CORRESPONDENCE

Re: Population-Based Case–Control Study of HER2 Genetic Polymorphism and Breast Cancer Risk

Human epidermal growth factor receptor 2 (HER2) is a proto-oncogene encoding a transmembrane glycoprotein with tyrosine kinase activity. The amplification and overexpression of this gene have been observed in breast and ovarian cancers and are associated with the response of breast cancers to chemotherapy. A single nucleotide polymorphism (SNP) at codon 655 resulting in a valine to isoleucine change (Val655Ile) was reported in the Journal *(1)* to be associated with an increased risk of breast cancer among women in Shanghai, China. The frequency of the valine allele varies among ethnic groups. The valine allele has a frequency of 20% in Caucasians and 24% in African-Americans but was not detected in an African population *(2)*. Studies among British *(3)* and German–Caucasian *(4)* populations showed that the valine allele was not associated with a higher risk for breast or ovarian cancer.

Because genetic heterogeneity exists among individuals from different geographical regions of China *(5,6)*, we investigated the frequency of the Val655Ile HER2 polymorphism in a southern Chinese-based age-matched case–control study in Hong Kong to determine whether it is associated with risk for ovarian cancer in this population.

Paraffin-embedded tissue blocks were retrieved from the files of the Department of Pathology, Queen Mary Hospital, a major referral center in Hong Kong for patients with gynecologic malignancies. Nontumor blocks were obtained from 205 Chinese women diagnosed with primary epithelial ovarian carcinoma and from 205 age-matched control subjects. Control subjects had undergone total hysterectomy for a benign condition and did not have ovarian cancer. The mean age of both groups was 50 years. The Val655Ile polymorphism was detected by restriction fragment length polymorphism as described *(1)* except that the primers were 5′-ATCCCTGACCCTGGCTTCC-3′ (forward) and 5′-CGCTTGATGAGGATCCCAAA-3′ (reverse). Statistical analysis was performed with a two-sided χ^2 test to compare the allele and genotype frequencies in the studied sample with those reported in ethnic control populations.

We did not detect a valine/valine homozygote among the 410 subjects studied. The valine allele frequency found in normal control subjects was similar to that reported in the Shanghai population *(1)* but was statistically significantly different ($P<.001$) from those in other ethnic group studies *(2–4)*. Both the valine allele frequency and the genotype frequency were statistically significantly different between patients with ovarian cancer and normal control subjects ($P = .022$ and .016, respectively). The genotypes were in Hardy–Weinberg equilibrium in both cancer and control groups. Heterozygote valine allele carriers had a statistically significantly decreased risk for ovarian cancer compared with homozygote isoleucine allele carriers ($\chi^2 = 5.831$; 1 *df*; $P = .016$; odds ratio = 0.517, 95% confidence interval = 0.310 to 0.865). These results differ from those for breast cancer reported by Xie et al. *(1)* and those in a British population in which the valine allele was not associated with breast or ovarian cancer risk *(3)* (Table 1).

We suggest that the risk for ovarian cancer of women in the southern Chinese population of Hong Kong who have the valine allele is lower than the risk of those without the valine allele. We note that an SNP in the RAD51 gene was also associated with a lower risk for ovarian cancer among BRCA1 and/or BRCA2 mutation carriers *(7)*. Our results need to be verified in a larger study, and the odds ratio for ovarian cancer among valine/valine homozygotes needs to be determined. It is possible that HER2 is in linkage disequilib-

Table 1. Summary of genotyping result for HER2 valine-655→isoleucine (Val655Ile) polymorphism in different ethnic groups

Population	Subjects*	No. of subjects	Genotype frequency, %			Val allele frequency, %	*P* value
			Val/Val	Val/Ile	Ile/Ile		
Hong Kong Chinese [this study]	Control	205	0	23.4	76.6	11.7	
	OvCa	205	0	13.7	86.3	6.8	.022†
Shanghai Chinese [Xie et al. *(1)*]	Control	361	0.3	21.7	78.0	11.1	
	BrCa	339	3.2	25.1	71.7	15.8	.011† .005‡
British [Baxter and Campbell *(3)*]	Control	256	6.6	39.4	53.9	26.4	
	BrCa	315	5.1	34.6	60.3	22.4	.13† .13‡
	OvCa	314	7.6	34.1	58.3	24.7	.56† .31‡
German-Caucasian [Wang-Gohrke] and Chang-Claude *(4)*	Control	1078	5	35	60	23	
	BrCa	615	6	36	69	24	.56† .83‡
Ghanaian [Ameyaw et al. *(2)*]	Total	200	0	0	100	0	
African-American [Ameyaw et al. *(2)*]	Total	90	4.4	38.9	56.7	24	
Caucasian [Ameyaw et al. *(2)*]	Total	257	5.4	29.2	65.4	20	

*OvCa = ovarian cancer; BrCa = breast cancer.
†*P* values are from the two-sided χ^2 test for comparison between Val allele frequency and Ile allele frequency.
‡*P* values represent the genotype frequencies as reported by previous authors.

rium with other candidate genes nearby on the same chromosome that are also associated with the risk for ovarian cancer. Consequently, the usefulness of the Val655Ile polymorphism for determining the risk for breast and/or ovarian cancer and its response to treatment may be limited.

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NOTES

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