ONCOLOGY

Involvement of Transforming Growth Factor β and its Type 1 Receptor in the Development of Breast Cancer

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Introduction of recent achievements of molecular biology into clinical practice contributes significantly to both prevention and early detection of breast cancer in women and development of new approaches, including genotyping, to screening for breast cancer. Screening for genetic polymorphisms in genes TGFβ1 and TGFβR1 reveals carriers of sporadic breast cancer. This provides an opportunity to reassess the role and place of preventive measures, also including surgical method, in the fight against breast cancer.

Key Words: *breast cancer; gene for transforming growth factor 1 (TGFβ1), genefor transforming factor receptor (TGFβR1), genetic polymorphisms of TGFβ1 and TGFβR1; bilateral prophylactic subcutaneous mastectomy with simultaneous allogeneic breast prosthesis*

Currently, hereditary and sporadic forms of breast cancer (BC) are recognized [1]. Hereditary BC is found in 5-10% cases. Mutations in genes BRCA1 and BRCA2 leading to the development of BC are best studied [3,4]. However, in recent years molecular studies revealed new genes associated with the development of BC [6-8,10], *e.g.* genes encoding transforming growth factor β (TGFβ1) and its receptor type 1 (TGFβR1) [11,12]. We have carried out oncogenetic screening for gene polymorphisms in genes TGFβ1 and TGFβR1. High-risk BC group (*N*=10) was identified based on the results of genetic screening and integrated clinical trial. All patients in this group underwent prophylactic subcutaneous mastectomy with simultaneous breast prosthesis [2,5,9,13]. According to the results of operational histology, BC not diagnosed at the clinical stage of the survey, was detected in 3 cases.

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MATERIALS AND METHODS

The study was conducted in the Russian Research Center of Radiology in 2004-2007. We examined 150 women at the age of 16-78 years with mammary gland pathologies; the patients were divided into two groups: with malignant (57 women) and benign (93 women) pathology.

All women underwent complex examination including general clinical examination, mammography and ultrasonography (USG) of mammary glands, chest radiography, USG of the abdomen and areas of regional lymph outflow, ECG, and invasive diagnostic methods (contrast mammography, fine-needle biopsy for cytological examination and/or punction biopsy with gun-needle system, for histological examination).

During the first phase of the study, all 150 women underwent screening for genetic polymorphisms in genes encoding TGFβ1 and its receptor TGFβR1 by PCR using standard procedures. For PCR, 1 ml venous blood was taken.

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RESULTS

During PCR study of polymorphisms in gene TGFβ1 and its receptor TGFBR1, several types of polymorphisms were detected in women with malignant and benign tumors (Table 1).

The data obtained are in accordance with the results reported earlier.

Polymorphisms associated with high-risk TGFβ1 and TGFBR1 types were detected in women with benign tumors in 10 cases: TGFβC/T–TGFβR1*9A/6A (1 case); TGFβT/T–TGFβR1*9A/6A (5 cases); TGFβC/T–TGFβR1*6A/6A (3 cases); TGFβT/T–TGFβR1*6A/6A (1 case; Fig. 1).

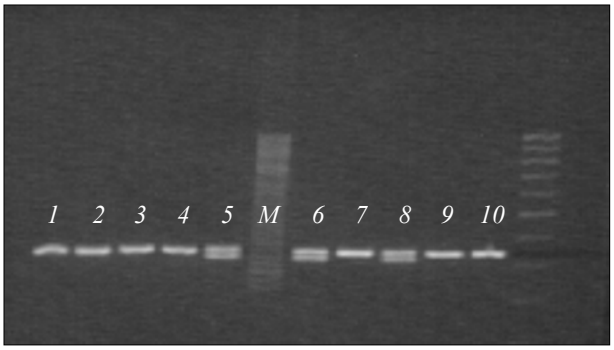

Fig. 1. TGFβR1 6A/9A genotype — Samples 5, 6, 8. Phoresis. M — molecular weight marker. 1-10 — the studied samples.

Mammography recealed pronounced fibrocystic, diffuse nodular mastopathy with multiple cysts and clusters of microcalcifications in all 10 cases (Fig. 2).

Cytological examination of mammary gland needle biopsy specimens in this group revealed cells of cuboidal epithelium with signs of proliferation and dysplasia; simple ductal, atypical hyperplasia, and dysplasia of II-III degree.

Based on the complex research of these 10 women at high risk of developing BC, subcutaneous mastectomy with simultaneous allogeneic breast prosthesis was proposed and performed as a prophylactic measure.

Histological examination of the operational material revealed BC in 3 cases; in one case, bilateral total involvement of the mammary gland tissue was found.

Here are some of histological conclusions.

Histological conclusion: patient A (patient card 6113/88). Infiltrating lobular carcinoma of scirrhous type against the background of severe lobular neoplasm and foci non-invasive lobular cancer in fibrous and adipous tissue.

Histological conclusion: patient B (patient card 13630/06). Multiple large foci of ductal adenosis and ductal hyperplasia in the mammary gland tissue, including those with moderate to severe atypia; peripheral intraductal atypical papillomas; foci of non-invasive intraductal cancer (Fig. 3).

Histological conclusion: patient B. (patient card 11844/06). Right mammary gland: microfoci of infiltrating lobular and non-infiltrating BC in the mammary gland tissue. Micrometastases in two lymph nodes. Left mammary gland: microfoci of non-infiltrating lobular BC in the mammary gland tissue, area of infiltrating lobular BC, and microfocus of infiltrating tubular cancer against the background of severe atypical ductal hyperplasia. lipomatosis in lymph nodes; metastases were not found.

TABLE 1. Distribution of Patients by the Type of Combination of Polymorphisms in Genes Encoding TGFβ1 and Its Receptor TGFβR1

Combinations of polymorphisms	Women with malignant tumors		Women with benign tumors	
	N	%	*N*	%
TGFβC/T–TGFβR1*6A/6A	20	35	3	3.2
TGFβC/T–TGFβR1*9A/6A	13	23	1	1
TGFβT/T–TGFβR1*9A/6A	8	14	5	5.3
TGFβT/T–TGFβR1*6A/6A	2	3.5	1	1
TGFβC/T–TGFβR1*9A/9A	6	10.5	13	14
TGFβT/T–TGFβR1*9A/9A	4	7	11	12
TGFβC/C–TGFβR1*9A/6A	2	3.5	9	9.6
TGFβC/C–TGFβR1*6A/6A	2	3.5	7	7.5
TGFβC/C–TGFβR1*9A/9A	NR	NR	44	47

Note. NR – not revealed.

Fig. 2. Fibrosclerosis. Multiple clusters of microcalcifications.

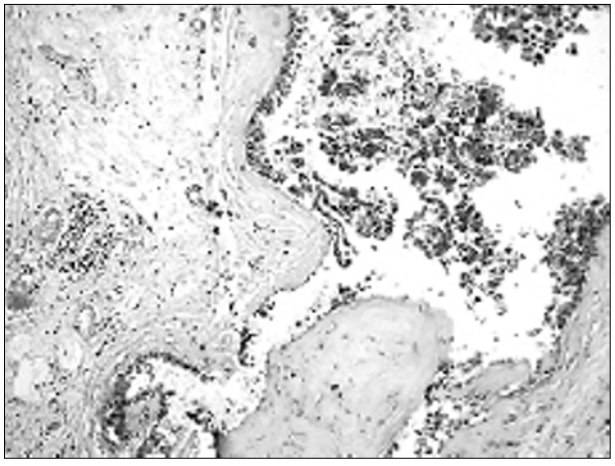

Fig. 3. Intraductal cancer. Staining with hematoxylin and eosin (×120).

In 7 women at high risk for BC, changes in mammary gland tissue were identified as fibrosclerosis, sclerosing adenosis foci, simple ductal and lobular hyperplasia, foci of weak ductal atypia and moderate atypical hyperplasia of the epithelium, foci of severe ductal epithelial atypia, numerous microcalcifications in the lumina of the ducts, and peripheral intraductal papillomas.

In three women of high-risk group, oncogenetic screening of polymorphisms TGFβ1 and TGFβR1 and complex instrumental methods of examination diagnosed BC. They underwent prophylactic subcutaneous mastectomy with simultaneous breast prosthesis as a curative measure.

Screening for cancer-related gene TGFβ1 and TGFβR1 mutations reveals the carriers of sporadic BC that appears at the 90-95% of cases.

REFERENCES

1. L. N. Lyubchenko, N. I. Garkavtseva, N. I. Pospekhova, *et al*., *The Possibilities of Modern Oncology in the Diagnosis and Treatment of Malignant Disease* [in Russian], Moscow (2003), pp. 44-47.
2. F. E. Barton Jr., J. M. English, W. B. Kingsley, and M. Fietz, *Plast. Reconstr. Surg*., **88**, No. 3, 389-392 (1991).
3. F. J. Couch, M. L. DeShano, M. A. Blackwood, *et al*., *N. Engl. J. Med*., **336**, No. 20, 1409-1415 (1997).
4. D. Ford, D. Easton, M. Stratton, *et al*., *Am. J. Hum. Genet*., **62**, No. 3, 676-689 (1998).
5. S. S. Kroll, F. Ames, S. E. Singletary, and M. A. Schusterman, *Surg. Gynecol. Obstet*., **172**, No. 1, 17-20 (1991).
6. R. M. Lyons and H. L. Moses, *Eur. J. Biochem*., **187**, No. 3, 467-473 (1990).
7. J. Massagué, *Nat. Rev. Mol. Cell Biol*., **1**, No. 3, 169-178 (2000).
8. J. Massagué, S. W. Blain, and R. S. Lo, *Cell*, **103**, No. 2, 295-309 (2000).
9. J. A. Pietenpol, R. W. Stein, E. Moran, *et al*., *Ibid*., **61**, No. 5, 777-785 (1990).
10. L. C. Verhood, C. T. M. Brekelmans, C. Seynaeve, *et al*., *J. Clin. Oncol*., **17**, No. 11, 3396-3402 (1999).
11. Q. Wang, H. Zhang, R. Fishel, and M. I. Greene, *Oncogene*, **19**, No. 53, 6152-6158 (2000).
12. P. L. Welcsh and M. C. King, *Hum. Mol. Genet*., **10**, No. 7, 705-713 (2001).
13. J. E. Woods, *Ann. Plast. Surg*., **11**, No. 6, 541-550 (1983).