A meta-analysis of correlation of ER gene polymorphisms and risk in Chinese population with coronary heart disease

Liping Ding[1,2], Lihua Hu[2], Zhitao Jin[2], Taohong Hu[2], Huili Ma[2], Lina Zhang[2], Xincheng Qiu[2], Caiyi Lu[1*]

[1]Institute of Geriatric cardiology,Chinese PLA General Hospital.
[2]Department of Cardiology, Second Artillery General Hospital of PLA.

Abstract: Objective:To investigate the correlation of the polymorphism of the estrogen receptor alpha gene Pvu II site and coronary heart disease (CHD) in Chinese population. **Methods**: Medline, EMBASE, CENTRAL. The range of time is 1995 to 2009. Two reviewers independently screened the studies for eligibility, evaluated the quality and extracted the data from all the eligible studies, with confirmation by cross-checking. Divergences of opinions were settled by discussion. Meta-analysis was finally processed by Rev Man 5.0 software. **Results:** Nine case-control studies were included, involving 1464 cases with coronary heart disease and 1 203 cases in the control group. The results of Meta-analyses showed that, as to the correlation of the polymorphism of ER alpha gene Pvu II site T/C and CHD, there was no signii cant dif erence in the risk of CHD between people with dif erent genotypes, i.e. the C allele versus T allele (OR=0.95, 95%CI 0.77 to 1.17, P=0.63), genotype of (TC + CC) versus TT (OR=0.97, 95%CI 0.73 to 1.28, P=0.81), genotype of TC versus TT (OR = 0.93, 95%CI 0.68 to 1.26, P =0.64). **Conclusion:** Estrogen receptor alpha gene polymorphism Pvu II site are not associated with the coronary heart disease in Chinese population.

[Liping Ding, Lihua Hu, Zhitao Jin, Taohong Hu, Huili Ma, Lina Zhang, Xincheng Qiu, Caiyi Lu. **A meta-analysis of correlation of ER gene polymorphisms and risk in Chinese population with coronary heart disease.** *Life Sci J* 2013;10(4):595-598]. (ISSN:1097-8135). http://www.lifesciencesite.com. 78

Key words: Estrogen receptor alpha; Coronary heart disease; Polymorphism; Chinese population; Meta-analysis

1.Introduction

It has been proved that the estrogen has a protective effect on the cardiovascular system by epidemiological and laboratory studies(Hanke et al.,1996). There are two mechanisms of prevention of atherosclerosis with estrogen: affecting the lipoprotein metabolism and vascular wall. The estrogen exerts biological effects mediated by its receptor (ER), and the polymorphism of ER gene is related to the expression and function of ER (Ushiyama et al.,1998). Therefore, the polymorphism of ER gene might affect the role of estrogen on atherosclerosis. Currently there are three kinds of most common ER gene polymorphisms, Pvu II, Xba I and BstU I. As the Pvu II and Xba I is located on intron 1, and the intron 1 is located on the transcriptional functional area of amino terminus, therefore, the point mutation may affect the expression and function of ERα, and the different ERα genotypes may decide the expression level and functional differences of ERα between different individuals, thereby affecting the biological role of estrogen in the body. Pvu Ⅱ polymorphism is the most common ERα gene polymorphism, which has been widely studied. However, the ERα gene SNP has large differences in different race and area, which cause the inconsistent results in home and abroad, or even in the same race but different area (Long et al .,2008).

In this study, we investigated the relationship of Pvu Ⅱ T/C polymorphism of ERα gene and coronary heart disease and performed meta-analysis, to evaluate the relationship of ERα gene mutations and coronary heart disease susceptibility in China.

2.Materials and methods

2.1Selection of studies

Six authors will take on the review. The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. Two authors will screen the search results and they will read the full text of eligible studies identified in this way. The two authors will decide on their suitability for inclusion in the review based on whether they meet the prespecified inclusion criteria. We will report disagreement and will resolve disagreement by a consensus procedure, if necessary, with a third review author.

2.2Data extraction and management

Two review authors will extract the data independently to a self-developed data extraction form. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one trial exists, only the publication with the most complete data will be included. We will write to study authors for further information when necessary. Disagreements will be resolved by majority vote, if necessary, of a third review author. One author will enter data into Review Manager software(RevMan 5.0.20), and a

second author will independently check the data entry.

2.3Assessment of risk of bias in included studies

Two authors will independently use the GRADE criteria to assess risk of bias for all included studies.

2.4Measures of treatment effect

For dichotomous data, results will be summarised as risk ratios(RR), with 95% confidence intervals (CI). For continuous out-comes we will use weighted mean difference (WMD) (when measures are in the same unit), or standardisedmean difference (SMD) (when different scales are used to evaluate the same outcome) with
95% CI as well.

2.5Unit of analysis issues

Cross-over trials will not be included in this review. We will try to identify cluster-randomised trials; they will be included and analysed in accordance with section 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions.

2.6Dealing with missing data

The authors of papers withmissing data will be contacted. We will make a note of all trials that do not use intention-to-treat (ITT)analysis; we will make every attempt to analysis our data by this principal.

2.7Assessment of heterogeneity

I^2 will be used to assess heterogeneity among studies. I^2 > 50% will be considered considerable heterogeneity.

2.8Assessment of reporting biases

We will assess reporting bias by funnel plots. We will search multiple databases, contact authors, utilize clinical practice guidelines and systematic reviews, to minimize reporting and publicationbias.

2.9Data synthesis and Sensitivity analysis

A ï¬xed-effects model will be used unless significant heterogeneity with I^2> 50% among studies. In that case a random-effects model will be used.

Subgroup analysis will be used to explore possible sources of heterogeneity. Heterogeneity among studies will be estimated by the I^2 statistic. Typically, values above 50% are deemed to suggest significant heterogeneity. Values of 25% to 50% are deemed to show modest heterogeneity, and values below 25% are deemed to represent low heterogeneity.

We will perform a sensitivity analysis if we find significant heterogeneity (I^2> 50%).

3.Results

3.1The basic information of included literature

A total of 21 literatures were obtained from the initial screening, and ultimately 9 literatures were included in this study according to exclusion criteria(Guo et al.,2002; Huang et al.,2002; Zheng 2002; Zhang et al.,2002; Chen et al.,2006; Li et al.,2006; Xu et al.,2008; Tang et al.,2008; Jin et al.,2010). The quality assessment results showed that in the nine studies, the sample size is adequate, the diagnostic criteria is clear, there is comparable between case group and control group, the method is PCR-RFLP, and the result data are reasonable, the genotype distribution of the 9 studies is accordance with H-W genetic equilibrium.

In the 9 studies, the cumulative coronary heart diseases were 1464 cases (including 121 cases of acute coronary syndrome), the control cases were 1203 cases.

3.2Meta-analysis results

3.2.1 C allele vs. T allele was associated with coronary

The heterogeneity test results showed that there was significant heterogeneity between the studies (χ^2=26.60, *P*=0.0008), so the random effects model was used to conduct meta-analysis. When the C allele was set as exposure factor, T allele as non-exposure factor, meta-analysis results showed that the coronary heart disease risk was similar between people carrying C allele and T allele [OR=0.95, 95%CI (0.77, 1.17), P=0.63] (Figure 1).

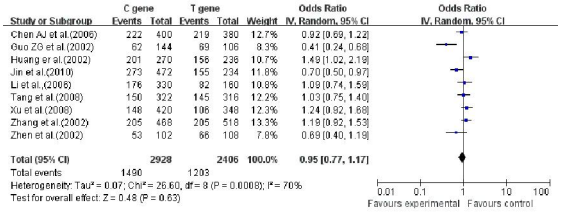

Fig 1. C allele and T allele for CHD.

3.2.2 Genotype TC+CC vs. TT was associated with coronary heart disease

The heterogeneity test results showed that there was significant heterogeneity between the studies (χ2=16.80, *P*=0.03), so the random effects model was used to conduct meta-analysis. When the genotype TC+CC was set as exposure factor, genotype TT as non-exposure factor, meta-analysis results showed that the coronary heart disease risk was similar between people carrying genotype TC+CC and TT [OR=0.97, 95%CI (0.73, 1.28), *P*=0.81] (Figure 2).

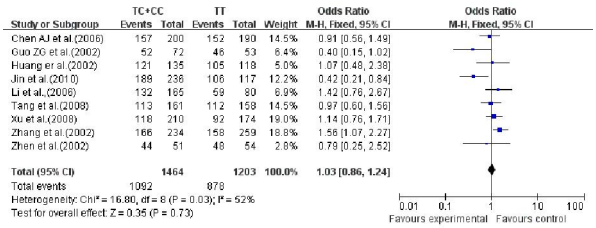

Fig 2. genotype TC+CC and TT for CHD.

3.2.3 Genotype TC vs. TT was associated with coronary heart disease

The heterogeneity test results showed that there was significant heterogeneity between the studies ($\chi 2$=17.36, *P*=0.03), so the random effects model was used to conduct meta-analysis. When the genotype TC was set as exposure factor, genotype TT as non-exposure factor, meta-analysis results showed that the coronary heart disease risk was similar between people carrying genotype TC and TT [OR=0.93, 95%CI (0.68, 1.26), *P*=0.64] (Figure 3).

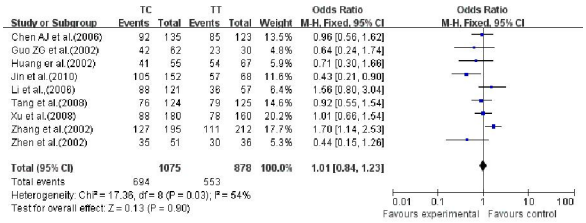

Fig 3.genotype TC and T for CHD.

4. Discussion

ER is a member of ligand-dependent transcriptional activity factor superfamily (steroid hormones, thyroid hormones, vitamin D3, retinoic acid, et al). Human ERα gene is located on chromosome 6q25.1, the wild-type ERα gene is about 140 kb, which is composed of 8 exons and 7 introns. The cDNA of ERα gene includes 6322 nucleotide pairs, in which 1785 bp encode 595 amino acid. Once ER is combined with estrogen, it will form a dimer, then binds with the estrogen receptor response element, stimulates transcription of target genes, thereby regulating the growth, reproduction, differentiation and function of target organs, including breast, uterus, vagina, ovaries, testes, bone, liver, cardiovascular system, nervous system, and so on. Studies have shown that PvuⅡ T/C polymorphism of ERα gene was associated with various diseases (Deng et al., 2004; Gold et al.,2004; Kobayashi et al.,2002).

Nine case-control studies were included in this study, which had 1464 cases of coronary heart disease and 1203 cases of control group. Meta-analysis results showed that there was no significant correlation between PvuⅡ T/C polymorphism and coronary heart disease susceptibility.

The research results of correlation of PvuⅡ T/C polymorphism and coronary heart disease susceptibility were different in home and abroad. Some foreign studies proved there was a correlation between PvuⅡ T/C polymorphism and coronary heart disease susceptibility(Mansur et al.,2005; Kunnas et al., 2000), but some studies believed there was no correlation (Karadağ et al.,2009; Boroumand et al., 2009). In China, it has been proved that there was correlation in some studies (Tang et al.,2008; Jin et al., 2010), but no in other studies (Zheng 2002; Zhang et al., 2002; Chen et al.,2006; Li et al.,2006; Xu et al., 2008). The main reason of the differences may be related to the genetic background, sample size, object, age, gender, CHD family history, and so on. For the research methods, all the included studies used the appropriate methods for genotype analysis, though there were some individual differences, the heterogeneity may be caused by these mixed differences. In this study, there were no significant stratified analysis factors in the included studies; therefore, we didn't perform subgroup analysis. In the further study, the above confounding factors should be excluded when study of the relationship between PvuⅡ T/C polymorphism and coronary heart disease susceptibility.

There are some shortcomings in this study: ① the language of the searching literatures is limited to Chinese/English, there might be language bias; ② the gender and age were not matched between the case group and control group.

In conclusion, this study performed meta-analysis of PvuⅡ T/C polymorphism and coronary heart disease susceptibility, the results found that there was no significant correlation. As the included studies and the number of cases were limited, our results still need strict design, maximize control of confounding factors, large sample size, homogeneity or prospective case-control studies to verify, meanwhile, it still needs to consider the interaction of gene and gene or gene and environment, in order to elucidate the pathogenesis of coronary heart disease.

Correspond to : Caiyi Lu
Institute of Geriatric cardiology, Chinese PLA General Hospital, Beijing, 100853, China.
Email: lu_caiyi@163.com

References

1. Hanke H, Hanke S, Bruck B, et al. Inhibition of the protective effect of estrogen by progesterone in experimental atherosclerosis. Athero-sclerosis 1996;121: 129-38.
2. Ushiyama T, Ueyama H, Inoue K, et al. Estrogen receptor gene pol-ymorphism and generalized osteoarthritis. J Rheumatol 1998; 25: 134-7.
3. Long L, Shan KR, Ren YX. Advances in the ESR Gene Polymorphism with Disease Association. INTERATIONAL JOURNAL OF GENETICS 2008;31: 124-8.
4. Guo ZG, Zheng H, Wu SZ. Association of Estrogen Receptor-α Gene Polymorphisms with Severity of Coronary Artery Disease. Chinese Journal of Geriatric Heart Brain and Vessel Diseases 2002;4: 374-7.

5. Huang XZ, Zhang PA, Li Y. Association of estrogen receptor gene polymorphisms with coronary heart disease CHINESE JOURNAL OF CARDIOLOGY 2002; 30: 78-81.
6. Zheng HM. The Study about the Association between the Polymorphisms of the Estrogen Receptor(ER) and Coronary Artery Disease or Thelipoprotein Metabolism in Women. Journal of Hebei medical university 2002.
7. Zhang Y, Xie RP, Wang YH. Study on the association of estrogen receptor gene polymorphism and cerebral infarction. BEIJING MEDICAL JOURNAL 2002; 82: 1443-6.
8. Chen AJ, Fu NK, Xu J. A study of the correlation between estrogen receptor gene polymorphism and coronary heart disease as well as serum lipid levels in postmenopausal women. Hebei Medical Journal 2006;28: 568-70.
9. Li LH, Zhao FM, Li GQ. Association Between Estrogen Receptor Alpha Gene Variation And Risks Of Cardiovascular Disease. MOLECULAR CARDIOLOGY OF CHINA 2006;6: 90-4.
10. Xu H, Hou X, Wang N, et al. Gender-specific effect of estrogen receptor-1 gene polymorphisms in coronary artery disease and its angiographic severity in chinese population. Clin Chim Acta 2008; 395: 130-3.
11. Tang ZZ, Li XP, Yang JH. Relationship of Estrogen Receptor α Gene Polymorphism and Risk of Cardiovascular Diseases.MILITARY MEDICAL JOURNAL OF SOUTH CHINA 2008; 22: 35-7.
12. Jin LZ, Chen YC, Ma YD.Association of estrogen receptor α gene Pvu Ⅱ and Xba Ⅰ polymorphisms with coronary artery disease. CHINESE JOURNAL OF BIOMEDICAL ENGINEERING 2010;16: 136-9.
13. Deng G, Zhou G, Zhai Y. Association of estrogen receptor α polymorphisms with susceptibility to chronic hepatitis B virus infec-tion. Hepatology 2004; 40: 318-26.
14. Gold B, Kalush F, Bergeron J. Estrogen receptor genotypesand haplotypes associated with breast cancer risk. Cancer Res 2004;64: 8891-900.
15. Kobayashi N, Fujino T, Shirogane T, Furuta I, Kobamatsu Y, Yaegashi M, Sakuragi N, Fujimoto S. Estrogen receptor alpha polymorphism as a genetic marker for bone loss, vertebral fractures and susceptibility to estrogen. Maturitas 2002; 41: 193-201.
16. Mansur Ade P, Nogueira CC, Strunz CM, Aldrighi JM, Ramires JA. Genetic polymorphisms of estrogen receptors in patients with premature coronary artery disease. Arch Med Res 2005; 36: 511-7.
17. Kunnas TA, Laippala P, Penttilä A, Lehtimäki T, Karhunen PJ. Association of polymor-phism of human alpha oestrogen receptor gene with coronary artery disease in men:a necropsy study. BMJ 2000; 321: 273-4.
18. Karadağ B, Güven M, Hacioğlu Y, Oz E, Batar B, Domaniç N, Ulutin T, Vural VA. Relationship between two estrogen receptor-alpha gene polymorphisms and angiographic coronary artery disease. Anadolu Kardiyol Derg 2009; 9: 267-72.
19. Boroumand M, Ghaedi M, Mohammadtaghvaei N, Pourgholi L, Anvari MS, Davoodi G, Amirzadegan A, Saadat S, Sheikhfathollahi M, Goodarzynejad H. Association of estrogen receptor alpha gene polymorphism with the presence of coronary artery disease documented by coronary angiography. Clin Biochem 2009; 42: 835-9.

9/26/2013