96	17.26	2.1	22.85	1.94	15.45	0.12
2017	17.08	3.6	42.55	2.67	44.98	4.92	20.29	2.3	20.2	1.82	15.76	0.13
2018	18.19	3.59	35.64	2.43	49.01	5.09	19.48	2.33	21.57	1.89	15.8	0.12
2019	14.50	3.14	39.92	2.56	51.37	5.33	22.10	2.44	18.38	1.75	15.38	0.12

Note: See the explanation of abbreviations in Tables 1-3 and Fig.1-2 in the text

Table 2

Annual values of CC ASMRs in the republics located in Siberia and in RF as a whole

Year	RA		RB		RT		Rkh		RSYa		RF	
	Value	Error	Value	Error	Value	Error	Value	Error	Value	Error	Value	Error
2007	15.97	3.57	11.46	1.37	5.38	1.71	8.32	1.47	5.04	0.91	5.11	0.07
2008	10.28	2.96	11.69	1.42	6.24	1.90	8.39	1.45	6.77	1.09	4.99	0.07
2009	12.91	3.28	11.60	1.38	9.20	2.33	6.60	1.27	5.29	0.96	5.13	0.07
2010	10.98	3.00	8.71	1.17	10.44	2.48	4.31	1.02	3.82	0.79	5.12	0.07
2011	6.18	2.21	11.13	1.33	13.46	2.85	5.77	1.23	4.91	0.93	5.27	0.07
2012	6.93	2.21	10.57	1.31	9.04	2.29	8.08	1.43	5.58	0.99	5.23	0.07
2013	11.19	2.82	12.47	1.42	12.00	2.59	10.55	1.72	6.95	1.06	5.35	0.07
2014	8.95	2.54	12.48	1.39	9.38	2.22	7.46	1.42	6.47	1.03	5.18	0.07
2015	8.21	2.37	11.46	1.36	12.21	2.64	8.50	1.50	6.21	0.97	5.39	0.07
2016	9.18	2.68	11.39	1.36	9.11	2.23	8.78	1.53	6.84	1.07	5.26	0.07
2017	7.61	2.12	13.09	1.47	9.41	2.17	8.55	1.45	6.11	1.01	5.18	0.07
2018	2.14	1.07	11.41	1.30	12.62	2.62	6.21	1.18	4.61	0.84	5.07	0.07
2019	5.12	1.86	14.32	1.53	13.60	2.81	7.93	1.40	5.49	0.93	5.01	0.07

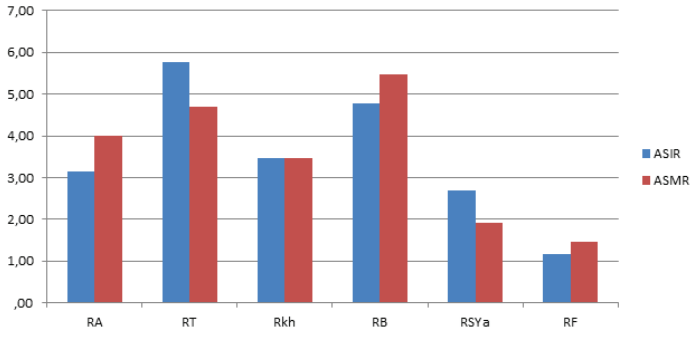

Fig. 1. Average ranks of CC ASIRs and ASMRs in RA, RB, RT, Rkh, RSYa and in RF as a whole from 2007 to 2019

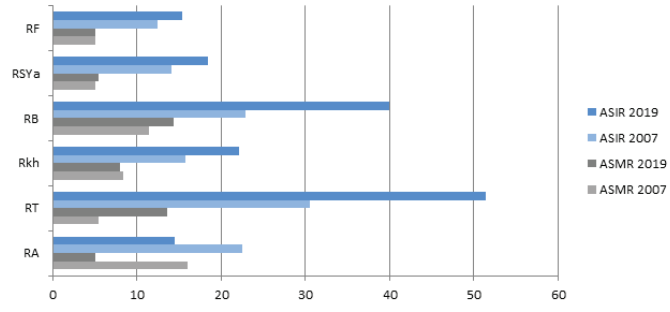

Fig 2. Values of CC ASIRs and ASMRs in RA, RB, RT, Rkh, RSYa and in RF as a whole in 2019 and in 2007.

with RT by 3.21 times (p=0.001 with RT), with RA by 2.73 times (p=0.006), with RKh by 2.37 times (p=0.002). CCM in RSYa also exceeded the all-Russian one by 1.32 times, and the significance of the differences was close to the level we have chosen (p=0.075).

Analysis of the differences in CCM in NSEs in 2019 compared to 2007 showed that CCM significantly increased in RT - 2.52 times (p=0.012) and decreased in RA - 3.11 times (p=0.007). The changes of CCM in these years in Russia as a whole and in the other republics did not reach the required significance. The CC ASMRs in 2017 and in 2019 in the republics located in Siberia and in Russia as a whole are shown in Figure 2.

The analysis of the relationship between the annual values of CC ASIR and ASMR in the state formations (see Table 3) showed the presence of moderately strong links only in RB.

Revealed in our study increased CCI and CCM in territories that are distinguished by a variety of races and ethnic groups have correlated with international studies [6, 11, 15].

The WHO global strategy to accelerate the elimination of CC as a public health problem contains a clause that in order to that all countries must achieve (and maintain) an incidence rate of less than 4 cases per 100,000 women per year [1]. That is, in NSEs located in Siberia, urgent medical and preventive measures are needed to reduce CCI. Based on the data of 2019, it is necessary to reduce the CCI from 3.6 times (in RA) to 12.8 times (in RT). The WHO strategy also calls on all countries to achieve CC vaccination of 90% girls by 2030 (by age 15) [1].

Our research shows that vaccination against HPV in the republics located in Siberia for the CC elimination is an urgent present time task.

Table 3

Spearman correlation coefficient (r) between the annual values of CC ASIR and ASMR (2007-2019)

ASIR		ASMR					
		RA	RB	RT	RKH	RSYa	RF
RA	r p N	0.456 0.117 13					
RB	r p N		0.641* 0.018 13				
RT	r p N			0.434 0.138 13			
RKH	r p N				-0.049 0.873 13		
RSYa	r p N					0.533 0.061 13	
RF	r p						0.165 0.590 13

Note: * - the r has the required significant p-value

Conclusion. CCIs in the period 2007-2019 in the republics, located in Siberia and inhabited by different ethnic groups with a close genetic portrait - RA, RB, RT, RKh, RSYa, were significantly higher than in Russia as a whole. In this period the highest CCI was in RT, while the lowest was in the RSYa and the increase of CCI in the republics exceeded such in Russia as a whole. In this period CCMs in the republics, except of RSYa, were also significantly higher than in Russia as a whole, and the highest CCM was in RB, while the lowest was in RSYa. CCM in 2019 compared to 2007 significantly increased in RT and decreased in RA. CCI and CCM have a statistical relationship in RB.

In our study we established significantly higher rates of CCI and CCM in the republics then in Russia as a whole and therefore there is a need for priority vaccination against HPV in the republics. In RT and RB, which have the highest CCI and CCM rates, the increase in CCM and the relationship between CCI and CCM, there is a need for urgent vaccination.

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FEATURES OF IMMUNE AND METABOLIC PROFILE OF AUTONOMIC DYSFUNCTION ASSOCIATED WITH POLYMORPHISM OF CANDIDATE GENES

Introduction. To preserve employable population's health is a most vital task contemporary medicine has to face. Chronic exposure to occupational factors can induce disorders in the immune, humoral, and nervous regulation in workers employed at an oil extraction enterprise and consequently result in work-related pathology. **Our research aim** was to examine peculiarities of immune and metabolome profile of workers who were employed at an oil-extracting enterprise and suffered from vegetative dysfunction that were related to working experience and combined with candidate gene polymorphism. **Materials and methods**. We examined 137 workers employed at an oil-extracting enterprise who had vegetative dysfunction including 66 workers with their working experience at the examined enterprise exceeding 10 years and 71 workers with working experience being shorter than 10 years. Contents of $CD3^+CD95^+$-lymphocytes, TNFR, Bax, and p53 were determined via flow cytometry. Leukocytes phagocytosis was examined with formalinized ram erythrocytes; contents of IL-6, NO, and homocysteine were determined via ELISA technique. We applied PCR in real time mode to identify SNP of *ApoE*(rs429358), *MTHFR*(rs1801133), *SULT1A1* (rs9282861) genes. **Results**. Immune and metabolome profiles of workers employed at an oil-extracting enterprise with their working experience being longer than 10 years had the following peculiarities: apoptosis, IL-6, and phagocytosis were hyper-activated (Bax, p53, TNFR), and homocysteine contents were elevated as well. These established changes are likely to reflect a pathogenetic relation with T-allele in *MTHFR*(rs1801133) gene which occurred among these workers more frequently than among those whose working experience didn't exceed 10 years ($\chi2=4.89$; $p=0.027$); this relation may well lead to atherosclerotic vascular disorders. Workers with their working experience being shorter than 10 years had higher NO levels, dopamine production, and greater CD3+CD95+-marker inhibition than reference levels ($p<0.05$). These established deviations are likely to reflect a pathogenetic relation with the highest frequency of C-allele in *ApoE* (rs429358) gene and A-allele in *SULT1A1* (rs9282861) gene which occurred in them authentically more frequently than among workers with working experience exceeding 10 years ($\chi2=4.77$-699; $p=0.008$-0.028). This, combined with established negative effects, indicates there is a risk than the immune system will be involved (excessive IL-6 and Bax deficiency), disorder in neuro-metabolome regulation will take place (excessive dopamine), and as a result vegetative dysfunction and vascular atherosclerotic changes will occur. Therefore, established imbalance in the immune (excessive apoptosis and phagocytosis), nervous (elevated dopamine), and metabolome (homocysteine hyper-expression and elevated NO due to its unstable forms) regulation that occurs against polymorphism of genes that participate in enzyme detoxification and metabolism such as *MTHFR*(rs1801133), *SULT1A1* (rs9282861), and *ApoE*(rs429358) characterizes peculiarities of immune and metabolome profiles that are related to working experience; workers with such profiles who suffer from vegetative dysfunction run a serious risk of atherosclerosis and hypertension. These peculiarities that are related to working experience and detected in immune and

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