

Null Results in BriefNo Association Between *OGG1* Ser326Cys Polymorphism and Breast Cancer Risk¹

Ulla Vogel,² Bjørn A. Nexø, Anja Olsen, Birthe Thomsen, Nicklas R. Jacobsen, Håkan Wallin, Kim Overvad, and Anne Tjønneland

National Institute of Occupational Health, DK-2100 Copenhagen, Denmark [U. V., N. R. J., H. W.]; Institute of Human Genetics, University of Aarhus, DK-8000 Aarhus C, Denmark [B. A. N.]; Institute of Cancer Epidemiology, The Danish Cancer Society, DK-2100 Copenhagen, Denmark [A. O., B. T., A. T.]; and Department for Epidemiology and Social Medicine, University of Aarhus, DK-8000, Denmark [K. O.]

Introduction

Breast cancer is the most common cancer among western women. Except for inherited mutations in the *BRCA1*, *BRCA2*, *ATM*, and *p53* genes, little is known about the genetic risk factors for breast cancer. Recently, polymorphisms in genes involved in repair of DNA double-strand breaks were associated with risk of breast cancer (1). It has been proposed that oxidative stress contributes to breast cancer carcinogenesis (2). *OGG1* encodes 8-oxo-guanine glycosylase, a key enzyme in repair of 8-oxo-guanine and other oxidative DNA damages. To investigate the possibility of an association between the polymorphism *OGG1* Ser326Cys and breast cancer risk in postmenopausal women, we studied 425 cases and 434 controls, all recruited from the Danish Diet, Cancer and Health cohort.

Materials and Methods

Diet, Cancer and Health is a prospective cohort study. A total of 79,729 women aged 50–64 years were invited to participate between December 1993 and May 1997, and 29,875 accepted the invitation. Eligible women were born in Denmark and had no previous diagnosis of cancer. The cohort has been described previously (3). Follow-up for breast cancer was from the age at inclusion until the age at the date of diagnosis of any cancer, date of death, date of emigration, or 31 December 2000, whichever came first.

A nested case-control study design was used (4). For each of the 434 breast cancer cases developing among postmenopausal women, a control was selected at random among women who were cancer free at the age at diagnosis of the case and who had the same baseline values of postmeno-

pausal status (known/probably postmenopausal), use of hormone replacement therapy (current/former/never), and age (half-year intervals). Nine cases were excluded due to missing blood samples.

The breast cancer rate was related to *OGG1* Ser326Cys. Due to the sampling design, the rate ratio equals the odds ratio estimated using matched logistic regression; thus, only known discordant pairs contribute to this analysis. The procedure PHREG in SAS release 6.12 (SAS Institute, Inc., Cary, NC) on Unix platform was used for statistical analyses.

The polymorphism *OGG1* Ser326Cys was determined on DNA from lymphocytes using real-time PCR on a Sequence Detection System ABI Prism 7700 (Applied Biosystems, Nærum Denmark). *OGG1* Ser326Cys (position 49231, AF176815) was genotyped as follows: Ten- μ l reactions contained 1 \times MasterMix, 100 nM each probe, 800 nM primers, and 0.5 μ l of genomic DNA. Cycling conditions were as follows: 50°C for 2 min; 95°C for 10 min; and 44 cycles of 95°C for 15 s and 60°C for 1 min. Primers were as follows: forward, 5'-cctcctacaggtgctgtcagtg-3'; reverse, 5'-atctagcctccggccctt-3' (tagc.com). Probes were as follows: G-probe (Cys allele), 5'-FAM-tgcgccaatGccgccaat-TAMRA-3'; C-probe (Ser allele), 5'-VIC-tgcgccaatCccgccaat-TAMRA-3' (Applied Biosystems). A 10% subset was retyped, yielding 100% identical genotyping. One sample of each genotype was sequenced as a further quality check. A DNA fragment encompassing the polymorphism was amplified using primers 5'-ttccacctccaacactgtca-3' and 5'-atctagcctccggccctt-3. Sequencing was performed using primer 5'-cctcctacaggtgctgttca-3'.

Results and Discussion

The allele frequencies of the variant G allele for *OGG1* Ser326Cys (0.225 and 0.240 for cases and controls, respectively) were in agreement with an allele frequency for Hungarians of 0.194 (5). The genotype distribution in the control group was in Hardy-Weinberg equilibrium. There was no association between genotype and breast cancer risk (Table 1). There was no effect of age at onset of breast cancer or family history of cancer (results not shown).

The design in this study is relatively strong for two reasons: (a) the study is fairly large; and (b) cases and controls were carefully matched, being recruited from the same cohort of 29,875 Danish women. Given the sample size and the allele frequencies of the controls, we had a 98% chance of detecting a halving of the rate between the wild-type homozygote and the other two genotypes (two-sided $P = 0.01$).

Several studies have been published on *OGG1* Ser326Cys with conflicting results (5, 6), but this is the first study on the association with breast cancer. The lack of effect of the polymorphisms may reflect that gene-environment interactions are required, for which the environmental exposures are not present in Danish women; that the gene is not important for breast

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² To whom requests for reprints should be addressed, at National Institute of Occupational Health, Lersø Parkallé 105, DK-2100 Copenhagen, Denmark. Phone: 4539165227; Fax: 4539165201; E-mail: ubv@ami.dk.

Table 1 Distribution of *OGG1* Ser326Cys genotypes and risk of breast cancer

	<i>OGG1</i> Ser326Cys genotypes		
	CC (Ser/Ser)	CG (Ser/Cys)	GG (Cys/Cys)
Cases	256	147	22
Controls	245	169	20
OR (95% CI) ^a	1.00	0.84 (0.64–1.10)	0.98 (0.52–1.86)

^a The CC genotype served as reference category. The odds ratios (ORs) are based on information from known discordant pairs only, due to matched design. CI, confidence interval.

cancer development; or that a putative linkage to the effective mutation differs between ethnic groups.

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