Null Results in Brief

The Fibroblast Growth Factor Receptor Gene *Arg*^{388} Allele Is not Associated with Early Lymph Node Metastasis of Breast Cancer

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Introduction

A common observation in clinically detected breast cancers and even in screening-detected cases is that a relevant percentage of tumors small in size (≤20 mm) are already nodal positive, *i.e.*, at advanced stage (1). On the other hand, other tumors are still nodal negative, although already relatively large in size. Because metastasis of tumors is not considered to occur at random, exploring underlying mechanisms is crucial for both the understanding of the natural history of the disease and the optimal targeting of screening modalities.

Elevated angiogenesis has been shown to be correlated with increased risk of metastasis and poor prognosis (2). Several polymorphisms in genes coding for angiogenesis and growth factors relevant for angiogenesis have been identified, and some have been found to be related to differences in breast cancer angiogenesis among humans (3).

Recently, a polymorphism in the FGFR4[2] has been identified and shown to be associated with a poor prognosis in breast cancer patients (4). On the basis of specimen of 84 human breast cancer cases and 123 healthy controls, Bange *et al.* (4) obtained the following results: (*a*) the *Arg*^{388} allele was *not* associated with an altered risk of breast cancer; (*b*) the carriers of the allele experienced a higher risk of early lymph node metastasis compared with wild-type gene carriers which was, however, not statistically significant; and (*c*) tumor-free survival was significantly reduced among carriers of the allele compared with the wild-type gene carriers. Result (*b*) was only addressed qualitatively, but based on the data presented in Table 3 of that article, carriers of the *Arg*^{388} allele had an OR of 2.2 (95% confidence interval, 0.9–5.3) to develop early lymph node metastasis compared with noncarriers.

Hypothesis. We hypothesized that among breast cancer patients with small tumors, the carriers of the *Arg*^{388} allele experience a higher risk of lymph node metastasis.

Materials and Methods

We used data and specimen of a population-based case-control study on breast cancer carried out in two areas of Germany in 1992–1995, including 706 cases and 1381 age-matched controls between the ages of 20 and 52 years [for details see Chang-Claude *et al.* (5)]. For most of the cases, the precise tumor-node-metastasis status was known. From the case series, women having a tumor size < 20 mm at time of diagnosis (n = 270) were selected and classified into two groups with respect to nodal involvement. We excluded 24 patients for whom no blood sample (n = 6) or no DNA (n = 16) was available. For the remaining 266 subjects, the genotype with respect to the FGFR4 *Arg*^{388} allele was determined with RFLP analysis. For 2 subjects, genotyping did not provide a result, leaving 246 cases for the final analysis (Table 1). Logistic regression (6) was carried out to assess the association, and the Jonckheere-Terpstra test for trend performed using the SAS procedures LOGISTIC and FREQ with the respective trend test option (SAS release 8.2; SAS Institute, Cary, NC). For power calculation, the arcsine approximation was used (6).

Table 1 Genotype and nodal status of 246 cases from the German breast cancer case-control study

Genotype[a]	Nodal status				Total	
	Negative		Positive			
	n	%	*n*	%	*n*	%
Wild-type	79	42.9	26	41.9	105	42.7
Heterozygous for Arg^{388} allele	88	47.8	28	45.2	116	47.2
Homozygous for Arg^{388} allele	17	9.3	8	12.9	25	10.2
Total	184	100	62	100	246	100

[a] $P_{\text{Hardy-Weinberg}} = 0.69$.

Results

Among the 246 subjects, 42.7% were homozygous carriers of the wild-type allele. A total of 47.2% was heterozygous, and 10.2% were homozygous carriers of the *Arg*^{388} allele (Table 1). Compared with noncarriers, *Arg*^{388} allele carriers had an OR of 1.04 (95% CI, 0.6–1.9) for lymph node involvement. The test for trend on the number of mutant alleles provided a P (one-sided) of $P_{\text{trend}} = 0.35$. Inclusion of age into the model did not affect the results.

Statistical Power, Study Limitations, and Conclusions. The study has a power of 81% to confirm an odds ratio in the magnitude of OR = 2.2 as found with the data of Bange *et al.* (4) on a one-sided significance level of $\alpha = 0.05$. Selection bias may have occurred but is likely to be negligible because of the population-based sampling of the cases and a high degree of ethnic homogeneity of the included cases. We might not have had enough power to detect a weaker association. However, the complete null result observed renders it rather unlikely that insufficient power was the reason that we failed to detect an association. We conclude that the FGFR4 *Arg*^{388} allele is not associated with increased risk of lymph node metastasis of small breast cancers.

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[2] The abbreviations used are: FGFR4, fibroblast growth factor receptor 4; OR, odds ratio.

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