STUDII ŞI SINTEZE

HEREDITARY THEORY OF LUNG CANCER

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Lung cancer (LC) - one of the most common malignancies. LC is the leading cause of cancer death in men and takes the second place (after breast cancer in women) [27,77]. In different geographical regions in men each year from 5.3 to 99.7 new cases of LC per 100000 person-years, the incidence of women in the 6-10 times lower. In Russia every year from LC kills over 60000 people, representing more than 20% of all deaths from malignant tumors [77]. In St.-Petersburg, LC remains the first place in the structure of mortality from malignant neoplasm [82].

The absence of notable achievements in the fight against LC is largely due to insufficient diagnostics. So far, the vast majority of people recognize the disease in the later stages of development in which the capabilities of modern methods of treatment can not be fully realized [78,85,87]. For this reason, the overall 5-year survival of radically operated for the past decades, progresses slowly, accounting for 20-25% [88,89].

Despite some advances in the knowledge of the clinical patterns of development and course of LC, many aspects of this problem, in particular, the etiology and pathogenesis remain ill-conceived. Analysis of the existing ideas about the origin of LC shows that there is currently no satisfactory concepts, that explain the development of LC. Discussed in the literature hypotheses are not exhaustive, as it does not contain an explanation of many facts. Among the latter occupy a prominent position data obtained from clinical and genealogical research, indicating the existence of cases of family savings of LC.

The hereditary nature of cancer most studied with such malignancies as embryonic tumors in children (retino-and nephroblastoma), colorectal cancer, cancer of the female reproductive system (breast cancer, ovarian), medullary thyroid cancer [76]. The problem of LC from these positions remains undeveloped.

LC is cancer in the unique position - it is a rare example of a malignant disease, it would seem, is firmly established and well defined etiologic factors. Indeed, in most cases the occurrence of LC can be associated with smoking, in addition, this tumor may be associated with other carcinogenic agents, located in the inspired air - dust, asbestos, exhaust fumes, etc. [83]. However, if the relationship between inhalation carcinogen and the occurrence of LC was complete, tobacco smoking is unlikely to remain a popular habit. Indeed, no cigarette smoke or other external factors are not absolute risk factors across human populations. Susceptibility to LC-associated substances varies considerably from individual to individual, and appears to be mediated primarily by genetic factors [9,11,22,26,27,29,30].

Because LC is heavily than other tumors, is a social disease, the main priorities in the search for the prevention of this disease have been directed not so much in his study of hereditary factors, as in the development of effective means to combat smoking and environmental pollution [80]. Therefore, only in recent years abroad, works have appeared devoted to the study of genetic aspects of LC [5,38,39]. This is understandable, as clinicians, this problem was not raised. At present, it is proved that the main cause of LC is smoking, which causes 80% of cases. However, the fate of cancer patients are not prepared for all smokers and this suggests the existence of individual susceptibility to LC. Such an individual predisposition, in all probability associated with polymorphisms of genes whose products are involved in the metabolism of tobacco smoke carcinogens. Obvious combination of hereditary factors (genetic polymorphisms) and environmental factors (tobacco smoke) makes an interesting model for LC in the study of individual cancer susceptibility.

All this confirms the need for an integrated clinical, molecular genetic studies of LC. Moreover, the need for such developments is determined by the fact that today there are no real prerequisites for the pathogenetic treatment of this disease.

It is important to establish new factors that would allow to understand the structure of the genetic predisposition to the disease and to develop

The distribution of LC patients with family history of the TNM system is given below:

$T_1N_0M_0$ – 45	$T_2N_0M_0$ – 46	$T_3N_0M_0$ – 33	$T_4N_0M_0$ – 5
$T_1N_1M_0$ – 15	$T_2N_1M_0$ – 25	$T_3N_1M_0$ – 15	$T_4N_1M_0$ – 2
$T_1N_2M_0$ – 14	$T_2N_2M_0$ – 42	$T_3N_2M_0$ – 45	$T_4N_2M_0$ – 17
$T_1N_1M_1$ – 2	$T_2N_1M_1$ – 6	$T_3N_1M_1$ – 4	$T_4N_1M_1$ – 0
$T_1N_2M_1$ – 6	$T_2N_2M_1$ – 31	$T_3N_2M_1$ – 46	$T_4N_2M_1$ – 3
$T_1N_3M_0$ – 2	$T_2N_3M_0$ – 3	$T_3N_3M_0$ – 1	$T_4N_3M_0$ – 1
$T_1N_3M_1$ – 1	$T_2N_3M_1$ – 3	$T_3N_3M_1$ – 3	$T_4N_3M_1$ – 1
$T_1N_0M_1$ – 4	$T_2N_0M_1$ – 6	$T_3N_0M_1$ – 1	$T_4N_0M_1$ – 2

evidence-based recommendations for medical and genetic counseling of individual families as a means of primary prevention of LC. We performed a study to some extent contribute to filling this gap.

The purpose of this study was to develop the hereditary theory of the lung cancer.

Materials and methods

1.1. General characteristic of the material of clinical studies

The study is based on data on about 2000 LC patients who were examined and treated at the Institute of Oncology, Moldova, and N.N. Petrov Institute of Oncology Russian Ministry of Health over the past ten years.

Clinical material included data on 1640 patients with LC. Of these, 430 (26.2%) hereditary history was burdened by the presence in blood relatives of cancer. Number of blood relatives of localizations were as follows: lung - 148 (34.4%), stomach - 122 (28.4%), esophagus - 40 (9.3%), intestines - 9 (4.4%), pancreas gland - 10 (2.3%), liver - 9 (2.1%), kidney - 8 (1.9%), larynx - 10 (2.3%), the uterus - 33 (7.7%); mammary gland - 19 (4.4%) other location - 12 (2.8%). These patients were grouped into the first group. The remaining 1210 (73.8%) patients assigned to the control, the second group. The ratio of LC patients the first and second groups was 2.8:1. Of the 430 patients with a history of hereditary factors in 39 (9.1%) of blood relatives in history took place on two localization of tumors, such as a mother - a cancer of the stomach, his father - lung cancer, 9 patients (2.1%) - three localization and in 1 (0.2%) - 4 localization. LC with a history of blood relatives of probands was observed in 148 (34.4%) cases, with respect to all patients - in 9.0%.

Of the 430 patients of the first group - 369 (85.7%) smoked (Table 1). Among the observed 1210 individuals of the second group of smokers had a few more - in 1073 (88.7%).

Of the 369 smokers, I-st group, suffering from LC, 129 (35.0%) started smoking before the age of 15 years. In the control group, early onset of smoking was observed in 402 (37.5%) from 1073. In the study of the intensity of smoking was found that more than 20 cigarettes or cigarettes smoked per day 335 (90.8%) of 369 patients with family history, that of 9.9 times the number of patients who smoked 20 cigarettes or cigarettes per day - 34 (9.2%). Duration of smoking at 71.2% of them was 20 years or more. Patients with the second group of indicators of intensive and early onset of tobacco smoking by about the same as in those of the first group. Thus, the number of those patients who smoked 20 or more cigarettes or cigarettes per day was 961 (89.6%) and 112 (10.4%) patients smoked per day to 20 cigarettes, or cigarettes. Duration of smoking at 89.5% of them was 20 years or more.

With regard to the availability of occupational

Table 1

Duration and intensity of smoking lung cancer patients I and II

Patients groups	*The number of cigarettes smoked per day*	*Number of patients*	*Duration of smoking (years)*				
			Till 5	*6-10*	*11-20*	*21-30*	*31-40 and more*
I	Till 10	11	4	2	1	1	3
	11-19	23	1	0	4	1	17
	20-25	67	3	4	9	22	29
	26 and more	268	3	8	24	50	183
	Total	369	11	14	38	74	232
II	До 10	38	1	0	1	12	24
	11-19	74	0	2	5	24	43
	20-25	283	2	4	20	36	221
	26 and more	678	9	13	56	127	473
	Total	1073	12	19	82	199	761

Table 2

The distribution of lung cancer patients by stage of disease

Patients groups	*Patients number*	*Of these had stage*											
		I		*IIa*		*IIб*		*IIIa*		*IIIб*		*IV*	
		Abs, number	*M±m*	*Abs, number*	*M±m*	*Abs, number*	*M±m*	*Abs, number*	*M±m*	*Abs, number*	*M±m*	*Abs, number*	*M±m*
I	430	45	10,5±1,48	46	10,7±1,49	40	9,3± 1,40	33	7,7± 1,29	116	27,0±2,14	150	34,8±2,30
II	1210	254	21,0±1,17	203	16,8±1,07	143	11,8±0,93	157	13,0±0,97	296	24,4±1,23	157	13,0±0,97

exposures, they are more than twice as likely to have occurred in patients of the second group than the first (10.1% vs. 4,0%) (P <0,001).

Considering the fact that almost all of our patients lived in St. Petersburg and Leningrad region, we can say that they were in the same environmental conditions and the influence of environmental factors exerted an equal influence on them. Therefore, the clinical course of LC in patients with a history of hereditary factor considered by us as having hereditary pathogenic variant (I group). The clinical course of LC control group II - as an environmental option.

In 2003, the International Union against Cancer (UICC) has published the 6th edition of the classification system of malignant tumors of TNM [25], which has been translated into Russian language by professor N.N.Blinov. In the process of co-operative managed to overcome all the differences between AJ and UICC TNM classification of lung tumors.

Since the basic principle of this classification is to determine the extent of tumor before treatment, it should be noted that often the TNM is underestimated in relation to the true spread of the tumor process. In this regard, the analysis of our material, we considered the classification of LC in stages, according to existing instructions, refined and adopted by the N.N. Petrov Institute of Oncology and Oncology Institute of Moldova.

The distribution of our patients by stage of disease is shown in Table 2.

In order to determine the size and location of the tumor, its relationship to the bronchi, determine the form of growth, visible boundaries of the tumor and the frequency of lesions of regional lymph node metastasis were studied in 217 postoperative preparatory radically operated patients with I-th group and 807 patients II-nd group according to the method proposed by professor A.I.Rakov et al. [84] Remote operation for lung preparations was brandy 10% formalin solution through the bronchi. The study of fixed postoperative preparatory held jointly with the pathologist, which easily cut through the course of the affected bronchus by the tumor. We determined the size of the tumor, its relation to the bronchi, the form of growth, sprouting into the surrounding structures. We determined the location and number of affected lymph nodes. Data characterizing the tumor were applied to the special scheme.

Interest to researchers and remote areas of the tumor for histological examination lymph nodes were placed in separate cassettes and, accordingly, their topography is the number marked on the chart. It is possible to study the characteristics of metastasis of LC patients with family history, depending on the size, location, shape and histological structure of the growth of tumors.

The fate of patients traced through organizational-methodological department of the Institute, through surveys of patients in the community or through a central office address, as well as personal examination during polyclinic reception.

The obtained data characterizing each patient with LC were entered in a special crypt card that printing was carried signs in a computer file, which was developed by a special code, and layout maps "Lung Cancer".

The data base consists of digits 1640x80 cryptographic file is processed on a computer system WYSE DOS (Programmer V.M.Tsybulsky). All numerical values were subjected to statistical processing (determination of the mean arithmetic error - m, the confidence factor - t and reliability - P).

1.2. Methods of molecular genetic analysis.

Subjects included an analysis of 53 samples of lung tumor and normal tissue, delivered from the operating thoracic branches in the laboratory of Molecular Genetics of N.N. Petrov Institute of Oncology. In Chisinau (Moldova) from blood samples of 10 ml of 51 patients with LC and 85 healthy donors using detergent Triton x100 core were obtained white blood cells, which are taken for further molecular genetic analysis in the laboratory of Molecular Genetics, N.N. Petrov Institute of Oncology.

Isolation of DNA from tumor tissue was performed and the unmodified phenol-detergent method [44].

For the fragmentation of the DNA samples using the following restriction endonucleases: Tag I., BamH I., Fvu II, Hind III, Msp I (NPO "Ferment", Vilnius). Electrophoretic separation of DNA restriction fragments was performed in 1% agarose gel («Pharmacia» Sweden) and transferred to a nylon membrane («Hybond-N», «Amersham», UK) [58].

We used the following probes: 517 bp Pst I fragment of the gene DRB (plasmid pRTV-I provided J.Bidwell, United Kingdom Transplant Service, Briestol, UK); 1,8 kb EcoR-I - Smal fragment of the gene L-myc (plasmid pJB 327, provided M.Schwab, Germany), 0.7 kb BamHI-EcoRI fragment of the oncogene ERBB-2 (plasmid perbB-2, "Amersham", England); complete copy of the oncogene C-MYC, a 5 kb (plasmid pKH-47 provided D.Stehelin, France), a complete copy of the oncogene HRASI (plasmid pHRAS-Th-3 provided P.G. Knyazev, prof. N. Petrov Research Institute of Oncology, St. Petersburg), the total copy of the oncogene ERBB-1 (plasmid CVN/HER-1 provided A.Ullrich, Germany), a complete copy of the p53 suppressor gene (p53 plasmid provided M.Oren, Israel), 3.8 kb suppressor gene fragment of the RB-1 (plasmid pRb1 provided M.Schwab, Germany); anonymous markers on short and long arm of chromosome 17 YNZ-22 (plasmid YNZ provided R.White, USA).

To control the equivalence of the nucleic acids DNA filters with a 1.6 kb reiterated hybridization Hind III-EcoR I fragment of the oncogene RAF-I ("Amersham", UK), and the filters with RNA - 2-kb fragment of the collagenase gene (plasmid pCllase/PX-7 provided P.Herrlich, Germany).

Plasmids were accumulated in the bacteria E.coli (strain HB101) and isolated by the method of H. Birnboim, J. Doly [10] with our modifications. Oncogene - specific inserts were isolated by preparative electrophoresis [44].

The specific radioactivity of the probe, labeled in the reaction of nick-translation with 32P-dCTP (NGO "Isotope", Obninsk), was $2x10^8$ counts / min / mg. DNA on the filters were hybridized in solution with the following composition: 50% formamide, 5x SSC, 0,1% SDS, 0,05% polyvinylpyrrolidone, 0.05% Ficoll, 0.05% bovine serum albumin, 100 mg / ml yeast tRNA and 2x10 imp / min / ml of labeled DNA probe at 42°C within 24-36 hours. Washed from unreacted label filters were exposed to X-ray film «Kodak» RX-5 (USA) in cassettes with intensifying screens at-20° C for 4-14 days. The intensity of hybridization was determined by densitometry or visual degree on X-ray film.

Statistical analysis was performed by the method of chi-square test.

Patients and donors. 157 older donors (ED) (age range: 75-95 years, mean age 79 years) were selected for study in hospitals in Chisinau and St.-Petersburg. 140 healthy blood donors (HD) (age range: 18-53 years, mean age 36 years) were presented to volunteers who visited blood point of Moldova Institute of Oncology and N.N. Petrov Institute of Oncology (St.-Petersburg). A group of patients with LC (age range: 30-77 years, mean age: 60 years) consisted of 325 patients treated at the Oncology Institute of Moldova (Chisinau) and the N.N. Petrov Institute of Oncology (St. Petersburg).

Genotyping of GSTM1. The source of the DNA of peripheral blood leukocytes served. DNA was extracted by a modified salt-chloroform method [49]. GSTM1 genotype was determined by the so-called Multiplex polymerase chain reaction (PCR) [8]. A pair of primers 5 '- GAA CTC CCT GAA AAG CTA AAG C - 3' and 5'-GTT GGG CTC AAA TAT ACG GTG G - 3 'amplified GSTM1-specific 215-bp sequence of size, oligonucleotides 5'-CAA CTT CAT CCA CGT TCA CC - 3 'and 5' - GAA GAG CCA AGG ACA GGT AC - 3 '268 bp was synthesized control fragment of -β globin gene. PCR was carried out under standard conditions.

Genotyping of CYP1A1. To identify the allelic variants of the CYP1A1 gene was used polymerase chain reaction (PCR) using primers: 5 '- GGC TGA GCA ATC TGA CCC TA - 3' and 5 '- ATA CCC CCC CCT CAC TCC AG - 3' [15] . The reaction was carried out in a final volume of 12 ml and contained 10-100 ng of target DNA, 1 unit. thermostable Taq-polymerase, a single PCR buffer, 1.5 mM magnesium chloride, 200 mkM desoxyribonucleotide, and 1 mM primers. PCR included 30 cycles consisting of denaturation phase (95°C, 35 sec.), annealing (58°C, 1 min.) and synthesis (72°C, 1 min.). The final phase of the synthesis took place at 72°C for 7 minutes. At the end of PCR to the 3 ml ampliphykate added restriction endonuclease MspI, an appropriate buffer and water, and after a 16-hour incubation, the product of the enzymatic reaction was analyzed by 2.5% agarose gel. The appearance of the site indicated the presence of the MspI variant allele of M2.

DNA extraction and SNP genotyping of the genes of apoptosis.

The source of the DNA of peripheral blood leukocytes served. DNA was extracted by a modified salt - chloroform method [49]. 3 ml of blood were diluted to 10 ml with water to produce hemolysis, mononuclear cells were split gentle centrifugation and re-diluted in 1 ml of TE solution (10 ml Tris-HCl (pH = 8.3), 1 ml EDTA). The cytoplasmic membranes were destroyed by adding Triton X-100 till 1%, and samples were centrifuged again for fragmentation of nuclei. This mass was diluted in a solution of TE and incubated with proteinase K (100 mg / ml) at 60^0 for 12 hours. Proteins were transferred to the sludge by addition of NaCl to 1.5 M and the lysate was exposed to chloroform extraction. Then there was added an equal volume of isopropanol, DNA was selected by

rotating a glass rod, washed with 70% ethanol and dissolved in TE buffer.

Samples from the archive have been analyzed and described by Imyanitov E. et al., [32]. 10 μm sections were archived in dewax in xelyte boil thoroughly 5 min. in lysis buffer (10 ml Tris-HCl (pH = 8.3); 1 ml EDTA; 0.5% NP-40, 0.5% Tween 20). Proteinase K was brought up to 500μg/ml and the samples were incubated at 60^0 C for 12 hours. Finally, proteinase K was inactivated by boiling for 5 min in the presence of Chelex -100, and the resulting lysate was used for PCR amplification.

List of 37 coding nonsynonymous SNPs in apoptotic genes was taken from our previous publication [31]. SNPs were genotyped allele-specific polymeric chain reaction (AS-PCR).

PCR reactions were brought to 20 ml of final volume using iCycler iQ Real Time Detection System (Bio-Rad). Each tube contained 50-100 ng of DNA genomic, 1 μM of each primer, 200 μM deoksinukleotid triphosphates, 1x PCR buffer, 2.5 мM $MgCl_2$, 0.5^xSYBR Green I, and 1 unit of Taq polymerase, quick start ("Termostar" Helicon, Moscow). Taq polymerase was activated 10 minutes warming up 95°C. 45 cycles of PCR reactions included denaturation at 95^0C for 20 sec., Dropping up to 55°C - 67°C for 30 sec., and synthesis at 72°C for 35 sec. The reliability of detection of alleles was systematically testable gel - electrophoresis of PCR fragments.

Genotyping of L-MYC. DNA from white blood cells stand out salt-chloroform method [15]. Then, restriction enzyme digested DNA preparations EcoRI, separated in 1% agarose gel and transferred to nylon filters. As a probe for Southern-blot hybridization using 1.8 kb SmaI-EcoRI fragment of the oncogene L-MYC. Identification of alleles was performed on the basis of information about the amount of L-MYC-specific bands [18]. The fragment length of 6.6 kbp fit the so-called S ("small") allele, 10 kbp - L ("large"). As an alternative method using PCR genotyping.

Statistical analysis. For data processing method was used chi-square, and compute the OR c confidence interval of 5%.

Results and discussion

With regard to the clinical section of our research we can say that the leading factors that determine the flow characteristics of LC, such as localization, morphological structure of the tumor and its growth form in both groups were similar, with few exceptions, which we were able to identify. Thus, the initial state of the primary lung tumors in patients with a history of hereditary factors and the control group patients were almost identical. It should be emphasized that this is not artificially created by a group of patients, and their natural distribution, as we have investigated all patients who were hospitalized in the last 10 years. So it was natural to assume that the further course and prognosis of LC in both groups will be identical. However, it was not.

Considering the dependence of the frequency of germination of LC in the adjacent anatomical structures and organs of a family history factors, it should be noted that the germination of LC in the above structure was observed more frequently in patients in group I than in II, respectively, in 37.6% and 25.2% (P <0.001) cases. The most frequent germination of LC in patients in group I was in the mediastinum (more than 2 times more likely than patients of group II) - 4.7% versus 2.0% (P <0.05), which is why the radical surgery is often provided impossible. Patients in group I prevailed in the germination of several structures of the tumor as compared with the control group (nearly three times more often) - 7.0% versus 2.2% (P <0.01).

Analyzing the data rate of regional metastasis of

Table 3

The incidence of lung cancer metastases in regional lymph nodes, depending on genetic factors (operated patients)

Patients groups	*Number of radically operated patients*	*Number of patients with meta-stases*	*In % with number operated patients ± m*	*Metastases localization*							
				I эман		*II эман*		*III эман*		*IV эман*	
				Num-ber of patients	*In % with number of patients with metasta-ses ± m*	*Num-ber of patients*	*In % with number of patients with metasta-ses ± m*	*Num-ber of patients*	*In % with number of patients with metasta-ses ± m*	*Num-ber of patients*	*In % with number of patients with metasta-ses ± m*
I	258	144	55,8±3,09	112	77,8± 3,46	119	82,6± 3,16	94	65,3± 3,97	78	54,2± 4,15
II	861	280	32,5± 1,60	185	66,1± 2,83	151	53,9± 2,98	112	40,0± 2,93	33	11,8± 1,93
Total :	1119	424	37,9± 1,45	297	70,0± 2,23	270	63,7± 2.34	206	48,6± 2,43	111	26,2± 2,14

LC found that metastases in regional lymph nodes were identified in 144 of 258 operated patients in group I (55.8%) and at 280 from 861 operated patients of group II (32.5%) (P <0.001) (Table 3).

In patients with a history of hereditary factor is much more common in lymph nodes of all stages of metastasis, compared with a control group of patients. And, noted an interesting pattern, which consists in the fact that with the increase of the difference in the phasing of metastasis is becoming more tangible. Thus, pulmonary lymph nodes were affected in patients with group I and II, respectively, in 77.8% and 66,1% (t = 2,62), (P <0,01), bronchopulmonary lymph nodes - 82.6%, respectively, and 53,9% (t = 6,61), (P <0.001), tracheobronchial lymph nodes and bifurcation - in 65,3% and 40,0% (t = 5,13), (P <0.001). The most frequent (54.2%) in patients with family history of mediastinal lymph nodes were affected (IV stage) compared with a control group of patients - 11.8% (almost 5 times more likely) (t = 9,26), (P <0.001).

Attention is drawn to multiple regional lymph nodes of all stages of metastasis in patients in group I, marked in 125 (48.5%) patients. In group II multiple metastasis was observed only in 146 (17.0%) patients. At the same time remained the same unfavorable pattern as that of a general metastasis. Thus, the difference in the plural lymph node I-th stage was low (68% vs. 62,3%) (P> 0,05). The essential difference is observed in multiple involvement of the lymph nodes of the subsequent stages. Thus, the second phase of the lymph nodes were affected, respectively, in groups I and II patients in 72.0% and 52.1% of cases (P <0.001), the third stage - in 61.6% and 52.1% (P <0.05 .) Particularly common in patients with a history of a hereditary factor involved in the process of multiple mediastinal lymph nodes (58.4%) compared with control group patients (14.4%) (more than 4 times more often) (P <0.001).

The study of the frequency of distant metastases showed that more than twice as likely as distant metastases were found in patients with hereditary pathogenic variant of LC compared with the ecological. Metastases were detected in 104 (24.2%) of 430 patients surveyed the first group and 121 (10%) of 1210 patients of the second group (P <0.001). Attention is drawn to the more frequent multiple organ failure in patients with family history, marked by us in 17.3% of cases in the control group - only 11.6%.

Biological features of hereditary variants of the disease could not help but reflect on the surgical treatment of patients with this group. Thus, the operability of LC patients of the first group was significantly lower than the second, respectively, 60.0% and 71.2% (P <0.001). The same can be said about resectability. Radical able to operate on 217 of 258 patients in group I. Resectability they reached 84.1% in the control group of patients - 93,7% (p <0,001). Saving operations were performed in 136 of 258 patients with family history, which is 52.7%, pneumonectomy - in 81 (31.4%), surgery was limited to a explorative thoracotomy in 41 (15.9%) patients. Among the control group of patients with saving resection was performed in 562 (65.4%) of 861 patients, pneumonectomy - in 245 (28.5%), explorative thoracotomy - in 54 (6.3%). The difference between the execution of test operations and savings thoracotomies in patients of both groups was highly significant (p <0.001). Thus, patients with family history saving operations were performed less often, compared with the control group (52.7% vs. 65.4%), and thoracotomy were performed explorative more than twice as likely (15.9% vs. 6.3 %).

Causes of the expansion of surgical intervention to pneumonectomy and high frequency test thoracotomies in those of the first group were the biological characteristics of tumors, we talked about earlier.

The biological characteristic of tumors in patients with hereditary pathogenic variant of the disease is particularly evident in the study of long-term results of treatment, describing the prognosis.

Analysis of long-term results of radical surgical treatment has demonstrated what a strong influence on life expectancy radically treated LC patients has a family history factor. It is clear that the survival rate of LC patients with a genetic predisposition is much lower than those in patients with indicators of ecological variant of the disease. According to our data indicated that 1 year experienced patients in group I by 1.3 times compared with controls (66.8% vs. 89.0%), 2 years - 1.6 times lower (49.5% vs. 77.8%), 3 years - 1.7 times lower (38.8% vs. 64.9%), 5 years - 1.8 times less (28.3% vs. 50.7%), 10 years - 3.4 times less (10.7% vs. 35.8%). All results were obtained with a high degree of confidence (P <0.001). A characteristic of this pattern is that with increasing survival interval of the difference in the number of patients who survived this period in both groups, increases progressively from 1.3 to 3.4.

The presence of metastasis of LC in the lymph nodes shows the output of the process beyond the local growth, which naturally affects the results of treatment. However, in the absence of metastases in regional lymph nodes in patients with long-term results of the first group is significantly worse than patients of the second group. Thus, the five-year

survival, respectively, they amounted to 37.7% and 59.7% (P <0.001), 10 years old - 16.7% and 42.6% (P <0.01). The same pattern is marked in the presence of patients with metastatic lymph nodes, especially multiple. In multiple regional lymph nodes in patients with five-year results of the first and second groups, respectively, were 16.1% and 24.4%, and 10-year-olds - 7.7% and 23.1%. From the foregoing it can be concluded that the presence of LC metastases in regional lymph nodes significantly affects the long-term results in patients of both study groups, especially in patients with hereditary aggravated history. Therefore, the detection of metastatic lymph nodes during surgery in patients with hereditary pathogenic variant of the disease needs to perform extensive surgery with removal of all collectors of regional lymph nodes.

When comparing the long-term results by stage of disease in patients of both groups should be emphasized that the first group of patients are significantly worse than patients of the second group. Based on our studies it becomes clear why, to the surprise of surgeons dealing with thoracic surgery, with stages I-II lung cancer (T1N0M0, T2N0M0, T1N1M0, T2N1M0), when the seemingly radical surgery is performed economical with minimal impact in terms of adverse factors prediction, a significant proportion of patients die from disease progression during the first year of observation. It turns out that a careful elucidation of family history, many of them fall into a heavy hereditary pathogenic variant of the flow. Thus, in the early stages of LC (I-II stage) after radical surgery for over a year live only 82.2% of patients with a genetic predisposition, whereas in the comparable group, the rate was 93.1% (P <0.001), more than two years, respectively, 64.0% live and 83.6% (P <0.001), more than three years - 51.9% and 73.2% (P <0.001), more than five years - 38.7% and 58.4% (P <0.01), more than 10 years - 21.4% and 36.8% of patients (P> 0.05).

Based on the above we can conclude that malignant lung tumors in hereditary diseases of the pathogenic form is far more aggressive than ecological option and are characterized by high rates of germination in the adjacent anatomical structures and organs, it is a high potential of metastasis in regional lymph nodes and distant structures and organs. Moreover, the high potential of metastasis most often manifested in the multiplicity of regional lymph nodes, especially mediastinal lymph nodes (IV phase metastasis) and distant structures and organs. Thus, the fact that family history dramatically alter the biological nature of the tumor, despite the fact that the major factors that determine the flow characteristics of LC, such as localization, morphological structure and shape of the tumor growth in both pathogenic groups were almost identical.

Identification of genes that determine the risk of developing LC, is one of the most attractive problems in molecular medicine. Ideally, molecular-biological preventive diagnosis should allocate people for whom contact with the carcinogen can be absolutely fatal. Such tests would significantly improve the health selection in hazardous industries, besides a certain focus efforts to control smoking and early detection of LC in high-risk groups seems justified, at least from a theoretical point of view [11,41,46,83].

With the advances of molecular biology and genetic engineering in recent years managed to detect and characterize a number of viral and cellular oncogenes involved in the process of carcinogenesis. With the discovery of retroviral oncogenes and their cellular progenitors - protooncogene - the opportunity (within the concept of oncogenes) appear the possibility to study the malignancy at all levels of the organization of cells, tissues and body as a whole. Modern ideas about cancer at the molecular level can be taken into account to determine a wide range of genome damage, including somatic mutations, as well as leading to the activation of protooncogenes, as well as damage to the genes (antioncogenes) governing their operation. However, no molecular genetic characteristics of the damage of oncogenes and suppressor genes in different pathogenic variants of LC were revealed. This is understandable, as clinicians, this problem was not raised.

Restriction analysis of DNA samples revealed LC patients and healthy donors, four major allele protooncogene HRASI: A1, A2, A3, A4, having the following dimensions BamH-I - restriction fragment: 6.6, 7.1, 7.7, 8,1 kb and PvuII-restriction fragments: 2.7, 3.2, 3.8, 4.2 kb, respectively.

The frequency of alleles A1 and A3 in lung tumors is not significantly different from control (Table 4). The frequency of A2 allele is slightly higher than that in normal (as normal using the aggregate published data on the distribution of alleles of protooncogene HRASI in healthy donors and our results: 15.4% to 12.3% (the ratio is 1.25), however, is almost identical with the occurrence A2 detected in our group of donors: 15.4% to 14.1% (1.09), frequency of allele A4 clearly higher in comparison with a healthy population of Leningrad region (p <0.2): 11.5% (12 out of 104 possible alleles, ie 10 out of 53 patients had one allele A4, and 1 of 53 - both alleles are A4) and 6.6% (13 of 196 alleles, ie 13 out of 98 donors contained this allele), 11.5% to 7.8% (1.47) and with total data in the literature: 11.5% to 8.8% (1.31).

Table 4

The distribution of alleles HRASI oncogene in lung cancer patients and healthy donors

Alleles	*Donors **	*Patients**	*Donors ***	*Patients ***
A1	42 (65,6%)	64 (60,4%)	859 (64,1%)	864 (61,6%)
A2	9 (14,1%)	17 (16%)	164 (12,2%)	171 (12,2%)
A3	7 (10,9%)	10 (9,4%)	146 (10,9%)	147 (10,5%)
A4	5 (7,8%)	12 (11,3%)	119 (8,9%)	126 (9,0%)
Rare	1 (1,6%)	3 (2,8%)	52 (3,9%)	94 (6,7%)
Total	64	106	1350	1402

*Note: * - the data obtained in our laboratory; ** - summary data in the literature*

Of the 53 patients with LC in only 3 (2.9%) revealed the presence of rare alleles in the genome (RA) protooncogene HRASI with the following values BamHI - restriction fragment: 6.3, 6.8 and 8.5 bp. That is, our results after the research Gerhard D.et al. [23], White G. et al. [71], and others do not support the hypothesis of the involvement of rare alleles in the emergence and development of malignant tumors in humans.

In lung tumors, characterized by increased frequency of allele A4 was found a significant prevalence of this allele, together with a reduction in the frequency of allele A3 in metastatic carcinomas, in contrast to what without metastasis. There was also an association with the A4 allele of an oncogene stage III-IV disease. For patients with LC, the allele containing the A4, shows decrease in 5-year survival compared with patients who have this allele absent. In addition, the frequency of rearrangements of locus HRASI oncogene in tumors was significantly associated with the presence in them of allele A4 ($P < 0.01$).

There are only a few publications that have been set higher frequency of allele A4 in patients with nonsmall cell lung cancer. Authors of studies have suggested that allele A4 HRASI indirectly or directly, because of the operation of ECP are associated with the occurrence of these carcinomas and may be used as a marker of genetic predisposition [24, 72].

When considering the ratio of alleles in a HRASI I group (hereditary pathogenic variant) and II (ecological option), groups of patients with LC of 53 surveyed in 15 patients revealed a family history factor (Table 5).

When comparing the groups revealed the following differences in the distribution of alleles A1, A2, A3, was negligible, but the A4 allele in I group, have met 2 times more likely than the II group of patients with LC ($p < 0,2$); in I group of 5 - year survival was 33%, while in group II - 42%. Moreover, in Group I mainly got sick with aggressive tumor characteristics nonsmall cell LC and healthy donors. The material was recruited at the Oncology Institute of Moldova.

The distribution of alleles HRASI oncogene is somewhat different from the Russian population, but similar to data reported by J.Heighway et al [24]. In the group of patients compared with healthy donors,

Table 5

The distribution of alleles HRASI oncogene in groups I and II lung cancer patients

Alleles	*I group*	*II group*	*Total*
A1	17 (57%)	47 (62%)	64
A2	5 (16,6%)	12 (15,8%)	17
A3	3 (10%)	7 (9.2%)	10
A4	5 (16.7%)	7 (9,2%)	12
Rare	1 (3,3%)	2 (2,6%)	3
Total	30	76	106

Table 6

The distribution of alleles HRASI oncogene in lung cancer patients and healthy donors Moldovan population

Alleles	*Donors*	*Patients*
A1	76 (61,3%)	55 (54%)
A2	17 (13,7%)	13 (12,7%)
A3	13 (10,4%)	12 (11,6%)
A4	12 (9,6%)	15 (14.7%)
Rare	6 (4,8%)	7 (6.9%)
Total	124	102

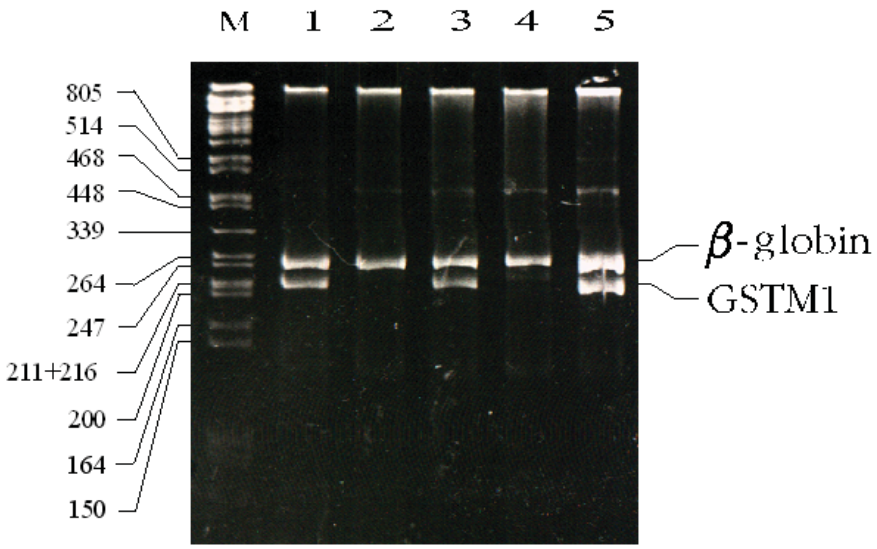

Fig. 1. *An example of genotyping GSTM1*

Lanes 1, 3, 5: genotype GSTM1 (+); lanes 2, 4: genotype of GSTM1 (-). DNA of phage lambda, hydrolysed with endonuclease PstI, was used as a marker of molecular weight.

there is a tendency to increase the frequency of allele A4, as noted in the Russian population (Table 6).

The hereditary history we have been able to identify 12 patients. As seen in Table 7, also varies the frequency of allele A4 in groups I and II patients. Differences on other minor alleles are negligible. (Table 7).

Proved interesting and the distribution of alleles HRASI on stages of the disease (Table 8). The table shows that the A2 and A4 alleles are more common in the genome of patients with aggressive tumor features. It was also studied the distribution of alleles in the genome HRASI patients with aggressive tumor features (Table 8).

Polymorphism of GSTM1 gene is expressed in an unusual way: about half the people do not have a glutathione-S-transferase activity because deletion of both alleles of this gene. Most researchers agree that the GSTM1-deficient genotype increases the risk of cancer in smokers [18, 47, 54,70]. Probably the GSTM1 gene polymorphism may play a role in situations where the development of neoplasms has no apparent connection to chemical carcinogenesis [18,54,63]. If the above is indeed true, then the genotype of GSTM1 (+), respectively, shall perform

Table 7

The distribution of alleles HRASI oncogene in Groups I and II lung tumors Moldovan population

Alleles	*Donors*	*Patients*	*Total*
A1	12 (50%)	43 (55%)	55
A2	3 (12,5%)	10 (12,8%)	13
A3	2 (8,3%)	10 (12,8%)	12
A4	5 (20,8%)	10 (12,8%)	15
Rare	2 (8,3%)	5 (6.4%)	7
Total	24	78	102

Table 8

The distribution of alleles oncogene HRASI on the stages of tumor

Alleles	*I*	*IIa*	*II6*	*IIIa*	*III6*	*IV*
A1	11	9	18	2	11	4
A2	0	1	7	0	3	1
A3	4	1	5	0	1	1
A4	1	0	7	0	6	1
Rare	0	3	0	0	3	1
Total	16	14	37	2	24	9

the function of tread. This suggests an increased incidence of GSTM1 (+) variant in a group of elderly oncological, healthy people, especially among older smokers. This assumption is tested in this study.

Figure 1 shows an example of genotyping GSTM1.

The results of genotyping are showed in table 9.

The frequency of GSTM1-deficient variants among a group of HD was 55%, which corresponds to the results of similar studies [18,43,47,54]. As expected, smokers and nonsmokers showed a similar distribution of genotypes (P = 0.785).

By ED of the occurrence of GSTM1 (-) was slightly reduced compared with the HD (45% vs. 55%; OR = 0.66 (0.42-1.04); P = 0.073). The distribution of genotypes of GSTM1 in smokers and non-elderly donors differed significantly (P = 0.721). However, the differences between the groups of ED and HD were more pronounced in smokers (GSTM1 (-): 43% vs. 57%; OR = 0.57 (0.31-1.04); P = 0.067), than non-

Table 9

The distribution of GSTM1 genotypes among groups of older donors, donors and the average age of patients with lung cancer

Groups	*GSTM1genotype (%)*		
	GSTM1(-)	**GSTM1(+)**	Total
Older donors (total)	**70 (45)**	**87 (55)**	**157 (100)**
Smoking (total)	35 (43)	46 (57)	81 (100)
Male	32 (44)	40 (56)	72 (100)
Women	3 (-)	6 (-)	9 (-)
Nonsmoking (total)	35 (46)	41 (54)	76 (100)
Male	15 (47)	17 (53)	32 (100)
Women	20 (45)	24 (55)	44 (100)
Male (total)	47 (45)	57 (55)	104 (100)
Women (total)	24 (44)	30 (56)	54 (100)
Middle age donors (total)	**77 (55)**	**63 (45)**	**140 (100)**
Smoking (total)	51 (57)	38 (43)	89 (100)
Male	24 (50)	24 (50)	48 (100)
Women	27 (66)	14 (34)	41 (100)
Nonsmoking (total)	18 (55)	15 (45)	33 (100)
Male	7 (-)	4 (-)	11 (-)
Women	11 (-)	11 (-)	22 (-)
No data about smoking	8 (-)	10 (-)	18 (-)
Male	6 (-)	5 (-)	11 (-)
Women	2 (-)	5 (-)	7 (-)
Male (total)	37 (53)	33 (47)	70 (100)
Women (total)	40 (57)	30 (43)	70 (100)
Lung cancer patients	**34 (59)**	**24 (41)**	**58 (100)**
Smoking (total)	27 (53)	24 (47)	51 (100)
Male	24 (50)	24 (50)	48 (100)
Women	3 (-)	0 (-)	3 (-)
Nonsmoking (total)	7 (-)	0 (-)	7 (-)
Male	3 (-)	0 (-)	3 (-)
Women	4 (-)	0 (-)	4 (-)
Male (total)	27 (53)	24 (47)	51 (100)
Women (total)	7 (-)	0 (-)	7 (-)

Note: *% is not counted if the group was less than 30 cases*

smokers (GSTM1 (-) 46% vs. 55%; OR = 0.71 (0.32-1.60); P = 0.417).

When comparing the GSTM1 polymorphism between samples, LC and HD increased frequency of "zero" option in patients was expressed to a small extent (59% vs. 55%; OR = 1.16 (0.63-2.14); P = 0.641). At the same time, the increased representation of variant GSTM1 (-) was more obvious when used as a control ED (59% vs. 45%; OR = 1.76 (0.96-3.23); P = 0.068).

In the present work found no association of GSTM1 genotype with the age of the patients and histological type of tumor (data not shown). However, among the 55 patients, which was characterized by stage of disease was established downward trend in the occurrence of genotype GSTM1 (-) patients with a marked proliferation of the process (GSTM1 (-): stage I-II - 17/24 (71%), stage III-IV - 15/31 (48%); OR = 2.59 (0.86-7.79); P = 0.097).

Conceiving this study, we planned to get answers to some questions. First, it was interesting to find out how pronounced "protective" the role of GSTM1 (+) genotype, is revealed an increase in its occurrence in the elderly oncological healthy individuals. Secondly, this study assessed the efficacy of the first inclusion in molecular epidemiological studies of additional control group, allegedly having an extreme degree of tolerance of cancer.

Our results suggest that the genotype of GSTM1 (+) really occurs in the ED group, more often than middle-aged donors. Such differences have not been demonstrated in a similar study by Chenevix-Trench G. et al. [14]. However, the design of Chenevix-Trench et al. [13,14] had several significant features that could affect the content of the conclusions. First, despite the fact that the average age in the ED Chenevix-Trench et al. [13,14] was similar to that in the present experiment (77 years and 79 years respectively), age ranges in geriatric groups differed significantly [14]: 53 - 95 years, this work is: 75 - 95 years). Secondly, Chenevix-Trench et al. [14] does not take into account the factor of smoking. We also have an extra emphasis on the involvement of ED is smoking: it was assumed that if the genotype of GSTM1, in fact, associated with carcinogen-induced tumors, the ED-smokers should show the maximum deviation from the standard population. In the context of the study of ED is also of interest in the work of [47], which was set routine of GSTM1 polymorphism in centenarians aged 99 years and older (average age - 101 years). However, smoking and history of cancer in the study [47], were not recorded, and the group consisted mainly of long-lived women.

Our data on the small prevalence of GSTM1-proficit status among ED are consistent with numerous, well-reproducible observations revealed a moderate association of GSTM1 null genotype with cancer risk [18, 43, 47, 54, 63]. The lack of pronounced differences between smokers and nonsmokers in the group of ED suggests that individual tolerance to the effects of smoking are mediated not only GSTM1 (+), but also some other factors. Moreover, the pattern of polymorphism of GSTM1 in ED indirectly confirms the hypothesis according to which the GSTM1-negative variant may increase the risk of some cancers that are not directly related to smoking [18, 54,63].

It is important to note that ED are attracted to this study, represent not only the oncological-tolerant individuals, but also, in a sense, long-lived as a whole. While the average life expectancy in Russia is 57.7 years for males and 71.2 years - for women [51], all ED managed to reach age 75 and older. Thus, some accumulation of genotype GSTM1 (+) in the geriatric group may indicate that the GSTM1-surplus is a protective factor not only for cancer but also for other pathologies.

The study of the "weak" factors of genetic predisposition is a difficult task, since the identification of "borderline" abnormalities requires immaculate design of the experiment. [15,60,69]. The traditional way to improve the informativeness of the findings is to increase the number of comparison groups. However, such an extensive expansion of research does not always bring results, adequate time and resources, especially if a new analysis of polymorphism. An alternative approach involves raising demonstrative data through more rigorous selection of patients and controls. In particular, many researchers are trying to balance as compared groups of parameters such as gender, age, exposure to carcinogens, etc. [54]. In this paper, we proposed a new strategy, which includes a comparison of cohorts with extreme characteristics of cancer risk. Cancer-tolerant group was represented by ED, including ED - smokers. Cancer-prone group consisted of patients with LC. It should be mentioned that, unfortunately, we failed to attract sufficient numbers to study non-smoking patients with LC, which is clearly illustrated by the greatest degree of genetic susceptibility to the disease. HD in this experiment played the role of population-based standard. We assumed that if the status of GSTM1 does play a role in the predisposition to LC, the differences in the frequencies of GSTM1-genotype will be most pronounced among patients with LC (especially non-smokers) and ED (especially smokers), and HD will occupy an intermediate position on this indicator. This assumption was fully confirmed by experimental data. Moreover, comparison of LC patients with

older donors appeared to be more effective than the traditional comparison of patients and HD.

Our results on the role of GSTM1 polymorphism in susceptibility to LC are in good agreement with similar work, both in qualitative and quantitative aspects. Indeed, most researches find some association between the GSTM1-deficiency and risk of LC. However, this association is very weak, so the comparison of LC patients and HD are rarely yields statistically significant results, and conclusion about the involvement of GSTM1 is rather comprehensive analysis of tens of molecular epidemiological studies than on the basis of any individual publications [8,13,23]. In our case, patients with LC also showed no significant deviations from HD, although the tendency to the predominance of GSTM1-negative option, of course, was observed. However, the involvement of additional comparative analysis, cancer-tolerant control group - older donors - allowed us to obtain statistically significant results.

In conclusion, our data support the role of the tread GSTM1, GSTM1 (+) genotype appears to increase the chances of surviving to old age without cancer. Furthermore, we demonstrated the feasibility of using an additional control group, namely the elderly oncological healthy donors to study the factors of weak predisposition to neoplasia.

Among the gene polymorphisms that may influence the risk of developing LC, special attention is attracted by the gene CYP1A1 of the cytochrome P450 family. It encodes an enzyme arilhydrocarbonhydroxilase (AGG). AGG metabolizes polycyclic aromatic hydrocarbons (PAHs), which are major carcinogenic components of tobacco smoke.

MspI polymorphism of the CYP1A1 gene has attracted much attention of researchers after the works of K. Kawajiri et al., that reported an increase in the risk of LC in carriers of the mutant allele (M2) of the gene [34,35]. However, in subsequent reports similar relationship was not confirmed by all authors [4,12,17,26,40]. Poor reproducibility of studies may be partly explained by methodological difficulties associated with finding low penetrate effects of alleles. For example, the control group in epidemiological studies of this kind is usually represented by persons of middle age. Due to the fact that the probability of developing cancer in their lifetime for women is 38%, while for men - 48%, similar to the control samples, there is a significant number of potential cancer patients. In order to increase the demonstrative molecular epidemiological analysis, we proposed to use an additional comparison group consisting of elderly oncological-healthy individuals. As our previous experiments, such an unconventional approach can significantly increase the effectiveness of the study of gene polymorphisms [6,7,74,86]. In this paper we present data on the distribution of alleles of the CYP1A1 gene in LC patients, donors, middle-aged and elderly oncological-healthy smokers and nonsmokers. An example of genotyping of CYP1A1 is shown in figure 2.

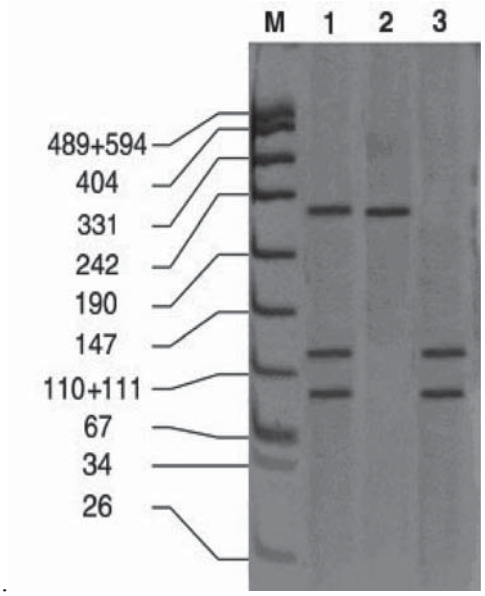

Fig. 2. *An example of genotyping of CYP1A1 gene*

Track 1 - heterozygote m1m2; lane 2 - homozygote for the wild-type allele m1m1 (m1 allele bears no restriction site for MspI); lane 3 - homozygote mutant m2m2 (m2 allele bears restriction site for MspI). As the molecular weight marker was used plasmid pUC19, restritsirovannaya enzyme MspI. Track M - size marker fragments(bp)

Table 10 presents data on the distribution of alleles and genotypes of CYP1A1 in elderly individuals, the middle age donors (HD), and LC patients. The frequency of genotype M1M1, M1M2 and M2M2 was a HD 79%, 20% and 1% respectively, which is comparable with the data obtained in the analysis of other European populations [4,17,26, 38,56]. ED showed a similar distribution of genotypes (Table 10). In patients with LC representation of genotypes M1M1, M1M2, M2M2 was somewhat different from that in control samples (73%, 25% and 1%), but statistical analysis did not confirm the authenticity of this effect. However, patients with squamous cell LC showed a statistically significant deviation from the norm, which is expressed in increasing the frequency of the variant allele of M2 (19% vs. 11% in each of the control group; $\chi^2 = 4,727$, $P = 0.03$). Other histological types of LC, namely, adenocarcinoma and small cell tumors, such laws did not show.

Thus, in this study, we demonstrated an association between the M2 allele of the CYP1A1 gene and risk of squamous cell carcinoma of the lung. Revealed the relationship is true, however, the low

Table 10

The distribution of genotypes and alleles among cancer-CYP1A1/Msp1 healthy elderly healthy donors and lung cancer patients

Groups	*Genotypes CYP1A1 (%)*				*Alleles CYP1A1 (%)*		
	M1M1	*M1M2*	*M2M2*	*Total*	*M1*	*M2*	*Total*
Elderly donors (Total)	**206 (80)**	**51 (20)**	**2 (1)**	**259 (100)**	**463 (89)**	**55 (11)**	**518 (100)**
Smoking (Total)	84 (80)	21 (20)	0 (0)	105 (100)	189 (90)	21 (10)	210 (100)
Men	74 (80)	19 (20)	0 (0)	93 (100)	167 (90)	19 (10)	186 (100)
Women	10 (83)	2 (17)	0 (0)	12 (100)	22 (92)	2 (8)	24 (100)
No smoking (Total)	113 (80)	28 (20)	1 (1)	142 (100)	254 (89)	30 (11)	284 (100)
Men	34 (83)	7 (17)	0 (0)	41 (100)	75 (91)	7 (9)	82 (100)
Women	79 (78)	21 (21)	1 (1)	101 (100)	179 (89)	23 (11)	202 (100)
Anamnesis of smoking not revealed (Total)	9 (75)	2 (17)	1 (8)	12 (100)	20 (83)	4 (17)	24 (100)
Men	4 (80)	0 (0)	1 (20)	5 (100)	8 (80)	2 (20)	10 (100)
Women	5 (71)	2 (29)	0 (0)	7 (100)	12 (86)	2 (15)	14 (100)
Total Men	112 (81)	26 (19)	1 (1)	139 (100)	250 (90)	28 (10)	278 (100)
Total Women	94 (78)	25 (21)	1 (1)	120 (100)	213 (89)	27 (11)	240 (100)
Middle age donors (Total)	**181 (79)**	**47 (20)**	**2 (1)**	**230 (100)**	**409 (89)**	**51 (11)**	**460 (100)**
Smoking (Total)	107 (80)	26 (19)	1 (1)	134 (100)	240 (90)	28 (10)	268 (100)
Men	54 (77)	15 (21)	1 (1)	70 (100)	123 (88)	17 (12)	140 (100)
Women	53 (83)	11 (17)	0 (0)	64 (100)	117 (91)	11 (9)	128 (100)
No smoking (Total)	54 (77)	15 (21)	1 (1)	70 (100)	123 (88)	17 (12)	140 (100)
Men	17 (74)	5 (22)	1 (4)	23 (100)	39 (85)	7 (15)	46 (100)
Women	37 (79)	10 (21)	0 (0)	47 (100)	84 (89)	10 (11)	94 (100)
Anamnesis of smoking not revealed (Total)	20 (77)	6 (23)	0 (0)	26 (100)	46 (88)	6 (12)	52 (100)
Men	9 (60)	6 (40)	0 (0)	15 (100)	24 (80)	6 (20)	30 (100)
Women	11 (100)	0 (0)	0 (0)	11 (100)	22 (100)	0 (0)	22 (100)
Total Men	80 (74)	26 (24)	2 (2)	108 (100)	186 (86)	30 (14)	216 (100)
Total Women	101 (83)	21 (17)	0 (0)	122 (100)	223 (91)	21 (9)	244 (100)
Lung cancer patients (Total)	**107 (73)**	**37 (25)**	**2 (1)**	**146 (100)**	**251 (86)**	**41 (14)**	**292 (100)**
Smoking (Total)	90 (73)	32 (26)	2 (2)	124 (100)	212 (85)	36 (15)	248 (100)
Men	86 (72)	31 (26)	2 (2)	119 (100)	203 (85)	35 (15)	238 (100)
Women	4 (80)	1 (20)	0 (0)	5 (100)	9 (90)	1 (10)	10 (100)
Non-Small cell lung cancer	71 (70)	28 (28)	2 (2)	101 (100)	170 (84)	32 (16)	202 (100)
Squamous cancer	46 (66)	22 (31)	2 (3)	70 (100)	114 (81)	26 (19)	140 (100)
Adeonocarcinoma	23 (85)	4 (15)	0 (0)	27 (100)	50 (93)	4 (7)	54 (100)
Small cell carcinoma	14 (78)	4(22)	0 (0)	18 (100)	32 (89)	4 (11)	36 (100)
No smoking (Total)	14 (78)	4 (22)	0 (0)	18 (100)	32 (89)	4 (11)	36 (100)
Men	4 (80)	1 (20)	0 (0)	5 (100)	9 (90)	1 (10)	10 (100)
Women	10 (77)	3 (23)	0 (0)	13 (100)	23 (88)	3 (12)	26 (100)
Age groups							
≥ 50 лет	11 (85)	2 (15)	0 (0)	13 (100)	24 (92)	2 (8)	26 (100)
> 50 лет	96 (72)	35 (27)	2 (2)	133 (100)	227 (85)	39 (15)	266 (100)
Anamnesis of smoking not revealed (Total)	3 (75)	1 (25)	0 (0)	4 (100)	7 (87.5)	1 (12.5)	8 (100)
Total Men	93 (73)	33 (26)	2 (2)	128 (100)	219 (86)	37 (14)	256 (100)
Total Women	14 (78)	4 (22)	0 (0)	18 (100)	32 (89)	4 (11)	36 (100)

penetrance of the observed effect is not possible to draw any conclusions about the clinical relevance of genotyping of CYP1A1.

Polycyclic aromatic hydrocarbons (PAHs) are major carcinogenic components of tobacco smoke. When ingested, they are first activated by enzymes cytochromes, particularly CYP1A1, and then inactivated by glutathione - transferase, particularly GSTM1. Both of these enzymes have a functional polymorphism. It is logical to expect that the combination of proficit variant of CYP1A1 genotype with deficient GSTM1 variant can significantly increase the risk of LC, especially the PAH-associated species - squamous cell carcinoma (SCC). In this paper we analyzed the distribution of genotypes of CYP1A1 and GSTM1 in LC patients (n = 141), middle-aged healthy donors (GS, n = 204), as well as oncological elderly - healthy smokers and nonsmokers (ED, n = 246). Allele CYP1A1-C^{3801} revealed significantly more common in patients with squamous cell carcinoma compared with healthy donors, the average age (OR = 2.22 (95% CI = 1.06-4.63)) and elderly donors (OR = 2.27 (95% CI = 1.14-4.52)) . The combined genotypes of CYP1A1-C^{3801} / GSTM1 (-) were characterized by increased occurrence in patients with squamous cell carcinoma (14/70, 20.0%) and lower representation of older donors (19/246, 7.7%) (OR for SCC vs. PD = 3.85 (95% CI = 1.43-10.33)). Thus, while the testing of isolated genotypes CYP1A1 and GSTM1 appear clinically unpromising; due to the severity of minor effect, the combination of unfavorable variants of these genes may be discussed as a medically significant factor increasing cancer risk.

Apoptosis plays an important role in the death of cells with damaged DNA, which protects the body from cancer. Some data suggest that normal variations in the chain of apoptotic genes may lead to suboptimal functioning of the system of programmed cell death and thus to an increased risk of developing cancer. It is assumed that individuals with suboptimal functioning of the system of programmed cell death may have increased susceptibility to LC as a result of incomplete elimination of mutated cells. Study participants polymorphic genes of apoptosis are still at an early stage [31,52,61,65].

Although LC is not part of a highly penetrable single gene cancer syndrome, normal genetic variations in humans likely play an important role in susceptibility to the disease. For example, the adverse combination of single nucleotide polymorphisms of the gene (SNPs), are involved in the metabolism of tobacco smoke carcinogens, showed a high risk of LC modifier. Currently, a systematic study of the involvement of DNA repair genes and apoptosis to the formation of the risk of LC [31,42,48,55].

Comparison of the „case - control“ frequency SNP was carried out two-step method. In the first stage of analysis involves comparing candidate SNPs subjects with high demonstrative characteristics of tolerance and susceptibility to LC. The group of „extreme“ predisposition to LC (n = 111) included patients from a total of 351 LC patients and included 17 non-smokers, and 94 patients, characterized by a relatively modest smoking history (10-40 packs of cigarettes / year in average - 30 packs of cigarettes / year) and earlier age of onset (32-64 years mean age, 54 years old.). Group „super control“ included hard-core smokers are not ill with LC, who were selected from a total cohort of 2791 healthy subjects, aged 75 years and older and contains samples of 110 individuals (age range 75-89 years, mean age, 79 years, the average exposure to smoking - 55 packs of cigarettes / year, with the range of 30-126 packs of cigarettes / year). SNPs, which showed the expected trends based on „comparison of extremes”, have been exposed to the traditional „case - control“ over. 351 LC cases (range - 30-84, the average age-61 years), including 303 smokers (mean number of packs of cigarettes / year - 41, the interval - 10-150 packs of cigarettes / year) and 48 non-smokers. The control group (n = 538, mean age - 61 year range - 32-84 years) did not include subjects who were genotyped at the stage of „comparison of extremes“ and amounted to 474 smokers (mean exposure to smoking - 22 packs of cigarettes / year interval - 1-111 packs of cigarettes / year) and 64 non-smokers. The sources of DNA for all groups were termed peripheral blood leukocytes. For genotyping polymorphisms Casp 8 His302Asp addition were selected and used 127 DNA samples from the archives of normal tissues in non-smokers suffering from LC (mean age - 61 year age range: 16-82). All DNA samples were obtained from residents of the Russian Federation (St.-Petersburg). Current standards require the reproduction of the molecular epidemiology of the correlations obtained for the other populations. In this project we used an independent set of „case-control“, which was derived from the other former Soviet republics, Moldova. This collection consists of 296 patients of LC patients (mean age, 58 years, age range 22-79), the 232 - smokers (mean exposure to smoking - 43 packs of cigarettes / year, range 3-123 pack of cigarettes / year) 64 non-smokers), 295 healthy blood donors (mean age - 56 years, age range 22-80), 207 - smokers (mean exposure to smoking - 25 packs of cigarettes / year, range 3-130 packs of cigarettes / year) and 88 non-smokers.

Table 11

Evaluation studies of candidates SNPs

SNP		*Russia*		*Republic of Moldova*	
		Lung cancer (%)	*Control (%)*	*Lung cancer (%)*	*Control (%)*
Casp5 Val318Leu (G/C)	GG	137 (39.0)	221 (41.1)	103 (34.8)	107 (36.3)
	CG	158 (45.0)	248 (46.1)	134 (45.3)	133 (45.1)
	CC	56 (18.0)	69 (12.8)	59 (19.9)	55 (18.6)
Casp8 His302Asp (C/G)	GG	263 (74.9)	420 (78.1)	226 (76.4)	232 (78.6)
	CG	83 (23.6)	112 (20.8)	67 (22.6)	58 (19.7)
	CC	5 (1.4)	6 (1.1)	3 (1.0)	5 (1.7)
DR4 Lys441Arg (A/G)	AA	250 (71.2)	399 (74.2)	210 (70.9)	222 (75.3)
	AG	89 (25.4)	126 (23.4)	83 (28.0)	70 (23.7)
	GG	12 (3.4)	13 (2.4)	3 (1.0)	3 (1.0)
Total		351 (100)	538 (100)	296 (100)	295 (100)

For the study, we examined 37 nonsynonymous coding SNPs in apoptotic genes, which were due to population frequency (SNP database of NCBI http:// www.ncbi.nlm.nih.gov/ SNP) and presented in our previous publications [31]. Polymorphism of p53 Arg72pro was excluded from the study because of its participation in the susceptibility to LC has been tested in detail in previous papers [46]. Successful genotyping was performed for 33 SNPs, in contrast to the analysis of the remaining three SNPs (Casp an Gln37Lys, DR3 Gly159Asp, DR5 Leu32Pro), despite repeated attempts to optimize the frequency and conditions for PCR. Another 14 SNPs (Bcl2 Thr43Ala, Bik Pro 148Leu, Bcl-x Gly160Val, Casp5 Leu13Phe, Casp5 His152Arg, Casp5 Leu201Val, Casp6 Glu34Ala, Casp6 Lys35 Glu, Fas Thr16Ala, Fas Ile122 Thr, DR4 Ile33 Thr, DR4 His297Asn, TNFR1 Leu 75 Pro , TRAIL Glu47Asp) showed zero frequency in our collection of DNA samples.

However, comparing the distribution of alleles in the groups with „extreme“ level of susceptibility and tolerance were conducted for 19 SNPs. Taking into consideration the category of involved patients, which have obvious characteristics of contrasting predisposition to LC, we assume that the named alleles, contributing to the development of LC will be identified to show exactly proportional to the difference (ORs). If we consider OR = 3 as a reasonable threshold for the comparison of „extremal» [81] and rely on the value of p = 0.1, the study may be possible to identify 99% of the risk - with a population allele frequency of 30% and 90% confirmation of the identification of alleles in 10% of subjects. 4 of 19 tested SNPs (Casp5 Ala90 Thr, Casp5 Val318 Leu, Casp8 His302 Asp, DR4 Lys441Arg) showed p <0.1. However, Casp5 Ala90 Thr polymorphism was excluded from further study because the difference in distribution between cases and controls was based entirely on changes in Hardy-Weinberg equilibrium (depletion of heterozygotes) in healthy elderly smokers, oncologic, and moreover, we analyzed data obtained from other categories of subjects (breast cancer (case - control), data not shown) and concluded that the variation Casp5 Ala90 Thr does not contribute to susceptibility to LC. A subgroup analysis of cases of LC according to smoking status and histological type of tumor did not reveal additional promising SNPs (data not shown).

Based on the previously presented results of primary screening, homozygous Leu / Leu for Casp5 Val318 Leu (OR = 2.41 (95% CI :1.02-5 .70)), His carriers for Casp8 His302 Asp (OR = 2.26 (95% CI :1.18-4 .3)) and Arg carriers for DR4 Lys441Arg (OR = 1.89 (95% CI :1.06-3.38)) polymorphisms were considered as candidates for the genotypes that predispose the development of LC and were therefore subject to an extended analysis. For groups of LC, we have added a set of genotypes in 240 cases out of 351, not included in our total collection, whereas the control group, we were able to identify an independent set of 538 is not affected by the subjects. In the project we have included an extra set of Moldova, which amounted to 296 patients LC patients and 295 controls. The study had 80% of the nominal significance level of 0.05 determine the Mantel - Haenszel OR = 1.48, 1.41, 1.38, respectively, for the risk genotypes, as described previously. Results of case-control comparisons are presented in Table 11.

It is noteworthy that all three of this genotype showed OR> 1 in both Russian and Moldovan in the groups ‘case – control’. However, the associations identified in the combined analysis of Mantel - Haenszel, did not reach statistical significance (Table 12).

Analysis of subgroups of patients with LC by histological type, sex, age and other parameters did not reveal any additional associations. However, taking into account smoking status, it is assumed

Table 12

Odds ratios and confidence intervals for candidate at-risk genotypes

SNP	*OR (95% CI) and p values*		*Mantel-Haenszel OR (95% CI) and p values*
	Russia	*Moldova*	
Casp5 Val318Leu , Leu/Leu-genotype	1.31 (0.87 - 1.98), $p = 0.20$	1.11 (0.71 - 1.76), $p = 0.64$	1.22 (0.90 - 1.65), $p = 0.21$
Casp8 His302Asp, His-carriers	1.19 (0.87 - 1.63), $p = 0.28$	1.14 (0.78 - 1.68), $p = 0.51$	1.17 (0.92 - 1.50), $p = 0.21$
DR4 Lys441Arg, Arg-carriers	1.16 (0.86 - 1.57), $p = 0.34$	1.24 (0.87 - 1.80), $p = 0.24$	1.19 (0.95 - 1.51), $p = 0.14$

association between the genotype and the risk LC of Casp8 in non-smokers. The frequency of His-carriers in the latter category of Russian patients (19/48 (40%)) significantly higher than the same data in the control (118/538 (22%) p = 0.006), and moreover, similar, but not statistically significant trend was found in the Moldovan subjects (16/64 (25%) versus 63/21 (p = 0.52)). Recent studies indicate that LC in non-smokers may be caused by genetic susceptibility determinants [64,66]. To confirm these correlations, we analyzed 127 additional sets of DNA from a Russian non-smoking patients suffering from LC, using the normal tissue from archival paraffin-fixed sets. The frequency of His-carriers in the new genotype of LC in non-smokers was identical previously surveyed in the control, ie 22% (28/127), which contradicts the previously identified association.

The study was designed to analyze associations between SNPs in genes coding for apoptosis and predisposition to LC. The preliminary selection of candidates for SNP was performed by comparing the subjects with „extreme“ levels of tolerance and susceptibility to LC. A group of patients with LC was made up of non-smokers, or with a low exposure to smoking combined with early establishment of the disease. It was expected that the actual risk allele will be expressed hyperprezentation in this group of patients, although the actual extent of this effect is difficult to determine. Studies on susceptibility to breast cancer have shown that the ability to identify options that predispose to breast cancer, increased by several times of the selected categories of patients [33,48]. However, similar calculations of the frequency of alleles associated with higher risk of LC patients against the environmental group LC is more complicated because of a shortage of well-proven disease-gene interactions and the corresponding data sets of case-control studies. On the other hand, studies of LC have a unique opportunity to enrich the category of control patients. Recent observations indicate that smokers have a lower chance to reach adulthood without the disease of LC [53]. At present, the exact prediction of the effect level is very difficult, as a result of diseases related to smoking, and different life expectancies in different geographic regions. Nevertheless, some authors will be expected to marked depletion, predisposing to the development of risk genotypes for LC in a group of elderly healthy controls, strongly smokers. These assumptions OR = 3 and p <0.1 may be considered as a possible threshold under “comparison of extremes”, and in this work, we have ample opportunity to determine the SNP candidate for advanced study.

Three SNPs were identified by the “comparison of extremes” (Casp5 Val318 Leu, Casp8 His302 Asp and DR4 Lys441Arg). It is noteworthy that all three of these genotype showed OR> 1kak in the Russian and Moldovan in the groups ‘case – control’. However, the associations identified in the combined analysis of Mantel - Haenszel, did not reach statistical significance (Table 12). The biological function of caspase-5 protein is quite understandable. Caspase-5 has a role in various aspects of inflammation [45], in addition Casp5 gene has been repeatedly identified as a target in a set of mutations in human cancer [57]. In comparison, the role of caspase-8 in programmed cell death has been investigated at a high enough level. Interestingly, the His-allele carriers for Casp8 His302 Asp were reported as having a low risk of developing breast cancer [16]. DR4 are coupled ligand-induction of apoptosis, and some data indicate that DR4 may be involved in the predisposition to tumor development [19,20].

If we believe that this polymorphism is unequivocally predisposes to the development of LC with OR = 1.2 (Table 12), to prove this association, we must analyze the 3000 LC cases and 3000 controls.

The collection of this size, to date, can not be collected at the same university, but may be in the covered by multicentric studies [28]. In addition to the size of a set of other potential limitation of the study due to the method of choice in SNP. Our study is based on a list of coding nonsynonymous SNPs in apoptotic genes, compiled in 2005 [31]. The number of identified SNPs is growing as a result of systematic research, and there are interesting new

candidates to be studied, except for planned in the study. For example, NCBI SNP database (http://www.ncbi.nlm.nih.gov/SNP) contains some new proven coding polymorphisms, which are characterized by a relatively high frequency (> 5%), and still attract attention at first sight (Boo Arg21Leu (rs2231292), Casp an His15Arg (rs1042743), Casp7 Glu4Asp (rs11593766), Casp 9 Arg176Gly (rs2308949), DcR2 Pro345Thr (rs34622674), DcR2 Ser310Leu (rs1133782), FasL Val266Leu (rs 35178418), XIAP Phe133Ser (rs28382722)). Moreover, the functional impact of polymorphisms of genes encoding is not less clear than SNPs, of course, that the ratio of the genotype - phenotype is not limited to amino acid variation. It is interesting that recent large-scale genomic analyzes of cancer-associated SNPs, led to the identification of several polymorphisms associated with risk, including some that are in the vicinity of apoptotic genes, without regard to the chain of amino acids that have already been presented [59,62]. No coding SNP apoptosis genes were not considered in this study. Finally, these studies did not consider the value of SNP combinations in determining susceptibility to disease. It is possible that certain SNPs alter the predisposition to cancer only in the particular context of the genetic, but a large set of samples and a wide subgroup analysis is needed to identify the current gene-gene interactions.

In conclusion, this study included a 2 - a landmark design for systemic analysis of coding nonsynonymous SNPs apoptotic genes. Three genotypes (Leu / Leu homozygotes for Casp5 Val318Leu polymorphisms, His carriers for Casp8 His302 Asp and Arg polymorphism carriers for DR4 Lys441Arg polymorphism) have demonstrated an association with risk of LC in the preliminary comparison of "extreme" groups of cancer susceptibility and tolerance. It is noteworthy that all three of this genotype showed OR> 1 as in the Russian and Moldovan in the case of groups - control. Although the association identified in the combined analysis of Mantel - Haenszel, did not reach statistical significance, the findings show the usefulness of large-scale genotyping of polymorphisms of genes Casp 5, Casp8 and DR4 in the framework of existing international consortia.

In this paper we have attempted to estimate the distribution of alleles of L-MYC oncogene in patients with lung cancer from other former Soviet republics, Moldova.

The results of genotyping oncogene L-MYC are shown in Fig. 3.

The results of genotyping lung cancer patients and HD are shown in table 13.

The distribution of alleles L-MYC in both groups was virtually identical. However, among patients with established considerable variation L-MYC genotypes depending on the involvement of regional lymph nodes, as well as the presence of distant metastases (Table13). In particular, the SS genotype is significantly higher ($p < 0.05$) was seen in patients with metastases (N1-2) than in the case of a localized process (N0). Moreover, the mere presence of S alleles in the genotype was correlated with both lymph nods lesions ($p < 0.02$), and the presence of distant metastases ($p < 0.05$). When comparing the "extreme" options, namely, patients without metastases and in patients with N2 or M1, S alleles differed by about 2-fold ($p < 0.02$). At the same time, no statistically significant variations in genotype L-MYC, depending on the size and degree of invasiveness of the primary tumor.

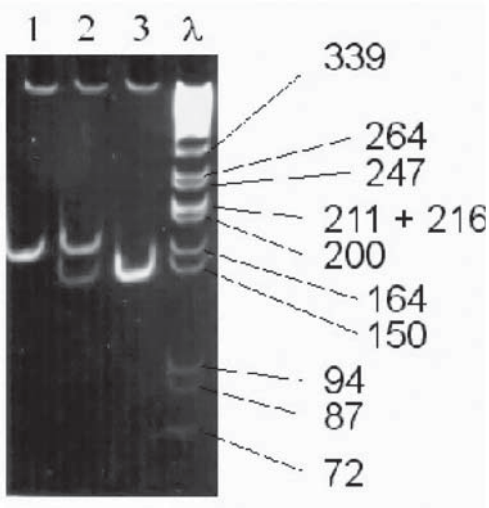

Fig. 3. *Identification of alleles of L-MYC oncogene by polymerase chain reaction*

L-allele is not hydrolyzed by restriction endonuclease Eco RI; S-allele containing the Eco RI site, was cleaved by the enzyme referred to the two smaller fragments. In the analysis of 177 bp in length amplifications S allele is represented by the splitting of product size 148 bp sequence and 29 bp, however, a 29-nucleotide bands are not visible in the figure. Used as a marker of DNA of phage lambda, hydrolyzed restriction endonuclease Pst I; the size of the fragments indicated in bp

Our experiments have confirmed the remarkable geographical conservatism in the frequencies of S and L alleles - nearly all previous studies have indicated approximately equal to the incidence of both variants of the gene L-MYC. The absence of differences in the distribution of L-MYC genotypes between patients with LC and donors is also consistent with the already published works [50,70].

However, we noted patterns of clinical need special comments. The predominance of S allele

Table 13

Distribution of oncogene alleles L-MYC lung cancer patients and healthy donors

Patients/control	*L-MYC genotypes (%)*				*L-MYC alleles (%)*		
	SS	**LS**	**LL**	**total**	**S**	**L**	**total**
Lung cancer patients	**10 (23)**	**25 (58)**	**8 (19)**	**43 (100)**	**45 (52)**	**41 (48)**	**86 (100)**
Primary tumor							
T_1	0 (0)	3 (75)	1 (25)	4 (100)	3 (38)	5 (63)	8 (100)
T_2	5 (26)	9 (47)	5 (26)	19 (100)	19 (50)	19 (50)	38 (100)
T_3	5 (25)	13 (65)	2 (10)	20 (100)	23 (58)	17 (43)	40 (100)
Involving of the regional lymph nodes							
N_0	0 (0)	8 (67)	4 (33)	12 (100)	8 (33)	16 (67)	24 (100)
N_1	3 (27)	7 (64)	1 (9)	11 (100)	13 (59)	9 (41)	22 (100)
N_2	7 (41)	8 (47)	2 (12)	17 (100)	22 (65)	12 (35)	34 (100)
N_x	0 (0)	2 (67)	1 (33)	3 (100)	2 (33)	4 (67)	6 (100)
Distant metastases							
M_0	5 (17)	16 (55)	8 (28)	29 (100)	26 (45)	32 (55)	58 (100)
M_1	5 (36)	9 (64)	0 (0)	14 (100)	19 (68)	9 (32)	28 (100)
Healthy donors	**21 (27)**	**38 (49)**	**18 (23)**	**77 (100)**	**80 (52)**	**74 (48)**	**154 (100)**

and SS genotype in LC patients with metastases was observed earlier in patients predominantly Mongoloid race [36,37]. Similar studies made on the "Europoids" The U.S., Australia and Norway, have not established such a correlation [21,67,68]. Nevertheless, the study of LC cases in Russia [73,81] and Moldova (present study) showed that the clinical significance of S alleles of our "white" compatriots are showing more similarities with the eastern race than immigrants from Europe. A similar trend is observed for some other polymorphic loci, such as cytochrome CYP2D6 [1, 81]. The emergence of the genetic characteristics of the Mongoloid race have "caucasoid" population of the former Soviet Union can be attributed to long-term Mongol-Tatar occupation in the Middle Ages, as well as long-standing historical ties with the neighboring Central Asian Republics [1, 81]. Apparently, the conclusion about the role of race in the clinical significance of genotype L-MYC is premature; in that context legitimate to pose the question of the geographical variations.

It remains unclear how the substitution of one nucleotide in the non-coding part of the L-MYC oncogene may influence the association of genotype with its clinical characteristics of LC [36,37,70,73]. At the moment there are two hypotheses. In accordance with the first assumption, the polymorphic site of the gene L-MYC, located in the second intron plays a role in the regulation of gene expresivness. An alternative explanation involves entanglement S allele of L-MYC with the "true" LC gene, located on the adjacent site of the genome. Our evidence on the impact of regional factors on the clinical significance of L-MYC, consistent with the second hypothesis more.

Justification for the direct application of L-MYC genotyping in the clinic is dubious in connection with the moderate strength of detected correlations. More promising might be working on the role in metastasis genes, genetically linked to the L-MYC.

In conclusion, it should be noted that, based on literature data and our investigations conclude that the participation of genetic factors in the development of LC is quite logical. From the above it is clear that one of the achievements in the field of LC should be recognized proof of its etiologic heterogeneity, ie the existence of hereditary and nonhereditary pathogenetic variants of the disease, even within the same location. Therefore, the identification of hereditary forms of LC by searching for reliable molecular genetic markers is a promising direction and puts one of the problems whose solution must recognize the fundamental step of genetic counseling in order to improve the timely diagnosis and treatment results.

Our main objective was to advance the concept and the theoretical basis of the two major pathogenetic variants of the flow of LC: hereditary and ecologic. In 1986 at the IV All-Union Congress of Oncologists in the report entitled "Pathogenetic approach to diagnosis and treatment of cancer," Professor R.I.Vagner [75]. gave the following definition of pathogenic variants of malignant tumors: "Under the pathogenic variant of malignant tumors, we understand a variety of malignant neoplasms characterized, despite the appearance in a single organ, and sometimes having the same origin in an organ a unique clinical presentation and course, with different potency to the local growth and regional metastasis, progression tumor, characterized by a response of the organism to tumor development and treatment".

At the time not yet been identified and developed pathogenic variants of LC, but was discovered and proved the existence of pathogenic variants of hormone-dependent tumors. Professor Ya.V.Bohman was justified the existence of two main clinico-pathogenetic variants of endometrial cancer (1 and 2 variants), Professor V.F.Semiglazov - 4 variants of breast cancer (thyroid, ovarian, adrenal, involutive). Revealed heterogeneity of these tumors have opened up new possibilities of pathogenetic prevention, diagnosis and treatment, which is already being implemented at this stage. Formulated R.I.Vagner definition of pathogenetic variant of a malignant tumor is fully consistent with a dedicated and theoretically substantiated pathogenic variants of LC and we hope that this study will help to improve the timely diagnosis and treatment of this terrible disease.

In general, based on development of hereditary theory of lung cancer the study appear the opportunity to raise the issue of early (preclinical) diagnosis and prevention of disease through specialized genetic counseling, which consists of the following steps: - Genetic screening (identification and registration of families burdened with cancer); - Genetic counseling (identification of genetic diagnosis and prognosis); - Formation of genetic risk groups and their clinical and genetic monitoring (early diagnosis and prevention of LC).

Testing of susceptibility genes for LC in clinically healthy relatives of cancer patients will be of great importance, since such an approach will completely change the tactics of genetic counseling, whose main task will be to identify individuals - carriers oncopathologic genes predisposing to the development of specific forms of LC which, in turn, will allow the scientific validity of all the steps to carry out genetic counseling, including the identification of genotypes of the counselee, the calculation of the risk of LC, early diagnosis and prevention of cancer in general. The results of the implementation of this approach to early diagnosis and prevention of LC will recommend it as a model for creating a common system of cancer control a new direction - a system of cancer care to families affected by cancer.

Conclusions

1. On the basis of clinical, molecular genetic studies of proposed and theoretically substantiated the concept of two major pathogenetic variants of lung cancer: hereditary and ecologic.

2. Malignant lung tumors in hereditary pathogenic form of the disease occur more aggressive compared with the environmental option and is characterized by high rates of germination in the adjacent anatomical structures and organs, it is a high potential of metastasis in regional lymph nodes and to distant organs and structures. The high potential of metastasis most frequently manifested multiple regional lymph nodes, especially mediastinal lymph nodes (IV phase metastasis) and distant structures and organs. Thus, the fact that family history dramatically alter the biological nature of the tumor, despite the fact that the major factors that determine the flow characteristics of lung cancer, such as tumor location, morphological structure and form of growth in the pathogenesis of both groups did not significantly differ.

3. The existing tendency to increase the frequency of allele A4 HRASI oncogene in patients with hereditary pathogenic variant of lung cancer in relation to patients with an environmental variant allows a certain degree of probability of the allele A4 HRASI as a marker of inherited predisposition to cancer of the lung.

4. The presented analysis of the distribution of alleles among the protooncogene HRASI nonsmall cell lung cancer patients compared with healthy donors showed that the increased frequency of allele A4 HRASI oncogene is associated with increased signs of aggressive tumors and poorer survival, and significantly correlated with the breakage locus HRASI. Thus, allele A4 HRASI essential for the progression of LC and is a prognostic factor.

5. The carriage of the polymorphic allele CYP1A1 increases the risk of squamous cell carcinoma of the lung. Accordingly, in patients with LC found an association between CYP1A1 genotype present in the mutant allele and an increase in these tumors when smoking.

6. The null genotype of GSTM1 was associated with an increased risk of lung cancer. There was a trend to an association of genotype GSTM1 (-) with early stage LC. Our data confirm the role of the tread GSTM1 (+).

7. A study on the combined effects of genes CYP1A1 and GSTM1 on the risk of LC showed that the combination m2-containing genotype of CYP1A1 and GSTM1 deficiency option increases the individual risk of lung cancer by more than 2 times.

8. The results indicate the feasibility of large-scale genotyping of polymorphisms of genes of apoptosis Casp5, Casp8 and DR4 in the framework of existing international consortia.

9. S-allele of the L-MYC gene is associated with metastasis of malignant tumors of the lung.

10. In this investigation we propose a new strategy, involving a comparison, including cohort with extreme characteristics of cancer risk. Comparison of LC patients with older donors appeared to be more

effective than the traditional comparison of patients and healthy donors.

11. On the basis of development of hereditary theory of lung cancer appear the opportunity to raise the issue of early (preclinical) diagnosis and prevention of the disease by testing the susceptibility genes for lung cancer in clinically healthy relatives.

12. The results of the implementation of this approach to early diagnosis and prevention of lung cancer can be recommended as a model for creating a common system of cancer control a new direction - a system of cancer care to families affected by cancer.

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Rezumat

Natura ereditară a cancerului este una din cele mai studiate în cazul tumorilor maligne, cum ar fi tumori embriogene la copii (retino-şi nefroblastomul), cancerul colorectal, cancerul sistemului de reproducere feminin (cancerul glandei mamare, ovarian), cancerul tiroidian medular. Problemele legate de cancerul pulmonar de pe aceste poziţii nu sunt dezvoltate. Studiul se bazează pe datele de la aproximativ 2000 de pacienţi cu cancerul pulmonar, care au fost investigaţi şi supuşi tratamentului în Institutul Oncologic, Republica Moldova şi Institutul de Oncologie N.N. Petrov, în ultimii 10 ani. Finalizată genotiparea genelor apoptozei, HRAS1, GSTM1, CYP1A1, L-myc. Pentru prima dată, ca urmare a dereglărilor complexe a fost propus şi bazat teoretic conceptul a două variante patogenetice majore de cancer pulmonar: ereditar şi ecologic.

Este prezentată o analiză comparativă a parcursului în variantele evidenţiate patogenetice, au fost studiate particularităţile de dezvoltare locală, a metastazelor, opţiunile de tratament şi rezultatul bolii în cazul variantei ereditare. A fost efectuată analiza genetico-moleculară de markeri şi asocierea lor cu susceptibilitatea la boală, care este un domeniu nou şi promiţător de cercetare. În baza teoriei ereditare a cancerului pulmonar apare posibilitatea de a ridica problema depistării precoce (preclinice), profilaxiei acestei boli prin oferirea consultaţei specializate medicale şi genetice.

Cuvinte-cheie: Tumori maligne, cancer pulmonar, patogeneză, metastazare.

Summary

The hereditary nature of cancer most studied with such malignancies as embryonic tumors in children (retino-and nephroblastoma), colorectal cancer, cancer of the female reproductive system (breast cancer, ovarian), medullar thyroid cancer. The issues of lung cancer (LC) with these positions are not developed. The study is based on data on approximately 2000 patients with lung cancer who were on a survey and treatment at the Institute of Oncology, Moldova, and NN Petrov Institute of Oncology in the last 10 years. Completed genotyping HRAS1, GSTM1, CYP1A1, L-MYC gene and apoptosis. For the first time as a result of comprehensive research proposed and theoretically substantiated the concept of two major pathogenetic variants of lung cancer: hereditary and environmental. A comparative analysis of the flow in isolated lung pathogenic variants, studied the characteristics of local growth, metastasis, treatment options and outcome of disease at the genetic variant. Carried out the molecular genetic analysis of markers and their association with susceptibility to the disease, which is a new and promising area of research. Based on the development of the theory of hereditary lung cancer the opportunity to raise the issue of early (preclinical) diagnosis and prevention of this disease by providing specialized medical and genetic counseling.

Keywords: Malignancies tumors, lung cancer, pathogenesis, metastasis.

Резюме

Наследственная природа рака наиболее изучена при таких злокачественных новообразованиях как эмбриональные опухоли у детей (ретино- и нефробластомы); колоректальный рак; рак органов женской репродуктивной системы (рак молочной железы, яичников); медуллярный рак щитовидной железы. Вопросы изучения рака легкого (РЛ) с этих позиций остаются не разработанными. В основу работы положены данные, касающиеся около 2000 больных РЛ, находившихся на обследовании и лечении в Институте онкологии Молдовы и НИИ онкологии им. проф. Н.Н.Петрова за последние 10 лет. Выполнено генотипирование HRAS1, GSTM1, CYP1A1, L-MYC и генов апоптоза. Впервые в результате комплексных исследований выдвинута и теоретически обоснована концепция о двух основных патогенетических вариантах РЛ: наследственного и экологического. Представлен сравнительный анализ течения РЛ при выделенных патогенетических вариантах, изучены особенности местного роста, метастазирования, возможности лечения и исход заболевания при наследственном варианте. Осуществлен молекулярно-генетический анализ маркеров и их ассоциаций с подверженностью к данному заболеванию, что представляет собой новое и перспективное направление исследований. На основе разработки наследственной теории РЛ появилась возможность ставить вопрос о ранней (доклинической) диагностике и профилактике данного заболевания путем организации специализированного медико-генетического консультирования.

Ключевые слова: Злокачественные новообразования, рак легких, патогенез, метастазирование.