ISBN : 978-602-17250-0-9

Proceedings of International Conference on Women's Health in Science & Engineering

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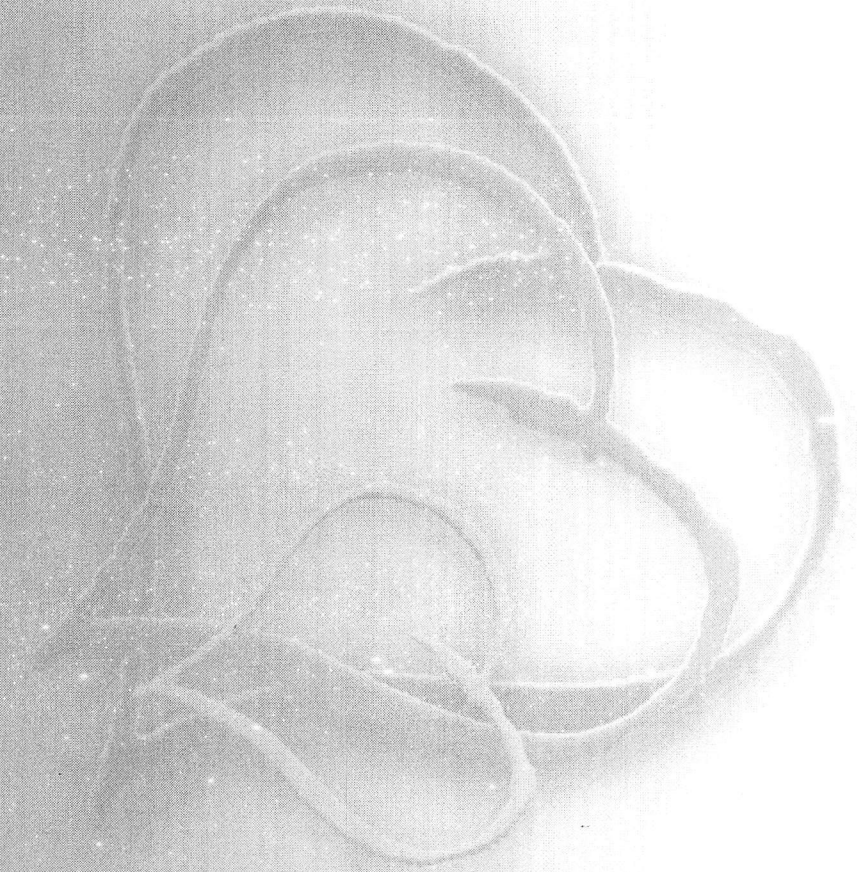

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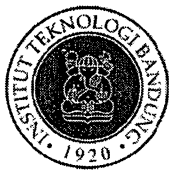

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Proceedings of

International Conference on Women's Health in Science & Engineering 2012

ISBN: 978-602-17250-0-9

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Preface

Good day,

Welcome to Bandung to the International Conference on Women's Health in Science and Engineering (WiSE-HEALTH) 2012.

On behalf of the organizing committee, we are delighted to welcome all participants to the WiSE-HEALTH 2012. This first conference is organized under the auspices of the Institut Teknologi Bandung (ITB), technically sponsored by Institute of Electrical & Electronics Engineers (IEEE) Indonesia Section, IEEE EMBS (Engineering in Medicine & Biology Society) Indonesia Chapter, Indonesian Biomedical Engineering Society (IBES), Indonesian Medical Doctor Association (Ikatan Dokter Indonesia – IDI) West Java, Indonesian Midwifery Association (Ikatan Bidan Indonesia - IBI) West Java, and IEEE WiE (Women in Engineering) Indonesia Chapter.

WiSE-HEALTH 2012 is the first international conference which incorporates multidisciplinary aspects in *Woman's health in Science and Engineering.* With the mission 'Empowering women's health awareness for a stronger and smarter future generation', the conference is basically aiming at *encouraging knowledge improvement and initiating multidisciplinary research collaborations in the field of women's health.* This conference also highlights the two points in the Millennium Development Goals (MDGs), Reduce Child Mortality and Improve Maternal Health, to be the main concerns in the discussion.

With the theme Trends in Women's Health Science & Technology : Engineering, Medical, & Scientific Approaches, WiSE-HEALTH 2012 is organized to gather healthcare professionals, scientists, educators, students, public policy professionals, organizations and services, government, and industries in the field of engineering, medicine, and science to contribute to an international dialogue, share their knowledge and experiences in women's health research topics in an interdisciplinary point of view.

Our gratitude to many people who helped making this conference a reality, to all of our invited speakers and guests, and for all of our committee members for their effort to ensure the success of this conference. Finally, we hope that all participants will learn new things, make new contacts, get new ideas, and have fruitful discussion while having a pleasant experience during our conference in Bandung.

Thank you,

Prof. Dr. Ir. Tati Latifah R. Mengko
Chair of WiSE-HEALTH 2012

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PAPERS

Prevalence of *XbaI* Polymorphism of ESR α Gene in Healthy Javanese Menopausal Women

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Abstract: Polymorphism of estrogen receptor alpha (ESR α) may cause pleitrophic effect to lipid levels, lipid response to hormone replacement therapy (HRT), myocardial infarction risk, stroke, migraine, bone fracture risk, bone mineral density (BMD). The polymorphism in the ESR α gene have associated with the incidence of breast cancer, menopausal osteoporosis, recurrent abortions, arterial hypertension, changes in serum lipid levels, cardiovascular heart disease (CHD), and diabetes mellitus. Recently there are two types of well-known polymorphisms in the ESR α gene i.e. *PvuII* and *XbaI*. Both are the most widely studied by researchers as a risk factor for many diseases in women. In several countries some studies of the *PvuII* and *XbaI* defined polymorphisms (ESR α rs2234693 and ESR α rs9340799, respectively) have also been shown to be predictive marker for some disease especially in menopausal women and have also shown the prevalence of *PvuII* and *XbaI* polymorphism in healthy menopausal women population. In this study we aimed to evaluate the prevalence of *XbaI* polymorphism in Javanese menopausal women. Our study has focused on *XbaI* polymorphism without PvuII based on previous study in Javanese menopausal women that *XbaI* has associated with diabetes mellitus. Subjects of our study were 34 consecutive menopausal women fragment length polymorphism (RFLP). The absence of *XbaI* restriction site was indicated by "X1" and the presence was indicated by "X2". *XbaI* genotype was distributed as follows: X2X2 8.8% (n=3), X1X2 20.5% (n=7), X1X1 70.6% (n=24). Prevalence of *XbaI* polymorphism of ESR α in Javanese menopausal women is similar to previously studied in other population.

Keyword: Prevalence ESRα-*XbaI* polymorphism-Javanese menopausal women

I. INTRODUCTION

Estrogen included one of the steroidal hormone in women that has decreased in menopausal age. Estrogen has influence to many phyisilogical processes including female reproduction, cardiovascular, bone integrity, energy metabolism, cognition and behaviour [1,2]. Menopausal women may increase for getting several disease because of the reduction of endogenous estrogen [3]. For some decades, there is assumption that decrease in estrogen cause vasomotor symptoms, vaginal athropy, and other menopausal complaint. Therefore, the use of estrogen in menopausal women has been available to prevent menopausal symptoms and also to prevent chronic disease [4]. In ESRα and ESRβ knock-out mice, estrogen is well known to be a morphogen, and its role in morphogenesis is evident from the structure of the uterus, ovary, mammary gland, prostate, lung, and brain [5].

The physiological effect of estrogen is mediated mainly through estrogen receptors i.e ESR α and ESR β [6]. At the promoters of some genes, particularly those involved in proliferation, ESRα and ESRβ can have opposite action, a findings which suggests that the overall proliferative response to estrogen is the result of a balance between ESRα and ESRβ signaling [5].

Effect of estrogen depends on interaction between estrogen and its receptor. Estrogen receptor alpha (ESRα) function is determined by ESRα gene with present of polymorphism and other mutation. Epidemiological findings have indicated that there are several disease suffered by menopausal women associated with polymorphisms of ESR α. Polymorphism of estrogen receptor alpha (ESR α) may cause *pleitrophic* effect including for normal condition such as lipid levels, lipid response to hormone replacement therapy (HRT) and for pathologic condition such as myocardial infarction risk, stroke, diabetes, migraine, bone fracture risk, bone mineral density (BMD) and changes in BMD over time [2].

The ESRα gene is large approximately 140 kb of DNA, encompassing 8 exons, encodes protein consisting of 595 amino acids with molecular weightof 66 kDa [7]. The ESRα is located on chromosome 6q25.1 [8,9]. The first intron of gene usually contains a larger number of regulatory sequen single nucleotide polymorphisms (SNPs) in

the ESRα have been identified and found to be associated with either an increased or a decreased of various diseases. The best characterized SNPs of ESRα are the *PvuII* and *XbaI* restriction site polymorphisms both located in first intron (Figure 2) [10]. The polymorphisms, c454-397T→C and c454A→G, are 397 and 351 bp unpstream of exon 2 and have been discribed by the name of detecting restriction enzyme, *PvuII* or *XbaI*, or their reference ID numbers, rs2234693 and rs9340799, respectively [11,12]. Our study have focused to XbaI polymorphisms because in Indonesia especially Javanese Population *XbaI* was proven by prior study contributing higher risk to suffer diseases especially in type 2 diabetes mellitus [13].

II. METHODOLOGY

Research Design

We carried out a cross-sectional study during Mei-August 2012 over 34 post menopause women.

Study Subjects

Thirty four healthy menopausal women aged 45 to 70 years from village Sumberharjo Prambanan Subdisrict, Sleman Distric were chosen for the study.

Physical examinations

We have performed physical examination to all subject encompassed blood pressure and anthropometric measurements i.e. waist circumference, height, weight, BMI, hip circumference and ratio waist circumference with hip circumference and blood pressure. Waist and hip circumference was measured using portable microtoise to the nearest 0,1 cm.

Biochemical analysis

Blood samples were collected from the subjects after a 10-12-h fasting. Total cholesterol, HDL cholesterol, and triglyceride levels were determined by standard methods using commercial kits from *DiaSys* Germany.

DNA Isolation

Isolation of DNA carried out with guanidine isothiocyanate method. DNA was isolated from peripheral blood leukocyte cells derived from the median cubity vein. Examination of the presence of *PvuII* and *XbaI* polymorphisms in the ESR alpha gene has been performed by PCR-RFLP. PCR reactions have used the forward primer 5'CTGCCACCCTATCTGTATCTTTTCCTATTC TCC-3' and reverse primer 5'TCTTTCTCTGCCACCCTGGCGTCGATTATC TGA3'. PCR reaction was performed by using a Biometra PCR thermocycler and reagents intron. PCR reactions using the total volume of 30 µl PCR reaction consisted of 2 ml DNA, 15 ml PCR master mix containing 1 × PCR buffer, 150 mM dNTP and U Tag DNA polymerase, 2 ml primer and 1 ml of each forward and reverse, 11 ml distilled water. Temperature conditions of PCR cycles that initial denaturation for 5 min at 95 ° C, followed by 35 cycles of PCR with denaturation at 95 ° C 30 sec, annealing at 62 ° C 30 sec, extension at 72 ° C for 30 sec, 2-minute final extension and cooling at 72 ° to 4 ° C.

Polymorphism Analysis

PCR products have been digested by using restriction enzyme of *XbaI*. Volume 8 µl of PCR products have incubated with 1 unit of *XbaI* for detecting polymorphism of X1/X2. Then we have added 1.5 µl of NE buffer 1x, 1.5 µl BSA10x, 3µl distilled water up 15 µl for each reaction. Incubation have conducted for 8 hours at 60°C. The enzyme restriction have digested the product PCR into X1 for absent restriction site and X2 for presence restriction site. Detection of X1 and X2 product have conducted using 2 % agarose electrophoresis gel and stained with ethydium bromide. The enzyme of *XbaI* will cut transition A/G in intron I (c.454-351A>G) because of transition G to A. The product of *XbaI* enzyme digestion are 1372 bp fragment as wild type by symbol X1X1, heterozygous mutant with 3 fragments 1372, 936, 436 bp by symbol X1X2 and homozygous mutant with 2 fragments 936 and 436 bp by symbol X2X2.

Statistics

Genotype distribution of the polymorphism was tested for Hardy-Weinberg equilibrium by χ^2. A p-value less than 0.05 was considered significant. Statistical analysis was performed with SPSS version 17.0 and THESIAS softwae version 6.0.

Ethical clearance

The study was approved by the Ethics Committee of the Medical Faculty of Gadjah Mada University and written consent was given by each participant.

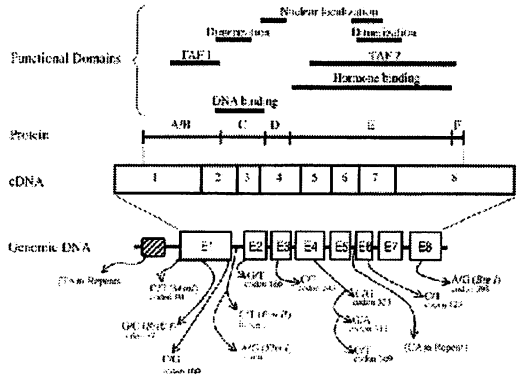

Fig.2. Structure of, functional domains of ESRα and described polymorphisms in the human estrogen receptor α gene.

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III. Results & Discussion

Characteristic of the subjects are presented in table 1. All variabels are in normal condition and fit to the criteria of this study for healthy menopausal women. All subjects is normal without any disease based on the result of examinations below. We did not examine the menopause symptoms and comorbid disease such as osteoporosis, dementia and psychological problem. In fact, normal of laboratory results is not always healthy especially in menopausal women.

TABLE I
CHARACTERICTIC OF SUBJECTS

Characteristic of Subjects	Menopausal Women (n= 34)
	Mean ± SD
Age (years)	53.41±3.29
Systole (mmHg)	125.44±16.62
Diastole (mmHg)	78.97±8.85
Height (cm)	151.19±6.18
Weight (Kg)	51.41±9.96
BMI	22.43±3.85
Abdominal Circumference (cm)	80.68±10.89
Cholesterol (mg/dl)	171.90±32.74
LDL (mg/dl)	101.74±32.79
HDL (mg/dl)	51.03±15.07
TGA (mg/dl)	108.89±70.92
Fasting-Glucose (GLU)	84.61±14.80
2 hours Post Prandial-GLU	108.48±22.79

The subjects have been examined for the genotype to determine the *XbaI* polymorphism. The results of genotype examination have presented in figure 3 table 2.

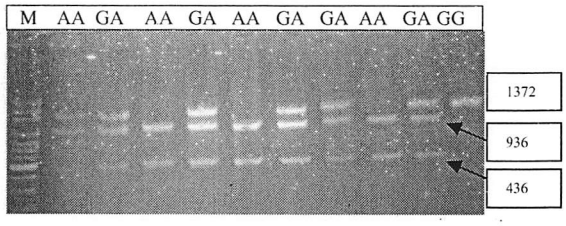

Fig.3 Detection of XbaI polymorphism in ESR α gene

TABLE 2.
DISTRIBUTION OF ESR α *XbaI* POLYMORPHISM IN JAVANESE MENOPAUSAL WOMEN

Genotype	Number of Subjects	%
X1X1	24	70.6
X1X2	7	20.5
X2X2	3	8.9

In comparison to the other studies in several countris, distribution of genotype of XbaI in Javanese Menopausal women is similar to India and Caucasian presented in table 3 [2,14].. The frequency of AA (X2X2), GA (X1X2), and GG (X1X1) genotypes were 8,9%, 20,5%, 70.6%. This result is similar with India population studied by Ganasyam et al [14]. There were 4%, 10% and 86% in distribution of X2X2, X1X2, X1X1 respectively in India menopausal women. The distribution of normal allel (G) and mutated allel (A) in both population were 89.5% and 10.5% respectively in India, and 80.9% and 19.1% in Indonesia, respectively. The difference between the two groups in genotype distribution was not significant (X^2= 7.255;P=0,02). By using *Chai Square* test, the difference allele of XbaI i.e. G and A were not significant in both country (X^2=2.602, P=0.10). It means that both frequency of allele in India and Indonesia is same. Then the HWE of XbaI polymorphism is not violated. So the equilibrium of XbaI polymorphism is normal in Javanese population analyzed by using THESIAS software (p=0.051).

ESRα polymorphisms have attracted great interest in the last few years and the PvuII and *XbaI* are the most extensively investigated issues. These study has only focused on XbaI polymorphism in healthy Javanese menopausal women.However, we do not know whether polymorphic alterations in the genes are responsible for ESRα function and, in particular, the alterations analyzed in the present study are responsible for higher or lower receptor expression. Also, it is not known how and to what extent the polymorphisms of the ESRα gene may act as genetic markers of diabetes [15].. *PvuII* and *XbaI* polymorphisms may be different in their effects on ESRα. Our study have focused only for XbaI polymorphism because previous study conducting by Akhmad *et al.* indicated that allele A/X2 as risk factor of DM type 2 in Javanese Menopausal Women (OR=3.66 CI=1.71-7.84) [13]. Distribution of allele X2 and X1 in previous study by Akhmad et al. in diabetic patients are 58.8% and 41.2% whereas distribution of allele X2 and X1 in control subjects are 28% and 72%. Frequencies of XbaI polymorphisms based on previous study are 56%, 32%, 12% respectively for X1X1, X1X2, and X2X2. The X allele (*XbaI* restriction site) was also found more frequently in genomic DNA from breast cancer patients than from control subjects [6]. After we compared the present finding with previous finding the result were same. The present finding is consistent in prevalence of XbaI genotype and allele frequencies with previous study in control groups. In women of Asian descent the X1 allele frequency ranged from 17% to 53% (overall 23%) and In subjects of Occident descent, frequencies ranged from 24% to 44% for the X1 allele (overall 35%) in menopausal women with bone mineral

density examination. *XX* served as a protective factor in postmenopausal from fracture spine bone and osteoporosis. Considering all women in the study, women with X1X1 had higher BMD than those with either X1X2 or X2X2 [16].

The *Xba*I polymorphism has been found to be significantly associated with upper-body obesity in middle-aged persons. Other observations indicated an association between ERα intron I RFLPs and height or body mass index. In one study the association of the A→G polymorphism or the combination of the T→C and A→G polymorphisms with not only a greater BMI, but also larger % fat mass, FM, waist circumference and WHR in middle-aged women had been shown [2].

The age of menarche was associated with the *Xba*I in healthy adolescent Greek girls. *Xba*I XX homozygotes or, in more general terms, subjects homozygous for the PX haplotype seem to have a modest delay in the age of menarche [2]..

The effects of *Xba*I are not clear. The biological pathway for *Xba*I that may affect the age of menarche is unknown. Restriction sites of *Xba*I polymorphisms are located in the intron 1 of the ERα gene. Some introns contain regulatory sequences such as enhancers, which means binding sites for elements that regulate the level of gene expression and thus also affect protein synthesis. The observed association may reflect linkage disequilibrium with some other functional polymorphisms in the *Xba*I vicinity. Regardless of the exact mechanism, if ERα gene polymorphisms can alter the estrogenic biological activity at the cellular level, this may influence the maturation of the hypothalamic-pituitary-gonadal axis, which determines the onset of menarche [2]..

TABLE 3. DISTRIBUTION OF XbaI POLYMORPHISM IN HEALTYH MENOPAUSAL WOMEN IN SEVERAL COUNTRIES

Reference	GG (%)	AG (%)	AA (%)	G	A	Country
[14] Ganasyam *et*	86 (86%)	10 (10%)	4(4%)	186 (89.5%)	22 (10.5%)	Asian India
[15] Golkhu *et*	26 (26%)	50 (50%)	24 (24%)	51 (51%)	49 (49%)	Asian Iran
[6] Qin *et al.*	150 (43.9%)	158 (46.3%)	33 (9.8)	456 (68.1%)	214 (31.9%)	Asian China
[2] Jakimiuk *et*	38 (59.4)	22 (34.4)	4 (6.25)	98 (76.6%)	30 (23.4%)	Caucasian Poland
[17] Hae-Sung *et*	117 (67.2%)	51 (29.3%)	6 (0.03%)	185 (74.6%)	63 (25.5%)	Asian Korean
[18] Jin Kim *et*	39 (61.9%)	18 (28.6%)	6 (9.5%)	96 (76.2%)	30 (23.8%)	Asian Korean
[19] Albagha *et*	1193 (41.6%)	1328 (46.3%)	347 (12.1%)	3714 (64.7%)	2022 (35.3)	Caucasian UK
[20] Gorai *et al.*	209 (66.3%)	97 (30.8%)	9 (2.9%)	515 (81.7%)	115 (19.3%)	Asian Japanese
[21] Saad *et al.*	7 (21%)	26 (78%)	-	40 (60.6%)	26 (39.4%)	Egypt Arabian
[13] Akhmad *et*	24 (70.6%)	7 (20.6%)	3 (8,8%)	55 (80.9%)	13 (19.1%)	Javanese Indonesia

heterozygous G/A (X1/X2), homozygous mutant A/A X2/X2), normal G/G (X1/X1)

IV. CONCLUSIONS

In conclusion, the prevalence of XbaI polymorphism in healthy menopausal women in Javenese population is no difference from India population. We have concluded therefore that these SNPs are very rare in our population. The present findings are limited in the way that they were obtained from a relatively small study population. The results of our study should be considered exploratory and confirmed by additional studies, which include larger sample size and other polymorphisms in estrogen receptor. Investigation of these polymorphisms in other ethnic groups and comparing premenopausal with postmenopausal women are recommended.

ACKNOWLEGDMENT

The present study was supported by a grant from HIBAH BERSAING (competitive research grant) General Directorate of Higher Education Ministry of National Education Republic of Indonesia Government.

Conflict of Interest: None declared

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