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SMOKING AND ITS INFLUENCE ON THE LEVEL OF ONCOMARKERS IN BLOOD SERUM OF THE POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA)

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Our results indicate that smoking stimulates the expression of tumor markers in the serum of smokers. The level of tumor markers increases with the increase in smoking history. In the body of smokers, the concentration of tumor markers increases at a young and middle age, rather than in the elderly. The decrease in the indicators of tumor markers in old age is explained by the natural premature dropout of smokers from the population.

Keywords: smoking, tumor markers, cancer-embryonic antigen (CEA), alpha-fetoprotein (AFP), prostate specific antigen (PSA), ovarian tumor marker (CA125).

Introduction. Smoking is a risk factor for many chronic diseases such as chronic obstructive pulmonary disease, hypertension, cardiovascular disease, atherosclerosis, diabetes, cancer and microbial infections (respiratory tract infections, bacterial meningitis), etc. [4, 5]. According to the World Health Organization (WHO), more than 8 million people die annually from tobacco-related diseases, of which more than 7 million are smokers and more than 1.2 million are passive smokers (non-smokers) [27]. Tobacco smoke contains about 4,000 known chemicals; 250 of them are known to be harmful to health and more than 50 cause cancer in humans [23].

There is sufficient evidence of the involvement of smoking in the development of the following cancers: lung [13, 16], oral cavity [7,10], pharynx [18,25], larynx [4,7], esophagus [5, 8], nasal cavity and nasal sinuses [7,18], stomach [5,8], liver [20], kidney [24], cervix [15], etc. Smoking is especially dangerous at a young age, because addiction develops very quickly (cravings, withdrawal symptoms). It has been proven that nicotine contained in tobacco products causes addiction symptoms. Analysis of the sources has shown a directly proportional relationship between the age of onset and the duration of smoking [16]. It should be noted that the World Health Organization and the American Psychiatric Association classify nicotine addiction as a “substance use disorder” [27].

According to various researchers, stopping tobacco use reduces the risk of developing cancer and increases the life expectancy of individuals [13, 14]. Smoking electronic cigarettes, pipes, hookahs and cigars can also cause lung cancer, but the highest risk of developing carcinogenic diseases is caused by cigarette smoking, since it is the most widespread form of tobacco use in the world [16,19]. In developed countries, long-term programs aimed at reducing the number of smokers contribute to a decrease in mortality from tobacco smoking [9,12,15].

According to the sources, researchers have noted a significant increase of tumor markers in the blood serum of patients with cancer: carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), prostate-specific antigen (PSA) and ovarian tumor marker (CA125) [3,26]. An increase in cancer markers among smokers has been noted [26, 28].

The aim of this study is to assess the level of tumor markers in smokers and nonsmokers in the Republic of Sakha (Yakutia), depending on age.

Material and Research Methods. This work was carried out within the framework of the research: "Epidemiological aspects of malignant tumors in the Far North, development of modern methods of early diagnosis and prevention with the usage of highly informative fundamental research methods" in the Department of Adaptation Mechanisms Research, Yakutsk Scientific Center for Complex Medical Problems. We examined 175 residentsof Megino-Khangalass district, aged 22 to 66, of which 83 were

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smokers and 92 were not. The study did not include people suffering from cancer, precancerous conditions and with exacerbation of chronic diseases. The surveyed were divided into age groups according to the classification adopted by the WHO Regional Office for Europe (Kiev, 1963). A questionnaire survey of all subjects was carried out according to a standard questionnaire for assessing the quality of life, modified by the laboratory of medical and social research of the Yakutsk Scientific Center for Complex Medical Problems. The study was approved by the ethics committee (No. 49 dated March 25, 2018).

The study material was blood taken on an empty stomach from the cubital vein. Identification of tumor markers in blood serum: carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), prostate-specific antigen (PSA) and ovarian tumor marker (CA125) was carried out by enzyme-linked immunosorbent assay (ELISA) using test systems (Vector-Best, Russia) , on a Multiskan FC device (Thermo Scientific, USA).

Statistical processing of the obtained data was performed using the IBM SPSS Statistics 19 applied statistical software package The Kolmogorov–Smirnov test was used to analyze the normality of the trait distribution. In cases where the distribution differed from normal, nonparametric statistical methods were used to determine the median of the trait in the groups and its quartile range of 25 and 75%. Differences were considered significant at the achieved level of statistical significance p <0.05.

Results and Discussion. The values of tumor marker levels in the blood serum of residents of the Republic of Sakha (Yakutia) were as follows: CEA - 2.83 (2.15-3.54) ng / ml; AFP - 3.60 (2.08-6.24) IU / ml; PSA - 0.07 (0.03-0.12) ng / ml; CA125 - 3.70 (1.57-6.69) U / ml. The content of tumor markers was within the reference values. The reference values corresponded to: CEA 0-5 ng / ml; AFP 0-10 IU / ml; PSA 0.3-4.0 ng / ml; CA125 0-35 U / ml.

Among smokers, there is a significant increase in the CEA level by 8.60% (Table 1). There are conflicting results in the literature, for example, studies [15] showed a 7.9% decrease in serum PSA levels in smokers and 12.2% in those who quit, compared with never nonsmoking people. In the study [17], on the contrary, an increase in the concentration of PSA in the blood serum of smokers was noted. The average value of the CA125 tumor marker in our group of women who smoked was significantly more by 27,40% in comparison with nonsmokers.

Researchers have found that the concentration of tumor markers depends on age [12,18,22]. The CEA value in young people was significantly lower than in middle and old aged people, by 17,20% and 14,57% respectively. At the same time, the levels of tumor markers AFP, CA125 and PSA tended to decrease depending on age. (Table 2)

In the group of nonsmoking residents of Yakutia, depending on age, the level of CEA significantly increases when comparing the young population with residents of middle and old age by 19.31% and 17.89%, respectively. The CA125 level, on the contrary, decreases when comparing young women with the elderly by 51.17%. The PSA value in men tended to increase depending on age, but we did not find statistically significant differences (Table 3).

According to the questionnaire data, the duration of smoking of young respondents was 15.00 (10.00-20.00) years, of middle aged respondents - 30.00 (24.50-37.00) years and of the elderly - 35.50 (17.5-45.00) years. At the same time, the intensity of smoking (the number of cigarettes per day) was for young people - 10.00 (8.50-15.00) pcs., for middle aged people - 15.00 (10.00-20-00) pcs. and for the elderly - 20 .00 (13.75-28.75) pcs.. Our correlation analysis showed that in all age groups, with an increase in smoking duration, the intensity of smoking increases as well, as evidenced by positive correlation coefficients (young age r = 0.435 (p = 0.05); middle age r = 0.305 (p = 0.05); old age r = 0.441).

The concentration of tumor markers in a group of smokers also depends on age (Table 4). A significant increase in CEA was noted by us in the group of middle-aged people in comparison with young people, which is consistent with the sources [1,11].

When comparing smokers with nonsmokers by age, we noted a significantly high CEA value in middle-aged smokers - 21.2% (p = 0.050). Our results are consistent with those of other studies such

Table1

Concentration of tumor markers in smokers and nonsmokers

Age	CEA(ng/ml)	AFP(ME/ml)	PSA(ng/ml)	CA125(U/ml)
Smokers	3.02 (2.22-3.81)	3.07 (1.94-4.87)	0.07 (0.03-0.12)	5.03 (1.23-8.11)
Nonsmokers	2.76 (2.09-3.40)	3.71 (2.14-5.30)	0.07 (0.05-0.17)	3.65 (1.45-6.30)
p 1-2	0.083	0.041	0.542	0.370

Примечание. В табл.1-4 единицы измерения РЭА, ПСА – нг/мл, АФП – МЕ/мл, СА – ЕД/мл.

Table2

The level of tumor markers depending on age

Age	CEA(ng/ml)	AFP(ME/ml)	PSA(ng/ml)	CA125(U/ml)
Young	2.52 (1.61-3.11)	3.73 (2.20-5.21)	0.08 (0.03-0.06)	4.72 (2.02-9.76)
Middle aged	3.04 (2.42-3.95)	3.32 (1.98-5.37)	0.06 (0.03-0.08)	3.74 (1.59-6.50)
Elderly	2.95 (2.02-3.54)	3.21 (1.80-4.45)	0.07 (0.02-0.13)	2.07 (1.10-4.44)
p 1-2	**0.000**	0.900	0.096	0.101
p 1-3	**0.028**	0.348	0.070	0.128
p 2-3	0.184	0.418	0.385	0.536

Table3

The content of tumor markers in nonsmokers depending on age

Age	CEA(ng/ml)	AFP(ME/ml)	PSA(ng/ml)	CA125(U/ml)
Young	2.34 (1.45-2.97)	4.15 (2.49-5.76)	0.02 (0.01-0.05)	4.24 (2.07-9.08)
Middle aged	2.90 (2.41-3.44)	3.39 (1.96-5.29)	0.06 (0.06-0.08)	3.89 (1.69-6.06)
Elderly	2.85 (2.07-3.61)	3.25 (2.28-5.08)	0.11 (0.07-0.13)	2.07 (0.69-3.65)
p 1-2	**0.004**	0.289	0.032	0.274
p 1-3	**0.017**	0.257	0.164	**0.030**
p 2-3	0.686	0.937	0.221	0.095

as [16] who found that CEA level in blood serum was significantly higher in smokers than in nonsmokers. It should be noted that CEA is known as a nonspecific marker indicating the development of a large list of cancers: pancreatic carcinoma [18], uterine cancer [15], lung cancer [13], breast cancer [14], etc.

The CA125 level tended to increase in the group of young residents, although in the older age groups (middle and elderly) its values were lower compared to nonsmokers. Perhaps the increase in CA125 at a young age is explained by the body's response to the toxic effects of tobacco. At the same time, with an increase in smoking experience, the concentration of CA125 decreases, as evidenced by a negative correlation coefficient (r = -0.191). Our results are consistent with the literature [26], according to the authors, smoking can reduce the concentration of CA125, reducing the level of endogenous estrogen in the body of women. In addition, the level of CA125 may decrease due to the fact that cigarette smoke damages the epithelium of the respiratory tract, which expresses this tumor marker. [6]

of smokers. Our results are consistent with the sources [1,21].

To prevent smoking-related diseases, many researchers suggest quitting tobacco use as early as possible. To combat smoking, developed countries have adopted laws restricting tobacco advertising, establishing age limits on buying and consuming tobacco products and organized special zones for smoking, thanks to the measures taken, mortality from tobacco smoking has reduced [2, 12, 14].

Meanwhile, modern studies have shown that there is a relationship between changes in the activity of the cytochrome P450 enzyme encoded by the CYP2A6 gene and the level of nicotine addiction. The enzyme cytochrome P450 plays a key role in nicotine catabolism; mutations in this gene affect its activity. People with a slower metabolism of nicotine tend to have lower levels of nicotine addiction, and therefore are able to quit using tobacco products relatively more easily [14].

According to some researchers, stopping the consumption of tobacco products normalizes the level of tumor markers, reduces the risk of developing cancer and increases life expectancy [16,17].

Table4

The content of tumor markers in smokers depending on age

Age	CEA(ng/ml)	AFP(ME/ml)	PSA(ng/ml)	CA125(U/ml)
Young	2.60 (2.19-3.26)	3.07 (1.97-4.26)	0.08 (0.03-0.06)	6.90 (1.67-11.50)
Middle aged	3.68 (2.47-4.67)	3.18 (1.94-6.87)	0.06 (0.03-0.08)	2.82 (1.10-6.80)
Elderly	3.17 (1.90-4.05)	3.13 (0.98-5.43)	0.02 (0.01-0.11)	1.82 (1.31-3.82)
p 1-2	**0.005**	0.725	0.481	0.132
p 1-3	0.429	0.070	0.274	0.885
p 2-3	0.293	0.170	0.361	0.487

In nonsmokers, we observed a tendency to an increase in PSA levels depending on age, and in smokers, on the contrary, to a decrease. At a young age, the PSA level in smokers was significantly higher by 4 times (p = 0.021), and in the elderly it was 5.5 times lower. At young and middle ages, we noted positive correlation coefficients with smoking duration and smoking intensity. Moreover, reliable values of the correlation coefficients were noted by us in the groups of young people - smoking duration and CEA content r = 0.337 (p = 0.001); middle aged people - smoking duration and CEA concentration r = 0.385 (p = 0.050), smoking duration and AFP level r = 0.265 (p = 0.050). Smoking duration probably has a greater influence on changes in tumor markers than the number of cigarettes smoked per day in various groups

Thus, our results indicate that smoking stimulates the expression of tumor markers in the blood serum of smokers. The level of tumor markers increases with the increase in smoking duration. In smokers, the concentration of tumor markers increases at a young and middle age rather than in the old age. The decline in tumor markers in the elderly can probably be explained by the natural, premature mortality of smokers in the population.

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