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REVIEW

Estrogen Receptors, Antiestrogens, and Non-Small Cell Lung Cancer

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Abstract—This review considers data on expression of different types of estrogen receptors (ERα and ERβ) in *in vitro* cultured cells of non-small cell lung cancer and also in human and animal lung tumors. Estrogens are shown to play an important role in genesis and development of non-small cell lung cancer because the estrogen-stimulated cell proliferation as well as antiestrogen-caused inhibition of proliferation occurred only in the cells expressing different types of estrogen receptors. In general, the situation is similar to that observed in breast cancer, but in the cells of non-small cell lung cancer not ERα are expressed in more than half of cases but ERβ. Just estrogen receptors β play the crucial role in inducing cell proliferation in response to estrogens, and ERβ is a prognostic marker of a favorable course of non-small cell lung cancer. Data on the interactions between ER and EGFR signaling pathways, as well as on the additive antitumor effect of antiestrogens (tamoxifen and fulvestrant) combined with tyrosine kinase inhibitors (gefitinib, erlotinib, and vandetanib) are considered. The review also includes data on the influence of estrogens on genesis and development of lung cancer in humans and animals and the frequency of ERα and ERβ expression in non-small cell lung cancer in tissues from patients of the two sexes. Problems of quantitative determination of α and β estrogen receptors in the tumor cells are also discussed.

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Key words: estrogen receptors, non-small cell lung cancer, antiestrogens

The wide distribution of lung cancer and the high lethality to patients with this disease make urgent the search for new pathogenetically based strategies for its treatment. No doubt, tobacco smoking is the major risk factor for development of lung cancer. But the data accumulated by now show that estrogens are involved in pathogenesis of lung cancer. Epidemiological data indicate sex-associated differences in the incidence of particular morphological variants of lung cancer. Squamous cell carcinoma is associated with smoking and is a prevalent subtype in men, whereas adenocarcinoma, which is more frequent in women, is a histological variant of the non-small cell lung cancer the least associated with smoking [1-3].

Estrogens are known to play an important role in the genesis and development of such malignancies as breast cancer, endometrial and ovarian cancer. The hormonal sensitivity of tissue is determined by expression in it of estrogen receptors. Binding of estradiol with the receptor activates various intracellular processes manifesting themselves in the enhancement of proliferating activity.

Estrogen receptors are extremely important cellular targets allowing not only control of carcinogenesis but also suppression of already transformed tumor cells. This has been brilliantly confirmed from the early 1970s by results of using tamoxifen in patients with breast cancer with a positive status of estrogen receptors. The drug allows physicians to significantly improve long-term results of surgical treatment due to decreasing the risk of relapse and mortality of the patients and is also effective in the adjuvant therapy. Its antitumor efficiency is first of all associated with its ability to selectively block estrogen receptors, which are present in the majority of tumor cells of patients with breast cancer.

Abbreviations: DPN, 2,3-bis(4-hydroxyphenyl)propionitrile; ER, estrogen receptors; ERE, estrogen-responsive element; GEN, genistein; NSCLC, non-small cell lung cancer; PPT, 4,4′,4″-(4-propyl-[1H]-pyrazole-1,3,5-triyl)tris-phenol.

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This review considers the available data on the presence of estrogen receptors in tumor cells of patients with non-small cell lung cancer (NSCLC). Results of experimental works about using antiestrogens in the cell lines of NSCLC and in transplanted tumors in animals are considered, as well as first results of clinical testing in this field.

ESTROGEN RECEPTORS IN CELL CULTURES OF HUMAN NON-SMALL CELL LUNG CANCER AND THEIR ROLE IN EFFECTS OF ESTROGENS AND ANTIESTROGENS

According to the literature, in *in vitro* cultured cells of human non-small cell lung cancer estrogen receptors β (ERβ) are a dominant subtype, whereas the expression levels of ERα vary greatly in different cultures. Thus, expression of ERα mRNA was found in four of 15 cell lines of NSCLC: in three adenocarcinoma lines (DB354, HCC-78, and NCI-H1435) and in the line of large cell carcinoma NCI-H460. All cultures were ERβ-positive, and the presence of the ERα mRNA protein product was confirmed by immunoblotting [4]. No expression of the full-size ERα was found by immunoblotting in different cell lines of NSCLC (the squamous cell carcinoma lines 273T and 128-88T; adenocarcinoma lines 201T, H157, Calu-6, H23, and A549; the large cell carcinoma line H1299), but ERβ was found in all specimens [5, 6].

Some studies on different lines of non-small cell lung cancer indicated that 17β-estradiol stimulated the *in vitro* and *in vivo* division of tumor cells, enhanced the expression of some genes associated with the tumor progression and growth (in particular, of E-cadherin and inhibitor of differentiation 2), secretion of VEGF, and also a rapid activation of MAPK, Akt, and CREB via their phosphorylation [4-12]. Attention should be given to work [13] investigating the role of each ER subtype (ERα and ERβ) in realization of the above-mentioned genomic and nongenomic effects of estrogens. The study was performed on the cell line 201T of lung adenocarcinoma, which was treated with selective agonists of ERβ (genistein (GEN); 2,3-bis(4-hydroxyphenyl)propionitrile (DPN)) and of ERα (4,4′,4′′-(4-propyl-[1H]-pyrazole-1,3,5-triyl)trisphenol (PPT)). As discriminated from PPT, GEN induced a pronounced (1.5-fold) increase in ER-dependent transcription. Agonists of the receptor of both subtypes (DPN and PPT) enhanced phosphorylation of MAPK. However, only a selective agonist of ERβ (DPN) enhanced the cell proliferation *in vitro* and the tumor growth *in vivo* in mice with a xenograft of adenocarcinoma 201T [13]. Studies on the influence of DPN and the ERα agonist PPT on proliferation of cells of the human adenocarcinoma line Calu-6 gave similar results [6]. Suppression of the ERβ synthesis by RNA interference abolished the proliferative response to estradiol [6]. Thus, it was concluded that ERβ plays a key role in the induction of proliferation of NSCLC cells. However, ERα seemed to be also involved in this process: RNA interference of ERα significantly suppressed the *in vitro* proliferation of NSCLC cells [11].

In work [6] ERβ were shown to be mainly located in the cytoplasm and could not be translocated into the nucleus in the presence of a ligand and to activate the transcription, but this contradicts earlier findings [8, 13, 14]. The induction of the ERβ-dependent proliferation is thought to be mainly (if not exclusively) caused by nongenomic mechanisms [6]. The distribution of functions between the two ER subtypes requires further studies.

The above-mentioned effects of 17β-estradiol are inhibited by antagonists of estrogen receptors. Thus, in the cells of the human non-small cell lung cancer lines BEAS-2B and DB354, which express ERα and ERβ, tamoxifen significantly suppressed the cell proliferation [4]. Antiestrogens suppressed the 17β-estradiol-induced transcription in the cells H23, 784T [8], and RERF-LC-OK [12]: upon cell treatment with tamoxifen [8] or fulvestrant [8, 12] the transcription decreased to the basal level. Fulvestrant inhibited the growth of cell colonies of the culture RERF-LC-OK [12]. Fulvestrant also decreased expression of the genes of E-cadherin and inhibitor of differentiation 2 in cultures of human cells—adenocarcinoma line 201T and squamous cell carcinoma line 273T [5]. A decrease in the gene expression was accompanied by a decrease in the amount of the corresponding protein products in the cells (confirmed by immunoblotting). EGF similarly to estradiol stimulated proliferation of the NSCLC cells but did not influence the expression of E-cadherin and inhibitor of differentiation 2, which seemed to be specific targets of ER-dependent signaling pathways [5].

In mice with a xenograft of non-small cell lung cancer line H23, fulvestrant suppressed the estradiol-stimulated growth of tumors. The *in vivo* experiments were performed on female mice not subjected to ovariectomy. The tumor volume was 44% diminished in the group of animals treated with 17β-estradiol and fulvestrant as compared to the animals treated only with estradiol. Fulvestrant caused a similar decrease in the tumor volume in mice untreated with exogenous estrogens [8]. A rapid phosphorylation and increased accumulation of MAPK in the nucleus induced by 17β-estradiol were suppressed upon the cell incubation with fulvestrant. Thus, nongenomic effects of estradiol also involve estrogen receptors and can be prevented by antiestrogens [9].

In the majority of published works there are no data on the sex of patients whose tumors were used for isolating cell cultures [4-7, 9-12]. However, this information could be important in connection with possible sex-related differences in pathogenesis of non-small cell lung cancer. Thus, sex-related differences in activities of estrogen receptors were revealed in some cell lines of adenocarci-

noma [15]. Although the cells isolated from tumors of patients of both sexes were similar in the ligand binding, estradiol stimulated proliferation only in the cell lines isolated from women's tumors (lines H1944, H1793, H1395, H1435, and H2073) and antiestrogens 4-hydroxytamoxifen and fulvestrant suppressed proliferation only in these cells. In the adenocarcinoma cell lines isolated from men's tumors (lines H23, A549, H1299, and H1792) neither estradiol nor antagonists of estrogen receptors influenced the proliferation. But in the earlier work [8] estradiol significantly stimulated both *in vitro* and *in vivo* proliferation in cell lines A549 and H23 also isolated from tumors of male patients. Obviously, the data are insufficient, and the studies must be continued.

The interaction of signaling pathways of estrogen receptors and EGFR is now intensively studied. The rapid transactivation of EGFR is a non-genomic effect of 17β-estradiol. Moreover, estrogens caused a decrease in the EGFR expression *in vitro*, whereas fulvestrant caused its increase. On the other hand, the ERβ expression in non-small cell lung cancer cells decreased in response to EGF and increased under the influence of gefitinib. Thus, the EGFR signaling pathway was activated when the ER-dependent signal transmission was blocked and vice versa [10]. Studies on cell lines of human NSCLC indicated that in combination antiestrogens (fulvestrant) and tyrosine kinase inhibitors (gefitinib [9, 10], erlotinib [11], and vandetanib [16]) were additive in suppression of cell proliferation, increasing apoptosis [10], decreasing the *in vitro* secretion of VEGF [9], lowering the size of tumor xenografts [10, 11, 16], and increasing the time to progression *in vivo* [16]. An increase in the *in vitro* cytotoxicity of gefitinib combined with tamoxifen and activation of apoptosis were also shown on cell lines A549 and H1650 of human lung adenocarcinoma as compared with cytotoxicity of gefitinib alone [17].

These studies were reasons for clinical testing of antiestrogen combinations with inhibitors of tyrosine kinase EGFR. Results of the first tests are published and seem to be promising (see below).

INFLUENCE OF ESTROGENS ON GENESIS AND DEVELOPMENT OF HUMAN AND ANIMAL MALIGNANT LUNG TUMORS

Hormonal sensitivity of lung tissue was shown in *in vivo* experiments. Transgenic mice with genome containing an ERE-incorporated construct with the reporter gene of luciferase demonstrated a fivefold increase in the luciferase activity in the lung in response to injection of estradiol [18]. In work [19] the influence of estradiol on initiated carcinogenesis in lung was studied. The carcinogenesis model was created as follows: transgenic mice were subjected to inhalation with an adenovirus vector containing Cre-recombinase, and this caused an activation of the oncogenic form of K-ras and deletion of the suppressor gene *Tp53*. This resulted in development of tumors with different degrees of malignancy: from adenoma to highly and lowly differentiated adenocarcinoma. In females not subjected to ovariectomy, tumors of greater size and malignancy developed than in ovariectomized females and in males. Injection of estradiol enhanced 3.5-fold the proliferative activity of the tumor cells. On the background of estradiol the size and number of tumors significantly increased in animals of both sexes. In estradiol-treated males the tumors developed to later stages than in the control mice. These data indicate that estrogens stimulate genesis and development of lung cancer.

Some clinical studies suggested that estrogens should promote the development of lung cancer. Women receiving estrogen replacement therapy displayed an increased risk of development of lung cancer, mainly adenocarcinoma [20]. It was also shown that early menopause (before and at 40 years) was associated with a decreased risk of development of lung adenocarcinoma. These findings were confirmed by another work, and hormonal therapy was shown to decrease survival in women with lung cancer [21].

By contrast, recently published data indicated that the adjuvant treatment of breast cancer with antiestrogens (most often with tamoxifen) significantly decreased the risk of development of metachronous lung cancer. Moreover, a decrease was also observed in the mortality caused by lung cancer developed in patients with breast cancer treated with antiestrogens [22]. We think that results of works [20-22] convincingly indicated the involvement of estrogens in pathogenesis of lung cancer.

Antiestrogen-including therapeutic schemes are now being clinically tested in patients with non-small cell lung cancer. In a pilot clinical study of the gefitinib/fulvestrant combination partial effects were obtained in 15% of the patients, the overall survival was, on average, 38.5 weeks, and the one-year survival was 41%. This study was performed with participation of post-menopausal women with NSCLC of the IIIB-IV stages. Note that the treatment efficiency depended on the receptor status of the tumor: the overall survival in patients with ERβ found in no less than in 60% of the cells was, on average, 66 weeks, whereas if ERβ were expressed in less than 60% of the tumor cells this parameter was 21 weeks [23]. Now we are waiting for the report of these authors about results of using erlotinib and vandetanib combined with fulvestrant in patients with non-small cell lung cancer.

EXPRESSION OF ESTROGEN RECEPTORS IN NON-SMALL CELL LUNG CANCER TISSUE

Data on the ERα content in the non-small cell lung cancer tissue are contradictory: according to different sources, from 0 to 75% of the tumors are ERα-positive [6,

11, 12, 24-38]. Such a diversity of the data can be caused by several reasons.

First, the lack of a unified approach. Before the early 1990s estrogen receptors were mainly determined by a nonselective biochemical (radioligand) method in the tumor cell homogenate. Different authors reported about expression of estrogen receptors in 17-40% of tumors from patients with non-small cell lung cancer [39, 40]. The sensitivity, accuracy, and selectivity of the biochemical method are rather limited: this method allows the researcher to determine only the total concentration of the ligand-binding estrogen receptors (together with numerous products of their degradation). The immunohistochemical approach is more sensitive and selective because the monoclonal antibodies can bind only with definite areas of the estrogen receptor molecule and, thus, provide for differentiation of estrogen receptors. But the immunohistochemical determination of estrogen receptors is not quantitative. The shortcomings of the method are also the absence of unified indices of positivity of the tumor receptor status, different immunoreactivities of antibodies used, and a subjective visual assessment of the receptor status by pathomorphologists. An ideal but not yet developed approach would be capable of giving an objective, differentiated, and strictly quantitative evaluation not only of number of cells expressing ERα and ERβ, but also of the average expression of each receptor in the tumor cells under study. Modern immunofluorescence diagnostics by flow cytometry is believed to be the most promising.

Second, many authors indicating the absence or a relatively low (3-38%) frequency of the ERα expression took into consideration only nuclear receptors [12, 14, 25, 30-32, 36], and this is another reason for discrepancy of the results. But it is established that, as discriminated from breast cancer, in the cells of non-small cell lung cancer ERα are mainly located outside the nuclei [8, 11, 24, 27]. Cytoplasmic ERα are found in 42-75% of the tumors [11, 24, 27, 38]. For the combined evaluation of nuclear and cytoplasmic staining, the presence of ERα was shown in 50-67% of the tumors [29, 35, 37]. However, even considering staining of the cytoplasm some authors did not find ERα expression in all or in a great majority of studied non-small cell lung cancer specimens [6, 26, 33, 34].

In this connection we note that there is no unified index of estrogen receptor positivity status in tumor tissues, including the tissue of non-small cell lung cancer. The immunohistochemical analysis staining intensity (most often on the scale 0-3+) and the fraction of stained cells in the preparation are usually taken into account. But the threshold value for determination of the estrogen receptor status in tumors differs greatly in different works, e.g. staining of at least one cell in the preparation; 1+ intensity in 10% of the cells; the 1+ in 25% of the cells; 2+ in 50% of the cells; mark 2 by an 8-mark scale; mark 5 by the 8-mark scale; 25% of the tumor cells with staining intensity no less than of the surrounding normal tissue, etc. [6, 11, 12, 24-27, 29-31, 33-36, 38, 41]. But on consideration that in ERα-containing tumors less than 25% of the cells are specifically stained [31, 32, 38] (nuclei – in 11-21% of the cells, cytoplasm – in 7-19% of the cells [38]), it can be concluded that in some works parameters for the ER-positivity are overstated [12, 26, 34]. At the 11th St. Gallen International Expert Consensus on the primary therapy of early breast cancer (March 2009) it was decided, until the development of strict quantitative parameters, to consider tumors with any content of estrogen receptors as ER-positive, independently of the staining intensity and percent of stained cells in the preparation. The presence of any amount of ER in the tumor is an indication for endocrine adjuvant therapy [42].

Discrepancies in the data on ERα contents in NSCLC cells are, in particular, caused by different immunoreactivities of the antibodies used. In immunohistochemical analysis a wide spectrum of monoclonal antibodies produced by different firms are used, whereas polyclonal antibodies to ERα are used less frequently. Mouse antibodies of the clone 1D5, which bound with the N-terminal fragment of the ERα molecule [12, 24, 25, 29-33, 38], and antibodies of the clone 6F11 specific to the full-length receptor [25, 29-31, 35, 36, 38] are used most frequently. In some experiments antibodies of these two clones were used for staining, and the number of ERα-positive cells detected with the 1D5 antibodies was usually lower than the number of the cells detected with the 6F11 antibodies. Thus, the staining of the cells with the 1D5 antibodies did not reveal the presence of ERα, whereas the staining of the same tumors with the 6F11 antibodies indicated that 67% of the tumors were ERα-positive [29]. Note that the clone 6F11 antibodies did not reveal cytoplasmic ERα [38]. In one of the last studies, the immunoreactivity of both widely used antibody clones 1D5 and 6F11 was shown to be significantly lower than the immunoreactivity of monoclonal antibodies of the SP1 clone specific to the C-terminal fragment of ERα. The frequency of ERα detection in the lung adenocarcinoma tissue by means of SP1, 1D5, and 6F11 antibodies was, respectively, 27, 8, and 14%. The differences between the immunoreactivities of the SP1 and 1D5, SP1 and 6F11 antibodies are statistically significant [30].

With polyclonal antibodies HC-20 cytoplasmic ERα were detected in 73% of tumors, whereas staining with 1D5 antibodies gave negative results [27]. These data were not confirmed later: the staining of ERα with the HC-20 antibodies revealed expression of cytoplasmic and nuclear receptors in 42 and 5% of tumors, respectively, whereas on using the 1D5 antibodies the results were, respectively, 18 and 34% [38]. Nevertheless, these data suggest that ERα can be expressed in the tumor cells as several isoforms, one of which can lack a part of the N-terminal

fragment [27]. This hypothesis was also supported by the above-mentioned data that the reactivity of the clone SP1 antibodies specific to the C-terminal fragment of ERα was higher than the reactivity of antibodies of the 1D5 and 6F11 clones [30].

Despite the multiplicity of splicing variants of ERα mRNAs [8], in the majority of cases the corresponding isoform and a full-length receptor are co-expressed [43], therefore, "standard" antibodies to ERα can be used for immunohistochemical studies. However, antibodies specific to regions absent in some particular isoform can give understated results on detecting of ERα. Thus, the exon 5 deletion is associated with generation of an ERα isoform with changes in the region responsible for binding of the ligand. Expression of such receptor in the tissue of hepatocellular carcinoma is specific for clinically very severe tumors insensitive to tamoxifen [44]. Therefore, finding of a prevalent ERα isoform in the tissue of non-small cell lung tissue is very important for clinical practice.

Data on ERβ expression in the tissue of non-small cell lung cancer are much more similar. ERβ is a prevalent subtype of estrogen receptors in the tumor tissue [4, 25, 26, 34, 38, 45]. In the tumor cells ERβ can be located both inside and outside the nucleus. According to the majority of works, these receptors are mainly located inside the nucleus [8, 12, 24, 26, 27, 34], but some authors reported approximately uniform distribution of the nuclear and cytoplasmic receptors [11, 25]. Some works indicated the prevalence of ERβ in the cytoplasm [6]. Expression of nuclear ERβ was detected immunohistochemically in 31-84% of cases [6, 11, 12, 24, 25, 36, 38, 41], and the cytoplasmic staining revealed these receptors in 10-100% of tumor tissue specimens [6, 11, 24, 25, 38].

Because the fraction of specifically stained cells in specimens of non-small cell lung cancer with expressed ERβ is relatively high (more than 25% [38]), different parameters of positivity of estrogen receptors in the tumors are sufficiently sensitive for detecting the ERβ expression even on assessment only of the nuclear (i.e. predominant) receptors and on using different specific antibodies. On average, 60-80% of the tumors are ERβ-positive [11, 12, 16, 24-27, 34, 36, 38, 41].

As a rule, there is no reliable correlation between the receptor status of the tumor and its histological type [24-26, 34, 46, 47]. However, some authors report more frequent incidence of ERα [38] and ERβ [12, 36, 38] in lung adenocarcinoma than in squamous cell carcinoma. In adenocarcinomas of solid subtype the ERβ expression is less frequent, and in bronchioloalveolar carcinoma more frequent than in adenocarcinomas of other histological types [30, 41].

Studies of a possible correlation between the expression level of estrogen receptors and sex of patients with non-small cell lung cancer are very interesting. According to the majority of data, the ERα content does not correlate with the patient's sex [4, 27, 30, 47]. However, there are data on higher incidence of ERα mRNA in the tumor tissue of women than the tumors of men (in 85 and 15% of the cases, respectively) [28], and in work [38] immunohistochemical study demonstrated higher incidence of nuclear ERα in women's tumors.

Data on ERβ are not in agreement: the frequency of ERβ expression is either independent of sex [4, 24, 27, 28, 41] or is higher in women [26, 34, 36, 38]. But in work [25] the ERβ frequency was higher in men, but the correlation of their expression with the male sex was not reliable. Obviously, the differential evaluation of the ERα and ERβ is clinically significant because consequences of inhibition of different estrogen receptors are different. In particular, on the interaction of some antiestrogens (tamoxifen, 4-hydroxytamoxifen, raloxifene) with ERβ only an antagonistic effect is realized, whereas the action on ERα is also accompanied by agonistic manifestations [48]. The significance of different type receptors is also different for prognosis of the aggressiveness of the disease.

Although ER are targets of proliferative stimulus by estrogens, their expression in the tumor in some cases predicts the less aggressive course of the disease. This unexpected finding can be rather strictly explained for the positive prognostic value of the ERα status of breast cancer. In breast cancer the ERα expression correlates with other factors determining favorable prognosis: elderly age, low histological malignancy, low content of cells in the S-fraction, low proliferation index. Similar correlations for the ERβ status can be expected in the case of non-small cell lung cancer. In particular, ERβ expression is specific for highly differentiated non-small cell lung cancer [36, 41], whereas ERα are more often expressed in tumors with low and moderate differentiation [37]. The expression of ERβ in the non-small cell lung cancer tissue predicts more favorable course of the disease as compared to patients without ERβ expression in the tumors: independently of sex, the overall survival of patients with ERβ-positive tumors was better [26, 27, 34, 37]. This was observed only in male patients in two works [24, 25]. The absence of ERβ expression is an independent factor aggravating the prognosis in non-small cell lung cancer [27].

By contrast, the presence of ERα in tumor tissue is an unfavorable prognostic sign [27, 37]. Expression of cytoplasmic ERα correlates with worse relapse-free survival [38]. The progress of the disease is accompanied by a decrease in ERβ expression [26] and by an increase in ERα expression [37]. The overall survival is lowest in patients with non-small cell lung cancer phenotype ERα(+)ERβ(−) [27]. The ERα expression in lung adenocarcinomas is also found to correlate with a mutation in the tyrosine kinase domain EGFR in exons 18-21 [38], and the concurrent hyperexpression of ERα and EGFR is an independent sign of bad prognosis [37]. This is a clin-

ical confirmation of the experimentally found cooperation of signaling pathways of estrogen receptors and EGFR.

Thus, the literature data suggest that estrogens should play an important role in genesis and development of non-small cell lung cancer. Stimulation of proliferation of non-small cell lung cancer cells by estrogens, as well as inhibition of proliferation by antiestrogens, occurs only in cells expressing different types of estrogen receptors. On the whole, the situation is similar to that in breast cancer, but in more than 50% of non-small cell lung cancer cases not ERα but ERβ are expressed. Just estrogen receptors β play a key role in the induction of proliferation in response to estrogens, and ERβ are a prognostic marker of favorable course of non-small cell lung cancer.

Nevertheless, up to now estrogen receptors in tumors are determined only in patients with breast cancer and only for expression of ERα. Moreover, the effectiveness of antiestrogens in the treatment of non-small cell lung cancer is not yet evaluated, except the work about the combined using of gefitinib and fulvestrant; this work has confirmed the reasonability of the idea about the interaction of signaling pathways of estrogen receptors and EGFR.

Results of drug therapy in non-small cell lung cancer are now improved, and it is urgent to differentially assess the expression in tumors of ERα and ERβ, which are not only prognostic markers of the disease course but targets for antiestrogens. This would allow us to broaden indications for rational use of antiestrogens. In particular, there are many theoretical prerequisites and experimental findings that allow us to expect that tamoxifen will be effective (as in patients with breast cancer), and first of all in the adjuvant therapy in patients with non-small cell lung cancer with positive status of estrogen receptors.

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