CYP2D6*3, *4, *6 GENOTYPES AND ENDOMETRIAL THICKNESS IN PATIENTS WITH BREAST CANCER DURING TAMOXIFEN THERAPY

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Tamoxifen therapy results in endometrial thickening in some patients with hormone-sensitive breast cancer (HSBC). The data on the impact of polymorphic variants of the *CYP2D6* gene encoding the CYP2D6 enzyme of the cytochrome P450 family on the efficacy and safety of treatment with tamoxifen are controversial. A prospective cohort study was aimed to explore the association of *CYP2D6*3, *4, *6* polymorphisms with the risk of endometrial thickness during adjuvant tamoxifen therapy for HSBC. A total of 145 patients with resectable HSBC, who received 20 mg of oral tamoxifen per day, were enrolled. The *CYP2D6*3, *4, *6* polymorphisms were identified by real-time PCR. Endometrial thickness was measured by ultrasonography after 3, 6 and 9 months of endocrine therapy. The study showed that endometrial hyportrophy was more often found in patients having no alternative alleles after 3 months of follow-up (40% against 23.2% in the group of "poor" metabolizers; $p = 0.034$). Meta-analysis of all follow-up periods has revealed that "normal" metabolizers show a significantly higher rate of endometrial thickness than "poor" metabolizers (OR = 1.88; 95% CI = 1.27–2.79; $p = 0.002$). A lack of significant differences in indicators of the state of endometrium between groups of patients with different *CYD2D6* genotypes and menopausal status requires further investigation.

Keywords: breast cancer, tamoxifen, endometrial thickness, CYP2D6, endocrine therapy

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Blokhin National Medical Research Center of Oncology (protocol № 10 dated 26 December 2019). Anonymized patient information was acquired and processed. Personal and medical data were not subject to transfer to a third party or to disclosure in the study results. All patients submitted the informed consent to study participation.

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ГЕНОТИПЫ CYP2D6*3, *4, *6 И ГИПЕРТРОФИЯ ЭНДОМЕТРИЯ У БОЛЬНЫХ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ НА ФОНЕ ТЕРАПИИ ТАМОКСИФЕНОМ

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Терапия тамоксифеном у части пациенток с гормоночувствительным раком молочной железы (ГР+РМЖ) приводит к увеличению толщины эндометрия. Данные о влиянии полиморфных вариантов в гене *CYP2D6*, кодирующем фермент CYP2D6 семейства цитохрома Р450, на эффективность и безопасность лечения тамоксифеном противоречивы. Целью проспективного когортного исследования было изучение ассоциации полиморфизмов *CYP2D6*3, *4, *6* с риском развития гипертрофии эндометрия в процессе адъювантной терапии тамоксифеном по поводу ГР+РМЖ. В исследование включено 145 больных операбельным ГР+РМЖ, получавших тамоксифен в дозировке 20 мг в сутки перорально. Полиморфизмы *CYP2D6*3, *4, *6* определены методом ПЦР в режиме реального времени. Проводили измерение толщины эндометрия ультразвуковым методом через 3, 6 и 9 месяцев гормонотерапии. В исследовании показано, что гипертрофию эндометрия чаще наблюдали у больных без альтернативных аллелей на этапе 3 месяцев наблюдения (40% по сравнению с 23,2% в группе «слабых метаболизаторов»; $p = 0,034$). Метаанализ всех периодов наблюдения показал, что среди «нормальных метаболизаторов» наблюдается значимо более высокая частота случаев гипертрофии эндометрия по сравнению со «слабыми метаболизаторами» (ОШ = 1,88; 95%ДИ = 1,27–2,79; $p = 0,002$). Отсутствие статистически значимых различий в показателях состояния эндометрия между группами пациенток с различным *CYD2D6*-генотипом в зависимости от менопаузального статуса требуют проведения дополнительных исследований.

Ключевые слова: рак молочной железы, тамоксифен, гипертрофия эндометрия, CYP2D6, гормонотерапия

Финансирование: медицинская часть исследования проведена без спонсорской поддержки в рамках межцентрового соглашения о некоммерческом научном сотрудничестве. Молекулярно-генетическая и статистическая часть исследования проведена в рамках темы бюджетного финансирования «Исследования полиморфизма на клеточном, организменном и популяционном уровне как основа создания генетических технологий» № 122022600161-3.

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Reduction of the hormone-sensitive breast cancer (HSBC) relapse risk by more than a third, significant decrease in the probability of death from this disease, and cost-effectiveness make tamoxifen hold a leading position in adjuvant endocrine therapy [1–3]. However, prolonged use of tamoxifen is associated with the risk of pathological processes in the reproductive organs [4–7].

Some studies consider tamoxifen as an independent risk factor of endometrial abnormalities, explaining this by partly estrogen-like effects of the drug, identify obesity as an inducing factor, and do not fully disclose biological mechanisms of this phenomenon [8–12]. There is an opinion that hyperestrogenism associated with obesity contributes to the development of endometrial disorder by creating low-grade inflammation in the reproductive system tissue and modulating endometrial microenvironment, thereby promoting carcinogenesis [13].

The role of tamoxifen effects on the currently known estrogen receptors (ERα, ERβ, GPER or 7-transmembrane G protein-coupled estrogen receptor) is actively discussed in the literature, along with activation and blocking of the mechanisms underlying the estrogen receptor signal transmission, since the lack of selectivity towards all types of receptors results in the emergence of multiple pharmacoterapeutic problems and severe side effects of therapy [14].

A number of studies focused on the role of tamoxifen metabolism involving the cytochrome P450 system enzymes in the development of endometrial disorders yielded ambiguous results [15, 16]. We have assumed that the development of disorder in the form of endometrial thickness during tamoxifen therapy for HSBC can be due to the features of metabolic profile of each specific patient related to different allele variants of the *CYP2D6* gene. To date, more than 40 alleles of this gene determining the decreased or no enzyme activity have been reported. Of the latter, the *CYP2D6 *4* allele is most often found in the populations of Caucasoid origin (frequency 20%), the next most common alleles are *3 and *6 (2 and 0.9%, respectively) [17].

The study was aimed to explore the association of the *CYP2D6* polymorphic variants for alleles **3, *4 *6* with endometrial thickness in patients receiving tamoxifen adjuvant endocrine therapy for HSBC.

METHODS

The study was conducted at Clinical Oncologic Dispensaru № 1 between January 2020 and September 2022. The molecular genetic part of the study was conducted in Vavilov Institute of General Genetics Russian Academy.

A total of 145 patients with resectable HSBC, who received combination or complex therapy followed by prescription of standard tamoxifen endocrine therapy (20 mg of oral tamoxifen per day every day), were enrolled. Inclusion criteria: the patients enrolled had no history of endocrine therapy, they did not use concomitant medications, including CYP2D6 inhibitors. Exclusion criteria: patients, who missed scheduled check-up, stopped using tamoxifen due to any reasons, refused to participate in the study during any phase, were excluded. Clinical protocols of patient management were compliant with the guidelines of the Ministry of Health of the Russian Federation on the diagnosis and treatment of breast cancer [18]. All patients were subjected to gynecological examination that included pelvic ultrasound scan before breast cancer treatment to rule out abnormalities of the reproductive organs. All patients were characterized in terms of anthropometric, anamnestic, clinical, morphological, and immunohistochemical parameters. Buccal epithelial samples were collected from the fasting patients before the start of tamoxifen therapy in accordance with the general rules of collecting biomaterial for genetic tests with mandatory labeling of each sample with the specific code reproducing the data from the roster. DNA was isolated by phenol–chloroform extraction in accordance with the general rules [19]. Genotyping by *CYP2D6*3, *4, *6* alleles was performed by real-time polymerase chain reaction (PCR) using the reagent kit for identification of the *CYP2D6* allele variants (catalogue number RUO-R1-H990-N3/4, DNA Technology TC; Russia) in accordance with the manufacturer's instructions. To perform statistical data processing, carriers of the *CYP2D6* alleles associated with normal enzyme activity were allocated to the group referred to as "normal" metabolizers, while carriers of *CYP2D6* alleles associated with reduced enzyme activity (homo- and heterozygotes) were allocated to the group referred to as "poor" metabolizers; the groups were relatively balanced.

The patients receiving tamoxifen therapy were examined on the milestone dates 3, 6 and 9 month after the start of therapy. In addition to common tests performed in accordance with the guidelines, transvaginal ultrasound involving measurement of endometrial thickness was performed in all patients with preserved menstrual cycle on days 5–7 of the cycle; in patients with amenorrhea, ultrasonography was performed routinely at the end of the 3-month interval. Eight millimeters in premenopausal patients and 5 mm in patients with amenorrhea were considered to be threshold values in accordance with the recommended standards of the endometrial disorder diagnosis [20, 21]. When forming subgroups based on the menstrual function status, patient with regular or irregular menorrhagia during endocrine therapy with tamoxifen were allocated to the premenopausal group, while patients receiving therapy, who had no menstruation throughout the follow-up period, including postmenopausal patients, were allocated to the amenorrhea group.

Statistical analysis and data visualization were performed using the R 4.2.2 environment for statistical computing (R Foundation for Statistical Computing; Austria). Descriptive statistics were presented as relative frequency of observations for qualitative variables and the mean (standard deviation) and median (1st and 3rd quartiles) for quantitative ones. When

Table 1. Frequencies of *CYP2D6* genotypes and alleles in the studied group of patients

Polymorphism	Genotype frequency, % (*n*)			Allele frequency (%) and statistical error (± se)		χ^2 (*p*)*
CYP2D6*3 (c.2549delA / rs35742686)	A/A	A/del	del/del	A	del	
	98.6 (143)	1.4% (2)	0	99.7 ± 0.7	0.7 ± 0.7	0.01 (0.933)
CYP2D6*4 (c.1846G > A / rs3892097)	A/A	A/G	G/G	A	G	
	4.8 (7)	39.3 (57)	55.9 (81)	24.5 ± 3.6	75.5 ± 3.6	0.58 (0.447)
CYP2D6*6 (c.1707delT / rs5030655)	T/T	T/del	del/del	T	del	
	97.2 (141)	2.8 (4)	0	98.6 ± 1.0	1.4 ± 1.0	0.03 (0.866)

Note: * — chi-squared test for deviations from Hardy–Weinberg equilibrium.

Table 2. Characteristics of the studied group of patients considering *CYP2D6* genotype

Characteristics	All patients *n* = 145	"Normal" metabolizers *n* = 76	"Poor" metabolizers *n* = 69	*p**
Demographic and anthropometric characteristics. The upper row contains the mean (SD), the lower row contains the mediana (1st–3rd quartiles)				
Age (years)	47.4 (6.2) 47 (44–51)	47.6 (5.9) 47 (44–52)	47.1 (6.5) 47 (43–51)	0.511
Body weight (kg)	73 (15.6) 72 (62–80)	72.9 (12.9) 72 (64–80)	73 (18.2) 72 (61–80)	0.602
Body length (cm)	164.6 (7.9) 164 (162–169)	164.4 (6.1) 164 (160–168)	164.7 (9.5) 164 (162–169)	0.19
Body mass index (kg/m²)	27.6 (13.1) 25.6 (22.7–30.1)	27.1 (5.5) 25.9 (23–30.1)	28.2 (18.2) 25 (22.1–30.1)	0.576
Anamnestic characteristics				
Smoking				0.396
Never-smokers	101 (69.7%)	56 (73.7%)	45 (65.2%)	
Former smokers	28 (19.3%)	11 (14.5%)	17 (24.6%)	
Current smokers	16 (11%)	9 (11.8%)	7 (10.1%)	
Clinical, morphological and immunohistochemical characteristics				
T. primary tumor size				0.231
1	82 (56.6%)	47 (61.8%)	35 (50.7%)	
2	46 (31.7%)	21 (27.6%)	25 (36.2%)	
3	5 (3.4%)	2 (2.6%)	3 (4.3%)	
4	12 (8.3%)	6 (7.9%)	6 (8.7%)	
N, presence, absence and prevalence of regional lymph node metastasis				0.963
	76 (52.4%)	39 (51.3%)	37 (53.6%)	
1	54 (37.2%)	30 (39.5%)	24 (34.8%)	
2	13 (9%)	6 (7.9%)	7 (10.1%)	
3	2 (1.4%)	1 (1.3%)	1 (1.4%)	
G, tumor grade				0.974
Grade 1	28/143 (19.6%)	15/74 (20.3%)	13/69 (18.8%)	
Grade 2	88/143 (61.5%)	45/74 (60.8%)	43/69 (62.3%)	
Grade 3	27/143 (18.9%)	14/74 (18.9%)	13/69 (18.8%)	
Estrogen receptor expression in tumor tissue showing its sensitivity to endocrine therapy, %				0.864
1–20	6 (4.1%)	3 (3.9%)	3 (4.3%)	
21–30	1 (0.7%)	0 (0.0%)	1 (1.4%)	
≥ 31	138 (95.2%)	73 (96.1%)	65 (94.2%)	
Progesterone receptor expression in tumor tissue showing its sensitivity to endocrine therapy, %				0.37
1–20	30 (20.7%)	17 (22.4%)	13 (18.8%)	
21–30	2 (1.4%)	1 (1.3%)	1 (1.4%)	
≥ 31	113 (77.9%)	58 (76.3%)	55 (79.7%)	
Human epidermal growth factor receptor 2 (HER-2/neu) expression status				0.069
0	74 (51%)	36 (47.4%)	38 (55.1%)	
1	52 (35.9%)	28 (36.8%)	24 (34.8%)	
2	6 (4.1%)	2 (2.6%)	4 (5.8%)	
3	13 (9%)	10 (13.2%)	3 (4.3%)	
Tumor proliferative activity (Ki-67 index) showing the percentage of actively dividing tumor cells, %				0.629
1–20	108 (74.5%)	57 (75.0%)	51 (73.9%)	
21–30	20 (13.8%)	9 (11.8%)	11 (15.9%)	
≥ 31	17 (11.7%)	10 (13.2%)	7 (10.1%)	
Chemotherapy				0.598
Not used	68 (46.9%)	37 (48.7%)	31 (44.9%)	
Used	77 (53.1%)	39 (51.3%)	38 (55.1%)	
Ovarian suppression				0.293
Not used	104 (72.2%)	57 (76%)	47 (68.1%)	
Used	40 (27.8%)	18 (24%)	22 (31.9%)	
Menstrual function before treatment				0.854
No	48 (33.1%)	26 (34.2%)	22 (31.9%)	
Preserved	97 (66.9%)	50 (65.8%)	47 (68.1%)	
Menstrual function during endocrine therapy				0.441
No	112 (77.2%)	56 (73.7%)	56 (81.2%)	
Preserved	33 (22.8%)	20 (26.3%)	13 (18.8%)	

Note: * — comparison of "normal" and "poor" metabolizer groups based on the Mann–Whitney U test (quantitative characteristics) and Fisher's exact test (nominal characteristics).

Table 3. Endometrial thickness (mm) based on ultrasonography data in the groups of patients considering the *CYP2D6* genotype

Period	"Normal" metabolizers	"Poor" metabolizers	*p***
All patients			
3 months	6.0 (4.0–10.0) *	5 (3.0–8.0)	0.131
6 months	7.0 (5.0–11.0)	6.0 (4.0–9.5)	0.122
9 months	8.0 (5.0–12.0)	6.0 (4.0–9.5)	0.088
*p****	0. 00045	0.005	
Premenopausal			
3 months	6 (3.75–10.25)	5 (4.0–8.0)	0.24
6 months	7 (5.0–11.25)	6 (4.0–9.0)	0.124
9 months	7 (4.75–12.25)	6 (4.0–9.0)	0.159
*p****	0.02	0.062	
Amenorrhea			
3 months	6 (4.0–8.5)	4.5 (3.0–8.5)	0.313
6 months	9 (5.0–11.0)	7 (4.0–12.25)	0.78
9 months	9 (5.0–11.5)	6.5 (3.75–11.25)	0.454
*p****	0.005	0.021	

Note: * — median values and qurtiles (25% and 75%) are provided; ** — comparison of "normal" and "poor" metabolizer groups based on the Mann–Whitney U test; *** — comparison of "3 months" and "9 months" groups for "normal" and "poor" metabolizers based on the Mann–Whitney U test.

comparing basic characteristics, the Mann–Whitney U test and Fisher's exact test were used for quantitative and qualitative variables, respectively. Comparative analysis of binary indicators involved the use of the mixed effects logistic regression models, which included the term of interaction between the group indicator and the follow-up period, as well as the odds ratio (OR) with appropriate 95% confidence interval (95% CI) as the effect size measure. Meta-analysis of all follow-up periods was conducted in accordance with the Mantel-Haenszel Fixed Effects model. The differences were considered significant at $p < 0.05$.

RESULTS

Genotypes for *CYP2D6* polymorphysms associated with reduced tamoxifen metabolism that are most common in the Russian population have been determined in the patients enrolled: alleles **3, *4* and **6* (Table 1) [22]. The determined allele frequencies are close to that reported for the population of Caucasoid origin [17].

Genotypes associated with reduced enzyme activity were found in eight individuals (5.5%): seven A/A *CYP2D6*4* homozygotes and one compound heterozygote (T/del *CYP2D6*6* / A/G *CYP2D6*4*). Other patients turned out to be homozygous for alleles determining normal enzyme activity (74 individuals, 51.0%) or heterozygous for one of the studied polymorphisms (63 individuals, 43.5%). Patients were divided into two balanced groups based on the presence/absence of nonfunctional CYP2D6 alleles.

No significant association of the risk of endometrial thickness with age 3 months (OR = 1.02 [95% CI: 0.97; 1.06], $p = 0.51$), 6 months (OR = 1.03 [95% CI: 0.98; 1.07],

Table 4. Rate of endometrial thickness in the groups of patients considering the *CYP2D6* genotype

Period	"Normal" metabolizers	"Poor" metabolizers	Comparison of "normal" and "poor" metabolizers: OR (*p*)
All patients *n* = 76 *n* = 69			
3 months	30 (40.0%)	16 (23.2%)	2.21 (0.034)
6 months	39 (52.0%)	26 (37.7%)	1.79 (0.096)
9 months	37 (49.3%)	25 (36.2%)	1.71 (0.131)
Comparison of 3 and 9 months: *OR* (*p*)	1.46 (0.324)	1.88 (0.136)	
Premenopausal *n* = 50 *n* = 47			
3 months	17 (34.0%)	9 (19.1%)	2.18 (0.114)
6 months	21 (42.0%)	12 (25.5%)	2.11 (0.133)
9 months	18 (36.0%)	12 (25.5%)	1.64 (0.282)
Comparison of 3 and 9 months: *OR* (*p*)	1.09 (1)	1.45 (0.621)	
Amenorrhea *n* = 26 *n* = 22			
3 months	13 (52.0%)	7 (31.8%)	2.32 (0.238)
6 months	18 (72.0%)	14 (63.6%)	1.47 (0.755)
9 months	19 (76.0%)	13 (59.1%)	2.19 (0.347)
Comparison of 3 and 9 months: *OR* (*p*)	2.92 (0.140)	3.1 (0.129)	

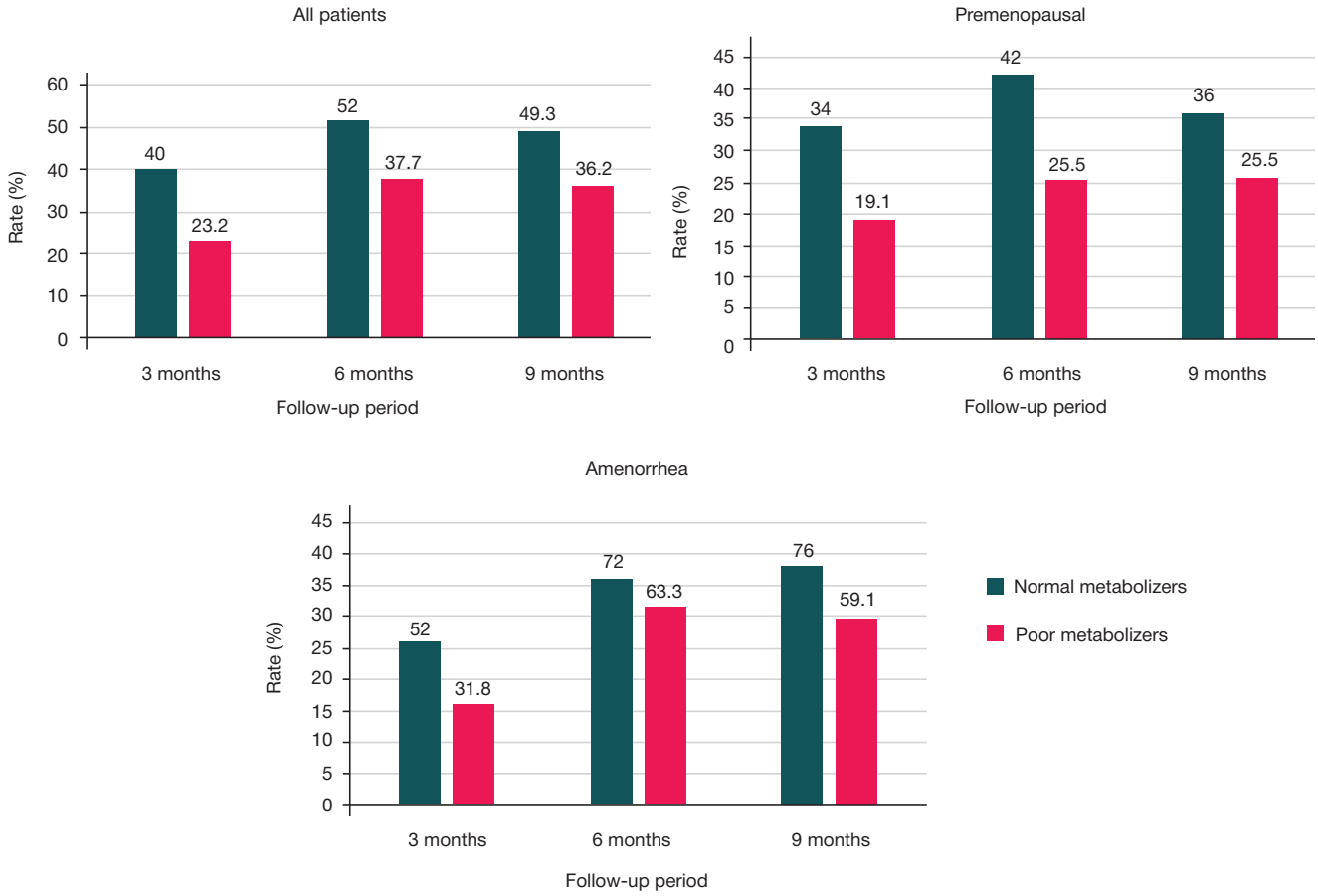

Fig. Rate of endometrial thickness in the general group and subgroups of patients depending on menopausal status and *CYP2D6* genotype

p = 0.292) and 9 months after using tamoxifen (OR = 1.0 [95% CI: 0.95; 1.04], *p* = 0.884), with body mass index after 3 months (OR = 1 [95% CI: 0.99; 1.02], *p* = 0.671), 6 months (OR = 1 [95% CI: 0.99; 1.02], *p* = 0.901) and 9 months of treatment (OR = 1 [95% CI: 0.99; 1.01], *p* = 0.99). Smoking status, clinical characteristics (primary tumor size, having or not having a history of chemotherapy, using ovarian suppression), as well as histological and immunohistochemical characteristics of breast tumor (primary lesion size, number of lymph nodes involved, estrogen and progesterone receptor expression, proliferative activity index, HER-2/neu status) were not considered to be significant predictors of endometrial hepertrophy in the studied cohort (Table 2).

Endometrial thickness was greater in "normal" metabolizers than in "poor" ones in all groups, however, the differences were non-significant (Table 3).

Among patients with amenorrhea, the increase in endometrial thickness after 9 months of tamoxifen therapy relative to that after 3 months of treatment was reported in both "normal" (the differences between mean values were 1.64 [95% CI: 0.269; 1.97] cm (*p* = 0.011) and 1.64 [95% CI: 0.683; 2.60] cm (*p* = 0.001), respectively) and "poor" metabolizers (the differences were 0.83 [95% CI: 0.01; 1.65] cm (*p* = 0.05) and 1.36 [95% CI: 0.46; 2.37] cm (*p* = 0.004), respectively).

No significant differences in the dynamics of thickening were revealed in the overall cohort (*p* = 0.052), premenopausal patients (*p* = 0.532) and patients with amenorrhea (*p* = 0,366) (Table 4; Fig.).

Higher rate of endometrial thickness cases in "normal" metabolizers relative to "poor" metabolizer was always reported in the studied cohort, however, the increase was significant only at around 3 months in all patients (OR = 2.21; *p* = 0.034). Regularity of these differences enables meta-analysis of three follow-up periods per group of patients (Table 5). The analysis has revealed a significant increase in the rate of endometrial thickness cases in "normal" metabolizers relative to "poor" ones (OR = 1.88; 95% CI = 1.27–2.79; *p* = 0.002).

DISCUSSION

Tamoxifen is a prodrug, the transformation of which into endoxifen, its most important metabolite, is ensured mainly by the CYP2D6 enzyme [23, 24]. Polymorphic variants of eponymous gene encoding the enzyme can cause changes in its enzyme activity associated with different tamoxifen efficacy in carriers of certain alleles [25]. However, the research data are ambiguous; the debate about the CYP2D6 genotyping clinical significance and interpretation of the results continues in the literature [26]. The impact of differences in tamoxifen metabolism on the treatment adherence is also discussed: early discontinuation of tamoxifen therapy decided by patient herself due to side effects affects the outcome of breast cancer treatment [27]. At the same time, little attention is paid to the issue of the association between the risk of side effects, including endometrial abnormalities, and the levels of CYP2D6 enzyme activity: sporadic small studies provide insufficient coverage of the issue [27–29].

In this paper we have tried to trace the risk of such adverse effect of tamoxifen therapy, as endometrial thickness in patients carrying various *CYP2D6* alleles found in the populations of Caucasoid origin and responsible for reduced tamoxifen metabolism [30]. There were no correlations between the *CYP2D6*3, *4, *6* alleles and such factors, as baseline tumor size, number of the lymph node involved, histological and

Table 5. Meta-analysis of differences in the rate of endometrial thickness between "normal" and "poor" metabolizers for all follow-up periods

Groups	OR (Mantel-Haenszel odds ratio)	95% CI	*p* (Fisher's exact test)
All patients	1.88	1.27–2.79	0.002
Premenopausal	1.95	1.17–3.26	0.014
Menopausal	1.96	0.97–3.97	0.089

immmunohistochemical characteristics of primary tumor, body mass index, smoking, in the studied group of patients. However, as for the association of the studied alleles with endometrial thickness and the rate of thickness, the findings suggest that patients with amenorrhea having no enzyme activity reducing alleles show a more frequent and prominent endometrial thickening depending on the endocrine therapy duration. Therefore, a cumulative effect of high endoxifen concentration is observed in the postmenopausal "normal" metabolizers.

Endometrial thickness was more often found in patients, who had no enzyme activity reducing alleles, after 3 months of follow-up (40% against 23.2% in the group of "poor" metabolizers; $p = 0.034$). Perhaps, three months of treatment with tamoxifen were enough for realization of the main estrogen-like effect of tamoxifen. The lack of data on endometrial thickness before the start of tamoxifen therapy is considered to be a problem of the study design. Future studies should involve conducting additional ultrasound examination of the uterus before using tamoxifen.

Premenopausal patients turned out to show minor dynamic changes in endometrial thickness, since endometrium was shed every time during menstruation. Ultrasonography enabled imaging of abnormal endometrium only, however, more time was probably required to form it. We performed ultrasound scan in the first phase of the menstrual cycle. In the future it is necessary to provide for ultrasound scan in the middle of the cycle in premenopausal patients, i.e. during the period characterized by maximum effects of estrogens and estrogen-like substances. This will enable a more precise investigation of estrogen-like tamoxifen activity. However, premenopausal patients having alternative alleles showed lesser endometrial thickness compared to premenopausal patients with no metabolism reduction. It can be assumed that tamoxifen exhibits temporary (within the menstrual cycle) estrogen-like effect in "normal" metabolizers.

The correlation between the *CYP2D6* genotype and endometrial thickness can be affected by endocrine factors, however, to date the impact of endoxifen concentrations on the ovarian, tissue steroidogenesis and regulation of the hypothalamic-pituitary axis is poorly understood. The lack of understanding of endocrine mechanisms along with trying to disconnect the interconnected factors may have been a limitation of the earlier studies yielding conflicting results. The role of hyperestrogenism in endometrial abnormalities has been proven [31], that is why it makes sense to clarify whether tamoxifen metabolism involving CYP2D6 is a factor contributing to formation of hyperestrogenic environment via stimulation of ovarial or tissue steroidogenesis.

CONCLUSIONS

The CYP2D6 enzyme metabolic activity alteration resulting from *CYP2D6*3, *4, *6* polymorphisms can modify the risk of endometrial thickness associated with tamoxifen therapy for HSBC, however, in these studies only trends have been revealed. The findings underscore the need for further study of the CYP2D6 enzyme activity with the better design and larger cohort of patients. The search for extraneous tamoxifen effects, primarily effects on ovarial steroidogenesis, and additional factors, with which pharmacogenetic testing will show maximum clinical significance, seems promising.

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