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PREVALENCE OF CYP2D6*4 AND ITS POSSIBLE RELATION TO THERAPEUTIC OUTCOMES OF ADJUVANT TAMOXIFEN THERAPY IN EGYPTIAN PREMENOPAUSAL WOMEN WITH BREAST CANCER

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Background: *Although tamoxifen is a main adjuvant therapy in estrogen positive breast cancer especially in premenopausal women, reliance on genetic polymorphisms of its CYP2D6 metabolizing enzyme and/or therapeutic drug monitoring of its active metabolite, endoxifen to determine tamoxifen-therapeutic outcomes is debatable.* ***Objective:*** *The goal of the study was to investigate the prevalence of CYP2D6*4 and possible association between its nonfunctional allele (A) and both tamoxifen-induced adverse effects and cancer relapse in premenopausal breast cancer patients.* ***Method:****Polymerase chain reaction -restriction fragment length polymorphism (PCR-RFLP) analysis was applied for detection of CYP2D6*4 (1846 G>A) genotypes.* ***Results****:Genotyping analysis of CYP2D6*4 showed a minimal allele frequency of 23%. Increased endometrial thickness in mm was significantly correlated with CYP2D6*4 GA and AA genotypes in comparison with GG genotypes (P< 0.01). No other relations were found between CYP2D6*4 alleles and other tamoxifen adverse effects (P > 0.9) or cancer relapse (P= 0.7).* ***Conclusion****: The prevalence of CYP2D6*4 polymorphism in Egyptian premenopausal females with breast cancer who are given tamoxifen is similar to that in Caucasians. The nonfunctional allele (A-allele) of CYP2D6*4 showed a significant association with increased endometrial thickness possibly related to tamoxifen, but no association with other drug adverse effects or cancer relapse.*

Keywords: *Tamoxifen, CYP2D6*4, premenopausal Egyptian females, breast cancer.*

INTRODUCTION

Pharmacogenomics and biotransformation of a drug can play a major role in the inter-individual variability in clinical response to that drug. Tamoxifen; an adjuvant therapy in estrogen receptor positive breast cancer especially in premenopausal women is an example.[1&2]

Tamoxifen is one of the selective estrogen receptor modulators. It is also a pioneering medicine for the reduction of breast cancer incidence in high-risk women[3&4]. The most common adverse effect of tamoxifen is the hot flashes "feeling of warmth, sometimes associated with flushing that spreads over the body"[5]. The antiestrogenic action of tamoxifen seems to be responsible for the development of hot flashes. Although tamoxifen has estrogen antagonistic action in some tissues, it has estrogen agonistic action in other tissues as endometrial tissues, uterus and ovaries leading to several adverse effects like endometrial thickness, uterine fibroid, vaginal bleeding and ovarian cysts[5&6].

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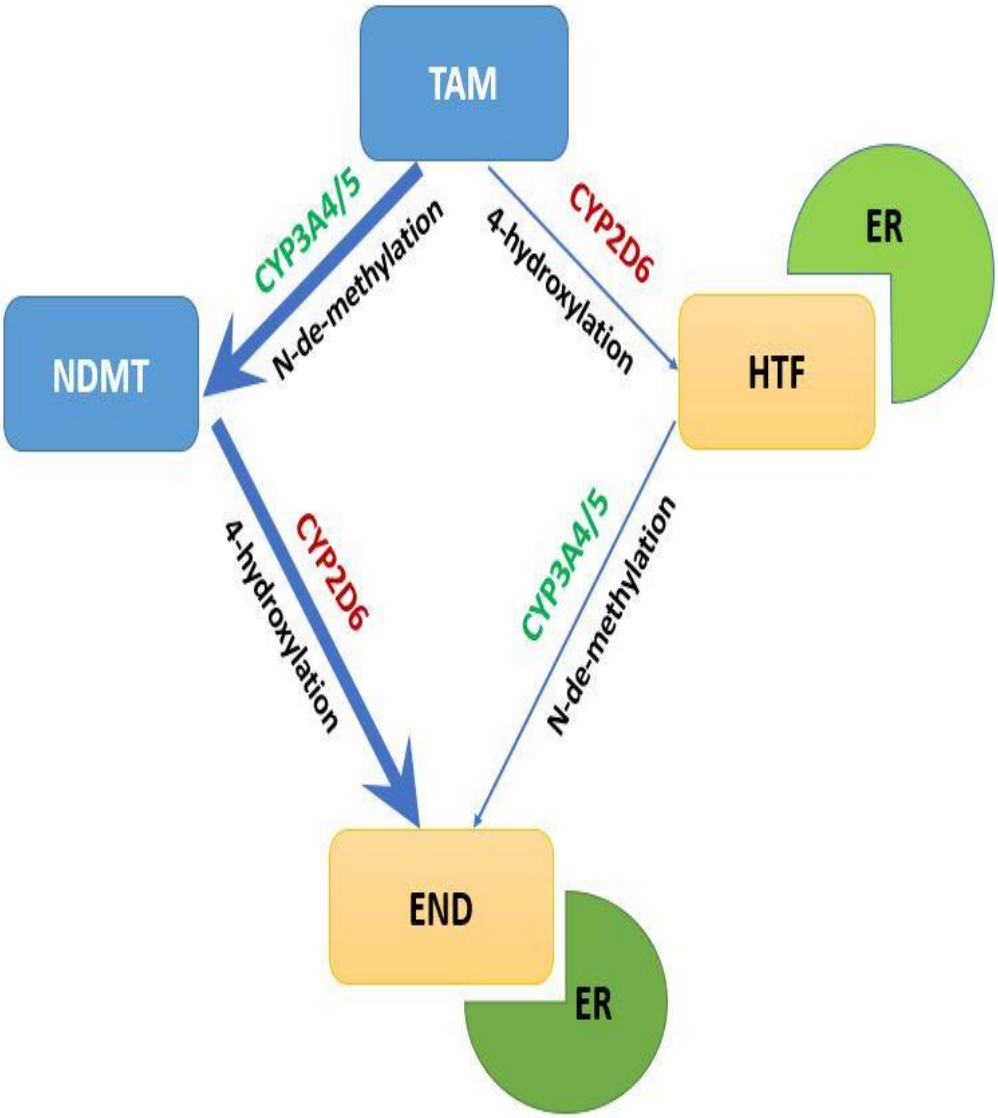

Fig. 1 : Metabolic pathways of tamoxifen.
TAM; tamoxifen, NDMT; N- desmethyltamoxifen, HTF; 4- hydroxytamoxifen, END; endoxifen and ER; estrogen receptor.

Hepatic metabolism of the drug occurs in the liver by microsomal enzymes, mainly CYP2D6 and CYP3A4 into a range of active and inactive metabolites (Figure 1). The active metabolites include 4-hydroxytamoxifen (HTF) and endoxifen (4-hydroxy-N-desmethyl-tamoxifen) (END) which have a 50-fold higher affinity for the estrogen receptor than tamoxifen. Endoxifen plasma concentrations are on average 5–10 times higher than concentrations of 4-hydroxy tamoxifen, making endoxifen the most active substance.[7&8] Although endoxifen steady-state concentrations is substantially lower than that of tamoxifen itself in blood, it is the most active metabolite with the greatest affinity to estrogen receptors in the breast.[9]

CYP2D6 represents the rate-limiting enzyme in biotransformation of tamoxifen into endoxifen. Prediction of metabolic activity of the enzyme can rely on studying its genotyping polymorphisms. Accordingly, individual classify into poor, intermediate and extensive metabolizers.[10] Poor metabolizers (PM) carry two non-functional alleles of the CYP2D6 gene and lack CYP2D6 enzyme activity. On the other hand, extensive metabolizers (EM) have two functional alleles and exhibit normal enzyme activity while, carriers of one functional and one non-functional allele are intermediate metabolizers (IM).[11&12]

The CYP2D6 gene is highly polymorphic.[13] Among Caucasians the most frequent inactivating polymorphism in CYP2D6 is the *CYP2D6*4*, which generates a G→A transition at nucleotide 1846, leading to generation of a non-functional gene product.[14] Furthermore, the *CYP2D6*4* allele has shown higher frequencies in Europeans (12–21%) than in other populations from different geographical origins, for instance, Asians (1%) or Black Africans (2%).[15]

The importance of CYP2D6 in tamoxifen metabolism and subsequent endoxifen formation have provided logical rationale for the hypothesis that CYP2D6 genotype correlates with tamoxifen efficacy, disease outcomes, and prediction of the risk of cancer recurrence.[16&17] However, other studies failed to provide conclusive evidence for recommending CYP2D6 genotyping as a predictive marker of tamoxifen efficacy.[18&19]

Given the limited data available regarding the genotyping of *CYP2D6*4* and plasma concentration monitoring of tamoxifen in Egyptian females with breast cancer who are given tamoxifen as an adjuvant therapy; we have designed a study on two parts. Part I is presented here where we investigate the prevalence of *CYP2D6*4* among one-hundred three Egyptian women with breast cancer who are given tamoxifen. In addition, we investigate if there is any relation between CYP2D6*4 alleles and tamoxifen-related adverse effects and/or cancer relapse. In part II, (not yet published) we will measure the plasma concentration of tamoxifen and correlate it with both CYP2D6*4 genotypes and tamoxifen therapeutic outcomes in Egyptian women with breast cancer.

MATERIALS AND METHODS

Type of the study

The present study is an observational cross sectional study, carried out on 103 Egyptian female patients diagnosed as breast cancer and received treatment according to the protocols followed at the South Egypt Cancer Institute (SECI). The ethics committee of faculty of Medicine, Assuit University, Egypt, approved the research (IRB local approval number: 17200217). ClinicalTrials.gov ID: NCT03582865.

The period of the study was between August-2018 and Feburary-2021

Patients

All selected patients were premenopausal,≥ 18 years old and diagnosed as breast cancer with estrogen receptor positive (ER + ve) (n= 93, 90.29%), negative (ER-–ve) (n= 7, 6.79%) or not reported (n=3, 2.9%). According to the medical records of each patient, all participants were exposed surgical interference in the form of lumpectomy (n= 27, 26.21%), mastectomy (n= 69, 66.99%) or lumpectomy followed by mastectomy (n= 7, 6.8%) according to the clinical condition and decision of the treating physician. Patients took tamoxifen adjuvant therapy at a fixed dose of 20 mg daily for five years. During the planned 5 years course of tamoxifen therapy, some of them (23/103) shifted to another therapy taking aromatase inhibitor medication and stopped tamoxifen. Shift of medication was due to either relapse of a lump or severe intolerable side effects of tamoxifen.

All patients enrolled in the study had normal liver and kidney functions and their blood picture were within the normal range. Each patient signed an informed written consent before participation in the study.

The exclusion criteria for selected patients included postmenopausal women, life-threatening diseases requiring a quick response (e.g. extensive hepatic or pulmonary involvement), CNS involvement, history of deep vein thrombosis (DVT). Other exclusion criteria included vaginal bleeding of unknown origin, endometrial hyperplasia (**diagnosed by transvaginal ultrasound**), or/ and concomitant use of drugs that can inhibit CYP2D6 enzyme activity and/or its expression like cimetidine, fluoxetine, haloperidol and paroxetine.

Table (1) demonstrates the demographic and clinical characteristics of the patients.

Table 1: Patients' demographics and clinical characteristics (n = 103).

Demographic data of patients	
Age (Mean ± SE; years)	38.43 ± 0.53 (range: 25 – 48)
Body weight (Mean ± SE; Kg)	67.47 ± 1.62 (range: 44 – 95)
	Number and percentage
Tumor stage:	
I	8 (7.77 %)
IIA	17(16.50 %)
IIB	23 (22.33 %)
IIIA	15 (14.56 %)
IIIC	13 (12.62 %)
Not reported	27 (26.21 %)
Tumor grade: (% related to total number)	
well differentiated	0 (0 %)
moderately differentiated	81/103 (78.64 %)
poorly differentiated	5 (4.85 %)
Not reported	17 (16.50 %)
Surgery :	
Lumpectomy only	27 (26.21 %)
Mastectomy only	69 (66.99 %)
Lumpectomy then mastectomy	7 (6.8 %)
Estrogen (ER) status :	
Positive	93 (90.29 %)
Negative	7 (6.79 %)
Not reported	3 (2.91 %)
Progesterone (PR) status :	
Positive	78 (75.73 %)
Negative	18 (17.48 %)
Not reported	7 (6.79 %)
Human epidermal growth factor receptor 2(Her2)	
Positive	24 (23.30 %)
Negative	57 (55.34 %)
Not reported	22 (21.36 %)
	Mean ± SE (range)
Liver functions (serum levels)	
AST (U/L)	27.16 ± 1.79 (10-41)
ALT (U/L)	27.76 ± 2.34 (7-60)
ALP (U/L)	81.9 ± 3.79 (40 – 150)
Total bilirubin (mg/dl)	0.28 ± 0.019 (0-0.9)
Albumin (g/L)	40.88 ± 0.88 (30-55)
Globulin (g/L)	35.68 ± 0.89 (24 -60)
Kidney functions	
Serum creatinine (mg/dl)	0.9006 ± 0.046 (0.6 – 1.2)
From CBC	
RBCs (10 ^ 6/uL)	4.387 ± 0.051 (3.19-5.58)
WBCs (x1000/uL)	6.332 ± 0.218 (4- 10.1)
HB (g/dL)	12.38 ± 0.13 (10 – 14.5)
Platelets (x 1000/uL)	252.4 ± 8.58 (150 – 435)

AST; aspartate transaminase, ALT ; alanine transaminase, ALP; alkaline phosphatase, CBC; complete blood counts, RBCs; red blood cells, WBCs; white blood cells and HB; hemoglobin.

Sample collection and DNA extraction

From each patient, 5 ml peripheral blood was drawn and stored in a tube containing EDTA anticoagulant. The samples were stored at -20˚C. Extraction of genomic DNA from 200 µl of the peripheral blood using QIAamp ® DNA Blood Mini Kit (Qiagen, Hilden, Germany) was according to the manufacturer's recommendations.

Genotyping

CYP2D6*4 (rs3892097; 1846 G>A) genotyping was performed using Polymerase chain reaction -restriction fragment length polymorphism (*PCR-RFLP*) method followed by Gel Electrophoresis. Spectrophotometer gene Quant 1300 determined the purity and concentration of DNA. The amplification of CYP2D6*4 1846 G>A gene utilized the primers: F: 5′-TGCCGCCTTCGCCAACCACT -3′ and R: 5′-TCGCCCTGCAGAGACTCCTC-3′. Polymerase chain reaction (PCR) needed a total volume of 20 µL (10 µL of master mix from (Willow fort, Birmingham, England), 1 µL for each primer and 8 µL for DNA extract). The amplification reaction steps were as follows: initial denaturation at 95°C for 5 min, followed by 40 cycles of denaturation at 95°C for 45 sec, annealing at 60°C for 45 sec, extension at 72°C for 60 sec and the final extension at 72°C for 10 min. Then, the restriction enzyme BstNI (New England biolabs) digested the amplified products of *CYP2D6*4* (1846 G>A) using *PCR-RFLP* technique.[16-18] The next step was to apply electrophoresis run using agarose gel 1%, at Volt 110, and Ampere 120 for 70 min. This allowed DNA fragments to differentiate for *CYP2D6*4* (1846 G>A) genotypes through determination of their sizes in comparison with known markers as follows: 309 base pair (bp) for AA, 201 and 108 bp for GG and 309, 201 and 108 bp for GA genotypes. Table 2 presents a summary of *CYP2D6*4* primers, product lengths (base pair; bp), enzyme used for *PCR-RFLP* analysis and products of digestion length.

Statistical analyses

In statistical analysis, we used Graph Pad Prism 7 software (Graph Pad, San Diego, CA). Chi square test determined the allelic frequencies and Genotype distribution with those expected from Hardy-Weinberg Equilibrium (HWE). Unpaired *t* test was used to compare the endometrial thickness in millimeters among different *CYP2D6*4* genotypes .Fisher exact test was used to compare the frequency of events among different *CYP2D6*4* genotypes. We consider statistical significance at p-value < 0.05.

Table 2: CYP2D6 variant primers, product lengths, enzyme used for polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis and products of digestion length.

Variant	rs no	Primers, 5′- 3′	Product length, bp	Enzyme	Products of digestion length	Ref
CYP2D6*4	3892097	F- TGCCGCCTTCGCCAACCACT R- TCGCCCTGCAGAGACTCCTC	309	*Bst*NI	Wild-type (GG): 201/108 Heterozygous (GA): 309/201/108 Mutant (AA): 309	[35]

CYP2D6, cytochrome P450 2D6; rs, reference single nucleotide polymorphism; F, forward; R, reverse; bp, base pair.

RESULTS AND DISCUSSION

Results

Baseline characteristics of Patients

Between August-2018 and Feburary-2021, 103 premenopausal women with breast cancer enrolled in this study. The mean age ± SE were 38.4 ± 0.53 years with a range between 25-48 years. Fifty five percent of the patients were HER2 negative. The majority of patients were estrogen receptor –positive (~90%) and progesterone receptor positive (~75%). Staging of the tumor showed that 38% of the patients were in stage II, while stage III represented around 27% of the cases. Most of the tumors were moderately differentiated (~78%). Table 1 demonstrates all clinical data of the patients.

Genotypes of the patients

Figure 2 shows the Pattern of *CYP2D6*4* digested fragments in gel electrophoresis where the distribution of cases of *CYP2D6*4* (rs3892097; 1846 G>A) in the studied patients was as follows:

- GG = 67 (65%) for the wild type, (normal enzyme activity)
- AA= 12 (11.7 %) for the homozygous mutant type (null activity of the enzyme)
- GA= 24 (23.3 %), for heterozygous type (intermediate activity).

The calculated minimal allele frequency (A-allele) was 0.23 and this distribution was deviated from Hardy Weinberg Equilibrium (HWE; *p*-value of Fisher exact test<0.05).

Table 3 shows the frequency *CYP2D6*4* variant in our study (23%) in comparison with other studies previously performed on Egyptians or other populations. Some studies showed similar frequencies like European Canadians, Australians and Russians while others showed lower prevalence like Saudi population.

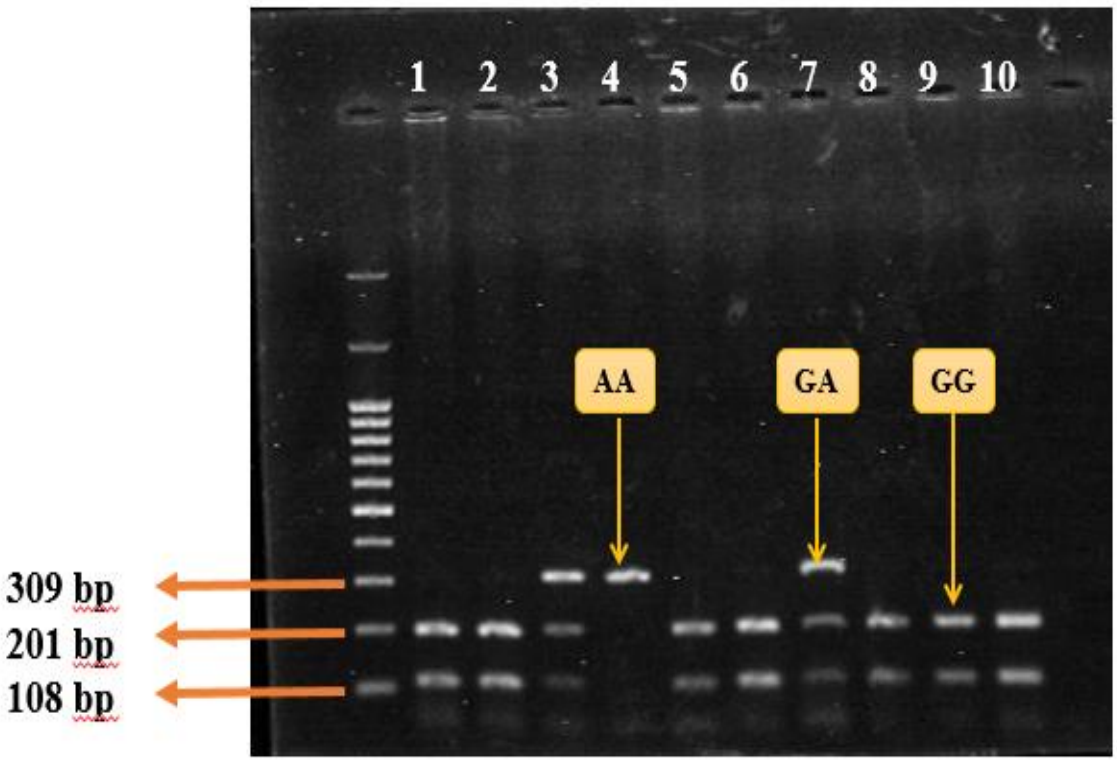

Fig. 2: The Pattern of 1% agarose gel electrophoresis of CYP2D6*4 digested segments in 103 Egyptian premenopausal females with breast cancer. Lane 4 shows homozygous samples for the mutant type (AA; 309 bp); lanes 1, 2, 5 , 6 , 8-10 for the wild-type samples (GG ; 201/108 bp) and lanes 3&7 for heterozygous samples (GA; 309/201/108 bp)**..**

Table 3: The frequencies of *CYP2D6*4* non-functional allele (A) in different populations including the current Egyptian study**.**

Country/ ancestry	Subjects (n)	Subject type	Frequency of CYP2D6*4	Reference
Egypt	103	Breast cancer women	23%	The present study
Egypt	59	Healthy+ organophosphorus intoxicated patients	22%	[23]
Egypt	60	Corona virus infected	25 %	[24]
Egypt	100	Tramadol intoxicated	14 %	[52]
Egypt	145	Healthy	9.6%	[53]
Middle Eastern	148	Human genome diversity Panel	6.8%	[48]
Saudi Arabia	101	Healthy	3.5%	[49]
European Canadians	235	Healthy	19%	[43]
Bari / in Venezuela	300	Healthy	25%	[44]
Russia	642	Healthy	17.4%	[45]
Russia	107	Healthy	21.5%	[46]
Russia	96	Depressive disorder men	27.1%	[47]
Australia	5,408	Healthy	17.8%	[41]
Australia	157	Australian Defense Force personnel	24.5%	[42]

Table 4 demonstrates the predicted phenotype distribution (metabolizing activity) related to *CYP2D6*4* genotypes in the Egyptian patients involved in the present study compared to Egyptians in previous two studies.[19&20] Our patients were classified as poor metabolizer (PM; two null alleles; A/A), intermediate metabolizer (IM; heterozygous; G/A) and normal or extensive metabolizer (EM; wild type G/G). The incidence of wild allele G/G was similar in the three Egyptian studies. However, the mutant alleles A/A (null activity) showed the least incidence in one of the Egyptian studies,[23] compared to our study and another Egyptian study.[24]

Regarding the relation between *CYP2D6*4* variant and different adverse effects of tamoxifen, endometrial wall thickness in millimeter increased in carriers of A-alleles ($p < 0.01$) compared to carriers of GG alleles (figure 3). However, other tamoxifen adverse effects like hot flashes, vaginal bleeding and ovarian cyst were not significantly related ($p>0.9$) to *CYP2D6*4* (table 5). The same non-significant relation also was reported as regards relapse of cancer in correlation to *CYP2D6*4* variant ($P> 0.78$) (table 6).

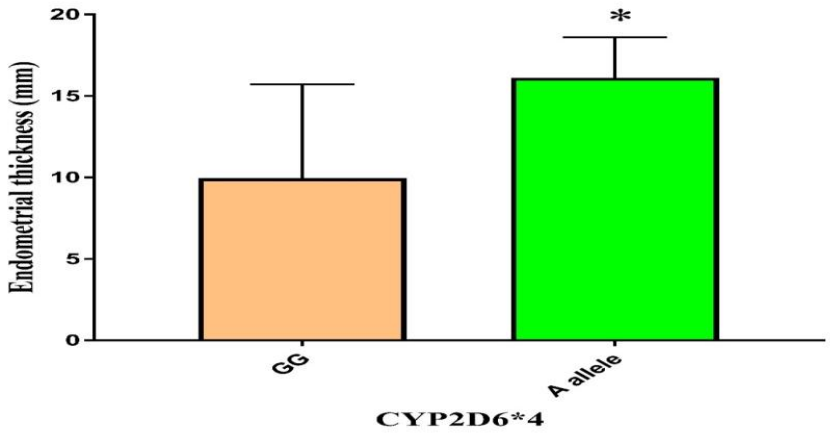

Fig. 3: The endometrial wall thickness in millimeters among different *CYP2D6*4* genotypes (GG vs. pooled A alleles: GA+AA).

Results are represented as mean ± SE, GG (n = 12) and carriers of pooled A allele (n = 8).
Endometrial thickness in millimeters: (9.967± 1.659 vs 16.13 ± 0.8750)
Unpaired t test test , $p = 0.0109$.

.**Table 4:** Distribution of metabolizing activity (predicted phenotyping) inferred from genotype of *CYP2D6*4* in Egyptian population.

Metabolizing activity (phenotype)	Genotypes	Present Study	Salem *et al* [24]	Khattab *et al* [23]
EM	**GG (wild type/ normal alleles)**	67(65)	40(66.66)	35(59.32)
IM	**GA (one null allele)**	24(23.3)	10(16.67)	22(37.29)
PM	**AA (two null alleles)**	12 (11.7)	10(16.67)	2(3.39)
N		103 (100)	60(100)	59(100)

Numbers and percentages (%) refer to subjects involved in the different studies
EM: extensive metabolizer, IM: Intermediate metabolizer, PM: Poor metabolizer.

Table 5: Relation between CYP2D6*4 nonfunctional allele (A) and the incidence of tamoxifen adverse effects in breast cancer premenopausal patients.

	GG alleles (Wild type)	Pooled A alleles (GA+AA)	Total	Relative risk	95% CI	*P*-value
TAM related adverse effects						
Yes*	29(65.909)	15(34.091)	44 (100)	1.039	0.6617-1.707	>0.9999
NO	38(64.407)	21(35.593)	59 (100)			

TAM: Tamoxifen, CI: Confidence interval, P value for Fisher's exact test
Data presented as number of subjects (%).

*adverse effects; hot flashes (n= 5), vaginal bleeding (n=9), endometrial thickness (n=20) and ovarian cyst (n=10).

Table 6: Relation between CYP2D6*4 non-functional allele (A) and the incidence of relapse in breast cancer premenopausal patients

	GG alleles (Wild type)	A alleles (GA+AA)	Total	Relative risk	95% CI	*P*- value
Relapse status						
Relapse*	10 (62.5)	6 (37.5)	16 (100)	0.8955	0.3712- 2.237	0.7843
NO relapse	57 (65.52)	30(34.48)	87 (100)			

CI: Confidence interval, P value for Fisher's exact test
Data presented as number of subjects (%)
*Relapse; breast cancer recurrence or metastasis.

Discussion

The inter-individual variability in response to tamoxifen is high and many factors play roles in this phenomenon such as gender, age, obesity comorbidity, liver and renal function, pregnancy, drug-drug interactions and genetic polymorphisms in CYP2D6 metabolizing enzyme.[25-31]

The DNA fragments obtained in the present study after application of *PCR-RFLP* technique on CYP2D6**4* (rs3892097; 1846 G>A) single nucleotide polymorphism (*SNP*)[32], gave a pattern in electrophoresis similar to that in other studies on CYP2D6**4.*[33-35]

The distribution of CYP2D6*4 genotypes among the Egyptian patients in the present study was as follows: GG = 67 (65%), GA= 24 (23.3 %), and AA= 12 (11.7 %) and this distribution was deviated from Hardy Weinberg Equilibrium (HWE). Many factors can affect this deviation such as the small sample size in the study, effect of different variants on breast cancer incidence, selection of cancer patients only and non-random mating pairs that was nearly the situation in our study. Egyptian patients selected are living in Assiut Governorate located in the South part of Egypt where increased inbreeding is a social habit that may lead to increased homozygosity and decreased heterozygosity.[36-38]

In the present study, the minimal allele frequency of *CYP2D6*4* in Egyptians is 23% matching with the frequency in Caucasians (26 %).[39] In Europe, the frequency of *CYP2D6*4* varies. In Northern and Central Europe, the frequency is between 20-25% reaching the highest frequency in the Faroe Islands (33.4%). In other European countries, it is low like Turkey (13.2%), Italy (16.4%), and Greece (17.7%).[40] Populations in other areas of the world like Australia (17.8-24.5%),[41,42] European Canadians (19%),[43] the Bari population in Venezuela (25%),[44] and the Russia (17.4-27.1%)[45-47] show allele frequency similar to our result. Some others, show the lowered frequency like Middle Eastern (6.9%),[48] Saudi (3.5%),[49] Chinese (1%),[50] and Japanese (not detected).[51]

Table 3 demonstrates also a variability in the frequency of *CYP2D6*4* among Egyptians in different studies[23,24,52,53] including the present study (i.e. intra-population difference). The variability may be attributed to differences in testing methodology, alleles assignment,[54] sample size in each study, gender difference, healthy or diseased subjects and inbreeding.[36,37&55] The discrepancy in the same population (i.e. Egyptians) for the same variant indicates that genetic polymorphisms in CYP2D6 enzyme occurs not only between different populations, but also within individuals of the same population.[39]

The translation of *CYP2D6* genotype into phenotype activity is a complex process and challenging.[7] Subjects described as poor metabolizers (PM) exhibit an absolute lack of CYP2D6 activity, whereas intermediate metabolizers (IM) have reduced CYP2D6 metabolic capacity relative to that of normal or extensive metabolizers (EM) while CYP2D6 ultra rapid metabolizer (UM) demonstrate a higher CYP2D6 activity than NMs.[56]

Table 4 demonstrates predominant distribution of extensive metabolizers (EM, wild alleles: GG) in Egyptians (59-66%) in our study and the other two Egyptian studies.[23& 24]

The variability in *CYP2D6*4* alleles widens (16-37%) as regards intermediate metabolizers (IM, heterozygosity: GA). However, poor metabolizers (PM, non-functional alleles: AA) show similar frequency between patients in our study (11.7%) and Hareedy et al (16.6%), [24] but very low (3.39) in Khattab et al study.[23]

Individuals with normal metabolic capacity (EM) constitute the majority of Arab populations with a frequency of about 70 % that is higher than that of Europeans (51 %), East Asians (51 %), and Americans (63 %). On the other hand, poor metabolizers (PM) accounted for only a small percentage of Arabs (3.39%), which was higher than that of East Asians (0.86%), Sub-Saharan Africans (1.53%), and Americans (2.18%), but lower than that of Europeans (6.47%). This can be attributed to the highest prevalence of the null *CYP2D6*4* allele among European populations (18.54%).[57]

Figure 3 shows an increase in the thickness of endometrial wall after therapy with tamoxifen. The incidence is significant ($P<0.01$) in carriers of(*CYP2D6*4 GA* and *AA* (i.e. pooled A-alleles) compared with GG genotype. In the literature, the *CYP2D6*4*-related endometrial status with tamoxifen is variable. Some studies reported significant stimulatory effect ($P < 0.05$) in carriers of the low active CYP2D6**10/*10* genotype,[58] while others found no difference.[59]

However, a Turkish study showed hyperplasia in the poor metabolizers and atrophy in ultra-rapid metabolizers for CYP2D6 at significant level (p= 0.01).[60] An interesting study on Chilean patients with breast cancer showed significant impact of *CYP3A5*3* A/G genotype (but not *CYP2D6*4)* on endometrial hyperplasia in patients on tamoxifen therapy.[61]

Regarding the other tamoxifen-related adverse effects like hot flashes, vaginal bleeding and development of ovarian cysts, no significant relation with the variant CYP2D6*4 in the present study (P > 0.9) (table 5). These finding coincde with other studies for the same variant.[62-64] However, other studies showed that PM and IM phenotypes had a statistically significantly increased risk of tamoxifen-induced hot flashes compared with the EM phenotype in the group with no previous chemotherapy (P= 0.02).[65]

The relation between C*YP2D6*4* genotypes and incidence of cancer relapse in the presence of tamoxifen is controversial. In the present study (table 6), and other previous studies,[65-70] no significant relation is observed. On the contrary, the incidence of cancer relapse decreased significantly in the presence of combined genotypes of *CYP2D6*4* and SULT1A1*1/*1,[71] GG alleles compared with AA alleles of *CYP2D6*4*,[62&72-74] and extensive metabolizer phenotype for CYP2D6 associated with Her2-neu positive breast cancer.[75]

A recent study on Egyptian patients with metastatic breast cancer and treated with tamoxifen demonstrated that patients who were refractory to tamoxifen therapy had *CYP2D6 *3* and **4* polymorphisms whereas patients carrying the variants *10/*10 and *10/*3 of CYP2D6 were more common in the responders to the treatment with tamoxifen.[22]

Conclusions

In the present study, 103 Egyptian premenopausal females with breast cancer who received adjuvant tamoxifen therapy were analyzed for *CYP2D6*4* genotypes. The minimal allele frequency of *CYP2D6*4* in the Egyptian sample was 23%. The frequency was similar to some Egyptian studies but different from others. In addition, it was matching with its prevalence in Caucasians, and different from others like Saudi population. The study showed also that endometrial thickness in some patients as a possible adverse effect of tamoxifen therapy increases in the presence of pooled A alleles of *CYP2D6*4*. On the other hand, other adverse effects related to tamoxifen such as hot flashes and vaginal bleeding and/or cancer relapse are not related to CYP2D6*4 genotypes. A second part (Part II) of the study is following to if plasma concentration monitoring of tamoxifen and its metabolites particularly endoxifen are matching with results of this genotyping study (Part I). Then, We need future well-designed, controlled, larger clinical studies to determine if we can use CYP2D6 genotyping and therapeutic drug monitoring of endoxifen concentrations to improve treatment outcomes in breast cancer patients.

Limitations of the Study

The limitations of this study include the imited sample size and the detection of only non functional allele *CYP2D6*4* in the sample. Other genes related to tamoxifen therapy should be analyzed as *CYP3A4, CYP3A5, SULT1A1 and UGT2B15*. This can allow detection more obviously of the effects of polymorphisms in these genes on the therapeutic outcomes of tamoxifen including adverse effects and cancer relapse.

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نشرة العلوم الصيدلية
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انتشار انزيم سيتوكروم ٢ دي ٤*٦ وعلاقته المحتملة بالنتائج العلاجية لعقار التاموكسيفين المساعد لدى النساء المصريات المصابات بسرطان الثدي في مرحلة قبل انقطاع الطمث

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محتوي الخلفية: على الرغم من أن التاموكسيفين هو العقارالمساعد الرئيسي في سرطان الثدي الإيجابي للإستروجين وخاصة في النساء في مرحلة قبل انقطاع الطمث، فإن الاعتماد على تعدد الموروفينات الوراثية لإنزيمه الأيضي سيتوكروم ٢ دي ٦ و/أو مراقبة الأدوية العلاجية لأيضاته النشطة، إندوكسيفين لتحديد النتائج العلاجية للتاموكسيفين أمر قابل للنقاش. هناك بيانات محدودة فيما يتصل بنمط الجينات من سيتوكروم ٢ دي ٤*٦ ورصد تركيز البلازما للأندوكسيفين في الإناث المصريات المصابات بسرطان الثدي. وكان الهدف من هذه الدراسة التحقيق في مدى انتشار سيتوكروم ٢ دي ٤*٦ والارتباط المحتمل بين نظيره المختل (A) وكل من التأثيرات الضارة الناجمة عن عقار التاموكسيفين وانتكاس السرطان.

تصميم الدراسة: الدراسة عبارة عن دراسة مرصودة متداخلة الأقسام بحثت في الجانب الجيني من سيتوكروم ٢ دي ٤*٦ في المصريات المصابات بسرطان الثدي اللاتي يتناولن عقار التاموكسيفين.
المقاييس والنتائج: تم تطبيق تحليل PCR-RFLP للكشف عن سيتوكروم ٢ دي ٤*٦ (G A ١٨٤٦) النماذج الجينية. وكانت النتيجة الرئيسية هي انتشار المتغير بين المريضات المصريات المصابات بسرطان الثدي. وكانت النتيجة الثانوية هي ربط النماذج الجينية بالآثار الضارة المتعلقة بعقار التاموكسيفين وانتكاس السرطان.

النتائج: مائة وثلاثمائة امرأة مصابات بسرطان الثدي تعالج بالتاموكسيفين في ٢٠ ملغ يومياً تم ادراجهم في الدراسة. تحليل النموذج الجيني لسيتوكروم ٢ دي ٤*٦ أظهر الحد الأدنى من تواتر ٢٣%. إن زيادة سمك بطانة الرحم بالمليمتر كأثر جانبي محتمل لعقار التاموكسيفين كانت مرتبطة إلى حد كبير بالنماذج الجينية سيتوكروم ٢ دي ٤*٦ GA وAA مقارنة بالنماذج الجينية GG (P=٠,٠١) ولم يتم العثور على أي

علاقات أخرى بين سيتوكروم ٢ دي ٤*٦ والآثار السلبية الأخرى للتاموكسيفين(P > ٠.٩) أو انتكاس السرطان(P = ٠.٧)

خلاصة القول: إن انتشار سيتوكروم ٢-دي ٤*٦ في المصريات المصابات بسرطان الثدي ويتم علاجهن بعقار التاموكسيفين يشبه مثيله في القوقازين. أظهر الأليل المختل من سيتوكروم ٢ دي ٤*٦ ارتباط كبير بزيادة سمك بطانة الرحم التي قد تكون مرتبطة بعقار التاموكسيفين، ولكن ليس هناك ارتباط بالتأثيرات الضارة الأخرى للعقار او انتكاس السرطان.