

## Possible association of $\beta$ 2- and $\beta$ 3-adrenergic receptor gene polymorphisms with susceptibility to breast cancer

### ABSTRACT

A potential association may exist between risk of breast cancer and polymorphisms in the ADRB2 and ADRB3 genes; further studies in larger samples and/or in different ethnic groups are warranted to investigate this potential association.

### INTRODUCTION

Introduction The incidence of breast cancer has increased greatly in Japan over the past 2 decades, and it has been estimated that breast cancer would become the most common malignant disease in Japanese females by the year 2000. One of the main risk factors for breast cancer in menopausal women is obesity. The increased amount of adipose tissue after menopause is considered to elevate estradiol production, which in turn increases the risk for breast cancer. Thus, genetic traits that are related to obesity may influence the risk of postmenopausal breast cancer in an indirect manner. It is now known that the adrenergic system plays a key role in regulating energy balance through both thermogenesis and lipid mobilization from brown or white adipose tissues, and that human fat cells are equipped with adrenergic receptors (adrenoceptors)  $\beta$ 1,  $\beta$ 2 (ADRB2) and  $\beta$ 3 (ADRB3). The degree of affinity for adrenaline (epinephrine) is  $\beta$ 2 >  $\beta$ 1 >  $\beta$ 3, and for noradrenaline (norepinephrine) it is  $\beta$ 1  $\geq$   $\beta$ 2 >  $\beta$ 3. The genes encoding ADRB2 and ADRB3, which have been cloned from humans, have therefore attracted much research attention with regard to their impact on obesity and obesity-related health problems. Among these adrenergic receptors, ADRB2 appears to be the most effective regarding the mobilization of lipids, especially from abdominal subcutaneous adipose tissues. An epidemiological study revealed a marked link between obesity and a polymorphism in codon 27 of the ADRB2 gene that features a replacement of glutamine by glutamic acid (Gln27→Glu). However, doubts have also been cast on the role of this polymorphism in obesity in German and Japanese women. A French study further pointed out that only in those with a sedentary lifestyle is there an association. A missense mutation in codon 64 of the ADRB3 gene that results in substitution of tryptophan by arginine (Trp64→Arg) in the first intracellular loop of the receptor protein has also been reported in various ethnic groups, including Japanese. Increased body mass index (BMI), a broadly used index of obesity, has been demonstrated in Japanese Arg allele carriers. A review identified a link between obesity and the Trp64→Arg polymorphism in 13 studies, but not in 15. Therefore, it is not possible to draw firm conclusions. To our knowledge, few studies have been conducted to investigate the combined effect of polymorphisms in codon 27 of ADRB2 and codon 64 of ADRB3 on female obesity and/or breast cancer. This combined effect more closely resembles the real physiological status. In the present study, associations with the Gln27→Glu polymorphism in the ADRB2 gene and the Trp64→Arg polymorphism in the ADRB3 gene were examined, both in premenopausal and in postmenopausal Japanese women. Although obesity is not a risk factor for premenopausal breast cancer, associations in premenopausal women were examined for comparison with findings in postmenopausal women. This exploratory analysis was expected to provide some clues for future investigations, and so the findings should be confirmed by studies with larger sample sizes and/or with samples from different ethnic groups.

## CONCLUSION

The present exploratory analysis suggests that an association may exist between risk of breast cancer and polymorphisms in codon 27 of ADRB2 and 64 of ADRB3 genes; further studies in larger samples and/or in different ethnic groups are warranted to investigate this potential association.