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EPIDEMIOLOGY

Differential roles of Angiotensinogen and Angiotensin Receptor type 1 polymorphisms in breast cancer risk

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Abstract While angiotensinogen (AGT) seems to have anti proliferative properties, angiotensin II (ATII) is a potent growth factor and it mediates its actions through the angiotensin type 1 receptor (AGTR1). In the AGT gene, the M235T polymorphism has been associated with the variation in angiotensinogen levels and in the AGTR1 gene; the C573T variant is associated with different pathologies. We aimed to evaluate the relationship of these two variants and the risk of breast cancer. These polymorphisms were genotyped in 3787 women participating the Rotterdam Study. We performed a logistic regression and a disease free survival analysis by genotype. The logistic regression yielded an odds ratio of 1.4 (95% CI: 1.1–1.9) for the MM genotype carriers versus the T allele carriers. The breast cancer free survival by AGT genotype was significantly reduced in MM genotype carriers compared to non-carriers (hazard ratio (HR) = 1.5; 95% CI: 1.1–2.2). We did not find any association of the AGTR1 polymorphism and breast cancer risk or disease free survival. Our results suggest that AGT plays a role in breast cancer risk in postmenopausal women, whereas the role of AGTR1 needs further studying.

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Introduction

Breast cancer is a major cause of morbidity and mortality among women worldwide especially in middle age [1] and growth factors have been found to play an important role in the etiology and progression of this disease [2]. Several proteins of the Renin–Angiotensin–Aldosterone system (RAS) have been implicated in the processes of growth promotion or inhibition [3–6] and are found present both in normal and cancerous breast tissues [7, 8]. We have previously reported an association between the angiotensin-converting-enzyme (ACE) I/D polymorphism and breast cancer risk in postmenopausal women. The DD carriers were at a higher risk for the disease [9]. This finding has prompted us to study other genes involved in the RAS system influencing the angiotensin II pathway.

Angiotensin II (ATII) has been proven to have growth factor and angiogenic activities [3, 7] and these activities are mediated through the activation of the angiotensin type 1 receptor (AGTR1) [8, 10]. On the contrary, angiotensinogen (AGT) may have antiproliferative properties [6]. Due to these distinct properties of different members of the same pathway on cell proliferation, the relationship between AGT and breast cancer risk remains to be clarified. An increase in AGT could either benefit women because of its antiproliferative properties; but on the other hand increase the risk for breast cancer since higher levels of AGT translate into a raise in ATII [11] with its growth factor and angiogenic activities.

There are many polymorphisms in the AGT gene located on chromosome 1q42–q43. In exon 2, a non-synonymous substitution of T by C in codon 235 of the AGT gene, leads to a change from Methionine to Threonine. In Caucasians, African and Japanese populations [6, 12–18] the T235 variant of this M235T polymorphism of this gene has been consistently associated with higher levels of angiotensinogen in plasma and an increased risk for hypertension [19]. In the AGTR1 gene, also various polymorphisms have been recently studied [20–23]. A T to C substitution at codon 573 has been found to be significantly more frequent in myocardial infarction cases [19] and microalbuminuria in hypertensive patients [20]. These two AGT and AGTR1 polymorphisms have not been studied in relation to the risk for breast cancer.

In this study we aim to examine the relationship of the AGT M235T and the AGTR1 C573T polymorphisms and the risk of breast cancer in Caucasian postmenopausal women.

Patients and methods

Study population

Our study population is part of the Rotterdam Study, a population-based follow-up study of determinants of diseases in the elderly. All inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years or older were invited to participate. The design of the study has been previously described [24]. From all subjects, informed consent was obtained and the Medical Ethics committee of the Erasmus Medical Center approved the study. Out of 7.983 participants (response rate of 78%) who were examined at baseline (1990–1993), 4878 (61.1%) were women.

Measurements

At baseline, information concerning age, smoking, parity and number of children, hormone replacement therapy, age at menarche and menopause, medication use and medical history was obtained by a standardized interview [24]. Body mass index (BMI) was calculated by dividing the weight in kilograms by the height (in meters) squared [25].

Case identification and validation

Three different databases were used for case identification. First, cases diagnosed by general practitioners in the research area (Ommoord) were collected (International Classification of Primary Care (X76)). Second, the Dutch National Registry of all hospital admissions (LMR) was consulted to detect all malignancy related hospital admissions for study participants. Finally, regional pathology databases were linked to the Rotterdam Study to identify cases. Subsequently, breast cancer cases were validated by a physician (CS) on the basis of medical records of the general practitioner, discharge letters and pathology reports. Only pathologically confirmed cases were considered in the analysis. The index date was defined as the earliest date found in the pathology report.

Genotyping

The AGT M235T and AGTR1 C573T polymorphisms were successfully genotyped in 3527 (73%) and 3787 (78%) postmenopausal women in the Rotterdam Study. DNA was isolated from blood samples using standard procedures (salting out method) [26] . The M and T alleles of the AGT gene were identified using a set of oligonucleotide primers flanking the polymorphic site in exon 2 (forward primer, 5′CTG GCT CCC ATC AGG3′, reverse primer, 5′CTG GCT CCC GTC AGG3′). Likewise, the C and T alleles were detected using a set of oligonucleotide primers flanking the polymorphic site in exon 5 (forward primer 5′-CAA AGT CAC CTG CAT CAT CA-3′, reverse 5′ -AGG AAA CAG GAA ACC CA3′ [19].

Data Analysis

Hardy–Weinberg equilibrium proportions (HWE) of the AGT M235T and AGTR1 C573T polymorphisms was tested using Markov–Chain Monte-Carlo approximation of the exact test, as implemented in the GENEPOP package V 3.3 [27]. Categorical variables (parity, hormone replacement therapy (HRT), smoking, antihypertensive drug use, thyroid hormone and corticoid use and ACE inhibitors use) were compared between genotype groups using the chi-squared test. Continuous variables, which were not normally distributed, (age at entry and BMI) were compared using the independent sample Mann–Whitney test. First, we performed a logistic regression analysis to assess the risk of breast cancer according to the AGT M235T and AGTR1 C573T polymorphisms, including incident and prevalent patients. For these analyses we implemented a regression model, which included all our proposed covariates. Additionally, we tested for the interaction between AGT genotype with HRT and BMI since these risk factors have been associated with an

increased AGT mRNA expression and increased AGT plasma levels [28–31]. As a second step, we studied only incident or newly diagnosed patients to determine a breast cancer free survival by AGT and AGTR1 genotype separately. For this analysis, a Cox proportional hazards model was fitted using age as the underlying time of the model. Interaction between genes was tested using a multiplicative model. Furthermore, we tested for interactions between these two genes and ACE. We used SPSS v 11 for the logistic regression analysis and S-plus v 6 for the survival analysis and the plots.

Results

At baseline, 62 women had been previously diagnosed with postmenopausal breast cancer. During the 13 years of follow-up, another 161 women were diagnosed of breast cancer. The allele frequencies of both polymorphisms were in Hardy–Weinberg equilibrium proportions ($P = 0.5$ for AGT and $P = 0.09$ for AGTR1) in the analyzed populations. Table 1 shows that breast cancer patients were significantly older (age at entry) ($P = 0.009$), died significantly earlier (age at death) ($P < 0.0001$) and had a higher BMI than controls ($P = 0.035$). As we are studying genes involved in hypertension, patients and controls were compared for hypertension related factors. There were no significant differences in the different risk factors between cases and controls.

Figures 1 and 2 show the number of prevalent and incident breast cancer cases for the AGT (Fig. 1) and

Table 1 General Characteristics of the study population

	Cases	Controls	Overall
Number of participants	203(3.8)	3323(96.2)	3526
Mean age of entry (SD)	67.6(7.8)	69.8(9.3)	69.7(9.2)*
Mean age at death	77.1(8.6)	83.6(8.7)	83.2(8.8)*
Mean age at menopause (SD)	49.47(5)	48.82(5.3)	48.85(5.3)
Mean number of children(SD)	1.9(1.5)	2.1(1.7)	2.11(1.7)
Parity (%) (≥1 child)	156(78.4)	2561(80)	2717(79.9)
HRT (%)	24(17)	535(16.3)	559(16.3)
Hypertension (%)	55(38.2)	1253(37.1)	1308(37.1)
Use of Anti-Hypertensives(%)	14(9.7)	430(12.7)	444(12.6)
Mean body mass index (SD)	27.4(3.9)	26.7(4.1)	26.8(4.1)*

*P-value < 0.05

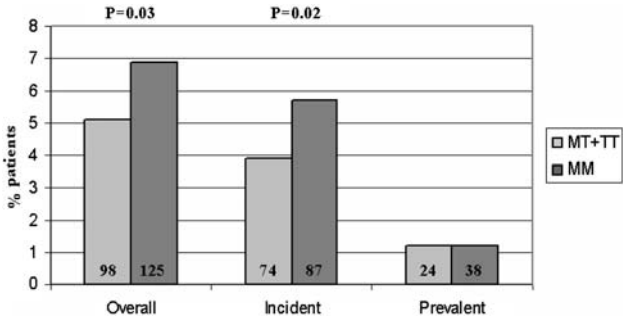

Fig. 1 Distribution of Breast Cancer by AGT Genotype

AGTR1 (Fig. 2) genes. When taking into account all cases, women carrying the MM genotype of the M235T AGT polymorphism at baseline were more likely to have breast cancer in comparison to the other two genotype groups (p = 0.03). The same effect is seen in incident cases ($P = 0.02$). For the AGTR1 polymorphism, there was a slight excess of TT carriers among patients, but no significant difference was seen among genotypes, neither in overall or incident cases.

To study the effect of other risk factors for breast cancer, we performed a logistic regression analysis entering our covariates using the forward method. This procedure left age at entry, HRT and BMI in the model as significant risk predictors. The odds ratio (OR) for MM carriers adjusted for age at entry, HRT and BMI was 1.4 (95% CI: 1.1–1.9, $P = 0.02$) when studying both prevalent and incident cases. When studying only the incident cases, the logistic regression analysis yielded an adjusted OR of 1.6 (95% CI: 1.1–2.1, $P = 0.01$) for MM carriers versus the MT and TT carrier group. Further adjustment of this model for antihypertensive drug use, smoking and parity did not modify these findings. There was no significant increase in breast cancer prevalence at baseline for MM carriers.

We tested for a possible interaction between the AGT gene and other risk factors that influence AGT plasma levels. When studying the interaction between the AGT gene and HRT we found that among carriers

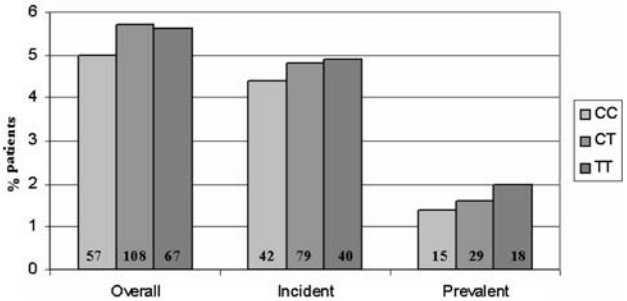

Fig. 2 Distribution of Breast Cancer by AGTR1 Genotype

of the MM genotype, those using HRT had an OR of 2.2 (95% CI = 0.9–5.8) for overall cases and an OR of 1.9 (95% CI = 0.6–5.6) for incident cases, when compared to non-users. Furthermore, there was no significant interaction between BMI and AGT (P for interaction = 0.36).

Next we performed a Cox regression analysis, using incident cases only, to calculate the age specific risk for MM carriers of the AGT M235T polymorphism. The analysis was adjusted for HRT and BMI. This model yielded a hazard ratio for breast cancer of 1.5 (95% CI: 1.1–2.2, P-value = 0.002) for MM carriers versus non-carriers (Fig. 3).

When studying the effect of the AGTR1 polymorphism on breast cancer risk using logistic regression, we found a non-significant difference in risk for CC carriers against TT carriers in overall (OR = 0.9, 95% CI = 0.7–1.3), incident (OR = 1.0, 95% CI = 0.7–1.4) and prevalent cases (OR = 0.8, 95% CI = 0.5–1.5). These odd ratios were adjusted for age at entry, HRT, BMI and age at last menstrual period. The disease free survival by AGTR1 genotype showed that the CC and CT carriers combined showed a lower risk for breast cancer, but the risk was not statistically increased compared to the TT genotype (Fig. 4).

Finally, we did not find any interaction between these two genes and the ACE I/D polymorphism (P interaction $_{AGT \times ACE} = 0.86$, P interaction $_{AGTR1 \times ACE} = 0.44$, P interaction $_{AGT \times AGTR1} = 0.9$).

Discussion

We found that postmenopausal women who were homozygous for the M allele of the M235T AGT polymorphism had a significantly increased risk for breast cancer. This was seen particularly in incident cases. This effect was maintained at all ages independently of well-known risk factors. On the other hand we found no association between AGTR1 C573T genotype and risk for breast cancer.

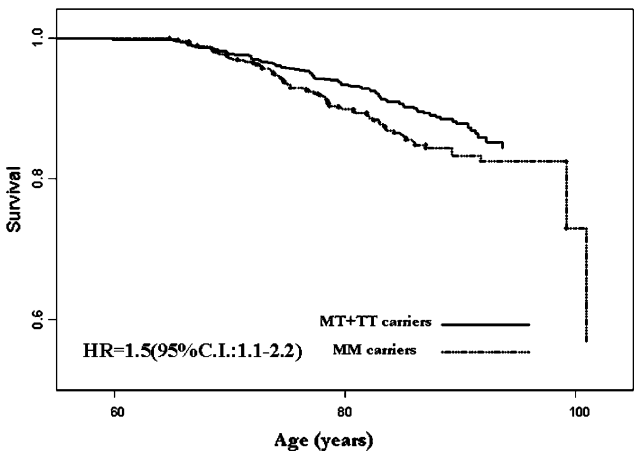

Fig. 3 Breast Cancer Free Survival by AGT M235T Genotype

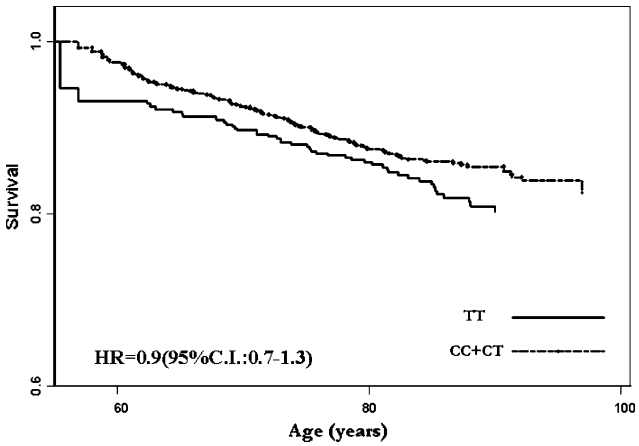

Fig. 4 Breast Cancer Free Survival by AGTR1 Genotype

Our study is the first one to assess the relationship between the M235T polymorphism in the AGT gene and the C573T variant in the AGTR1 gene and the susceptibility to breast cancer. Our aim was to unravel the relationship between these two polymorphisms and breast cancer risk in postmenopausal women. An increase in AGT could hypothetically lead to an increase in ATII, which is a potent growth factor, this might not be necessarily the case, since unlike ATII, AGT has antiangiogenic actions and reduces endothelial cell proliferation and migration [6]. Our findings suggest that the antiproliferative actions of AGT may override the proliferative effects of angiotensin II, since women who carry the allele associated with low levels of AGT are at an increased risk for breast cancer.

Although the M235T polymorphism is not the functional one [32], it is in linkage disequilibrium (D' = 0.94–1) with two functional variants located in the promoter region of the AGT gene. These two variants, the G-6A [17, 32–35] and the C-20A [17, 33, 36] are situated within an estrogen responsive element [17, 29, 35]. It has been well documented that estrogen increases AGT mRNA expression [28] and this could be assumed by our results of the interaction of AGT genotype and the use of HRT.

The functionality of the different variants of the AGTR1 gene has not yet been unraveled. The + 1166A/C polymorphism located in the 3′ UTR [19] is in complete LD with the C573T [19], and has been consistently associated with hypertension, cardiovascular disease and responsiveness to AGTR1 receptor blocking agents. Moreover, the C allele of the C573T variant has

been found to be significantly more frequent in cases on myocardial infarction [19] and microalbuminuria in hypertensive patients [20], although results have been inconsistent for the latter [37–39].

There is only one other study assessing the risk of breast cancer by AGTR1 polymorphisms. Koh et al. performed this study in Chinese women in Singapore, including three different polymorphisms [40]. He found that carriers of putative risk alleles of polymorphisms in the AGTR1 gene had a non-significantly decreased risk of breast cancer. Our results show the same trend as Koh et al., although the studied polymorphisms were different. These results ask for further studies on this polymorphism in larger case series.

Our findings suggest that the M235T polymorphism in the AGT gene may play a role as susceptibility factors in breast cancer development and disease free survival in Caucasian postmenopausal women. This finding is in line with the association we have found between the ACE gene and breast cancer [9]. The role of AGTR1 C573T polymorphism on the other hand, remains to be further studied.

Contributions

A. Arias Vásquez contributed with the design of the study and also participated in the data analyses. C van Duijn participated in the design and writing of the manuscript. M Yazdanpanah, JWW Coebergh, BHCh Stricker and A Hofman aided in the data collection and the writing of this manuscript as well.

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References

1. Bernstein L (2002) Ethnicity-related variation in breast cancer risk factors. Cancer 97:222–229
2. Folkman J (2002) Role of angiogenesis in tumor growth and metastasis. Semin Oncol 29:15–18
3. Ruiz-Ortega M, Lorenzo O, Ruperez M, Esteban V, Suzuki Y, Mezzano S, Plaza JJ, Egido J (2001) Role of the renin-angiotensin system in vascular diseases: expanding the field. Hypertension 38:1382–1387
4. Muscella A, Greco S, Elia MG, Storelli C, Marsigliante S (2002) Angiotensin II stimulation of Na+/K + ATPase activity and cell growth by calcium-independent pathway in MCF-7 breast cancer cells. J Endocrinol 173:315–323
5. Walther T, Menrad A, Orzechowski HD, Siemeister G, Paul M, Schirner M (2003) Differential regulation of in vivo angiogenesis by angiotensin II receptors. Faseb J 17:2061–2067
6. Celerier J, Cruz A, Lamande N, Gasc JM, Corvol P (2002) Angiotensinogen and its cleaved derivatives inhibit angiogenesis. Hypertension 39:224–228
7. Greco S, Muscella A, Elia MG, Salvatore P, Storelli C, Marsigliante S (2002) Activation of angiotensin II type I receptor promotes protein kinase C translocation and cell proliferation in human cultured breast epithelial cells. J Endocrinol 174:205–214
8. Greco S, Muscella A, Elia MG, Salvatore P, Storelli C, Mazzotta A, Manca C, Marsigliante S (2003) Angiotensin II activates extracellular signal regulated kinases via protein kinase C and epidermal growth factor receptor in breast cancer cells. J Cell Physiol 196:370–377
9. Gonzalez-Zuloeta Ladd AM, Vasquez AA, Sayed-Tabatabaei FA, Coebergh JW, Hofman A, Njajou O, Stricker B, van Duijn C (2005) Angiotensin-converting enzyme gene insertion/deletion polymorphism and breast cancer risk. Cancer Epidemiol Biomarkers Prev 14:2143–2146
10. Greco S, Elia MG, Muscella A, Storelli C, Marsigliante S (2002) AT1 angiotensin II receptor mediates intracellular calcium mobilization in normal and cancerous breast cells in primary culture. Cell Calcium 32:1–10
11. Gould AB, Green D (1971) Kinetics of the human renin and human substrate reaction. Cardiovasc Res 5:86–89
12. Ward K, Hata A, Jeunemaitre X, Helin C, Nelson L, Namikawa C, Farrington PF, Ogasawara M, Suzumori K, Tomoda S et al. (1993) A molecular variant of angiotensinogen associated with preeclampsia. Nat Genet 4:59–61
13. Vinck WJ, Fagard RH, Vlietinck R, Lijnen P (2002) Heritability of plasma renin activity and plasma concentration of angiotensinogen and angiotensin-converting enzyme. J Hum Hypertens 16:417–422
14. Bloem LJ, Manatunga AK, Tewksbury DA, Pratt JH (1995) The serum angiotensinogen concentration and variants of the angiotensinogen gene in white and black children. J Clin Invest 95:948–953
15. Bennett CL, Schrader AP, Morris BJ (1993) Cross-sectional analysis of Met235–> Thr variant of angiotensinogen gene in severe, familial hypertension. Biochem Biophys Res Commun 197:833–839
16. Jeunemaitre X, Gimenez-Roqueplo AP, Celerier J, Corvol P (1999) Angiotensinogen variants and human hypertension. Curr Hypertens Rep 1:31–41
17. Morgan L, Crawshaw S, Baker PN, Broughton Pipkin F, Kalsheker N (2000) Polymorphism in oestrogen response element associated with variation in plasma angiotensinogen concentrations in healthy pregnant women. J Hypertens 18:553–537
18. Jeunemaitre X, Soubrier F, Kotelevtsev YV, Lifton RP, Williams CS, Charru A, Hunt SC, Hopkins PN, Williams RR, Lalouel JM, et al. (1992) Molecular basis of human hypertension: role of angiotensinogen. Cell 71:169–180
19. Su S, Chen J, Zhao J, Huang J, Wang X, Chen R, Gu D (2004) Angiotensin II type I receptor gene and myocardial infarction: tagging SNPs and haplotype based association study. The Beijing atherosclerosis study. Pharmacogenetics 14:673–681

20. Chaves FJ, Pascual JM, Rovira E, Armengod ME, Redon J (2001) Angiotensin II AT1 receptor gene polymorphism and microalbuminuria in essential hypertension. Am J Hypertens 14:364–370
21. De Paepe B, Verstraeten VL, De Potter CR, Vakaet LA, Bullock GR (2001) Growth stimulatory angiotensin II type-1 receptor is upregulated in breast hyperplasia and in situ carcinoma but not in invasive carcinoma. Histochem Cell Biol 116:247–254
22. Duncan JA, Scholey JW, Miller JA (2001) Angiotensin II type 1 receptor gene polymorphisms in humans: physiology and pathophysiology of the genotypes. Curr Opin Nephrol Hypertens 10:111–116
23. Egami K, Murohara T, Shimada T, Sasaki K, Shintani S, Sugaya T, Ishii M, Akagi T, Ikeda H, Matsuishi T, Imaizumi T (2003) Role of host angiotensin II type 1 receptor in tumor angiogenesis and growth. J Clin Invest 112:67–75
24. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA (1991) Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 7:403–422
25. Garrow J (1986) Quetelet index as indicator of obesity. Lancet 1:1219
26. Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16:1215
27. Raymond MRF (1986) Genepop (version 1.2): population genetics software for exact tests and ecumenism. J Heredity 86:248–249
28. Corvol P, Jeunemaitre X (1997) Molecular genetics of human hypertension: role of angiotensinogen. Endocr Rev 18:662–677
29. Azizi M, Hallouin MC, Jeunemaitre X, Guyene TT, Menard J (2000) Influence of the M235T polymorphism of human angiotensinogen (AGT) on plasma AGT and renin concentrations after ethinylestradiol administration. J Clin Endocrinol Metab 85:4331–4337
30. Chaves FJ, Giner V, Corella D, Pascual J, Marin P, Armengod ME, Redon J (2002) Body weight changes and the A-6G polymorphism of the angiotensinogen gene. Int J Obes Relat Metab Disord 26:1173–1178
31. Prat-Larquemin L, Oppert JM, Clement K, Hainault I, Basdevant A, Guy-Grand B, Quignard-Boulange A (2004) Adipose angiotensinogen secretion, blood pressure, and AGT M235T polymorphism in obese patients. Obes Res 12:556–561
32. Brand E, Chatelain N, Paillard F, Tiret L, Visvikis S, Lathrop M, Soubrier F, Demenais F (2002) Detection of putative functional angiotensinogen (AGT) gene variants controlling plasma AGT levels by combined segregation-linkage analysis. Eur J Hum Genet 10:715–723
33. Sato N, Katsuya T, Nakagawa T, Ishikawa K, Fu Y, Asai T, Fukuda M, Suzuki F, Nakamura Y, Higaki J, Ogihara T (2000) Nine polymorphisms of angiotensinogen gene in the susceptibility to essential hypertension. Life Sci 68:259–272
34. Inoue I, Nakajima T, Williams CS, Quackenbush J, Puryear R, Powers M, Cheng T, Ludwig EH, Sharma AM, Hata A, Jeunemaitre X, Lalouel JM (1997) A nucleotide substitution in the promoter of human angiotensinogen is associated with essential hypertension and affects basal transcription in vitro. J Clin Invest 99:1786–1797
35. Chaves FJ, Corella D, Sorli JV, Marin-Garcia P, Guillen M, Redon J (2004) Polymorphisms of the renin-angiotensin system influence height in normotensive women in a Spanish population. J Clin Endocrinol Metab 89:2301–2305
36. Zhao YY, Zhou J, Narayanan CS, Cui Y, Kumar A (1999) Role of C/A polymorphism at -20 on the expression of human angiotensinogen gene. Hypertension 33:108–115
37. Bonnardeaux A, Davies E, Jeunemaitre X, Fery I, Charru A, Clauser E, Tiret L, Cambien F, Corvol P, Soubrier F (1994) Angiotensin II type 1 receptor gene polymorphisms in human essential hypertension. Hypertension 24:63–69
38. Redon J, Luque-Otero M, Martell N, Chaves FJ (2005) Renin-angiotensin system gene polymorphisms: relationship with blood pressure and microalbuminuria in telmisartan-treated hypertensive patients. Pharmacogenomics J 5:14–20
39. Poirier O, Georges JL, Ricard S, Arveiler D, Ruidavets JB, Luc G, Evans A, Cambien F, Tiret L (1998) New polymorphisms of the angiotensin II type 1 receptor gene and their associations with myocardial infarction and blood pressure: the ECTIM study. Etude Cas-Temoin de l'Infarctus du Myocarde. J Hypertens 16:1443–1447
40. Koh WP, Yuan JM, Van Den Berg D, Lee HP, Yu MC (2004) Polymorphisms in angiotensin II type 1 receptor (AGTR1) and angiotensin I-converting enzyme (ACE) genes and breast cancer risk among chinese women in Singapore. Carcinogenesis