Evidences for association of the -652 6N del promoter polymorphism with age at diagnosis in familial breast cancer cases

Giovanna Vecchi, Paolo Verderio, Sara Pizzamiglio, Siranoush Manoukian, Monica Barile, Stefano Fortuzzi, Fernando Ravagnani, Marco A. Pierotti, Paolo Radice, Paolo Peterlongo

► To cite this version:

Giovanna Vecchi, Paolo Verderio, Sara Pizzamiglio, Siranoush Manoukian, Monica Barile, et al.. Evidences for association of the -652 6N del promoter polymorphism with age at diagnosis in familial breast cancer cases. *Breast Cancer Research and Treatment*, 2008, 113 (3), pp.607-608. 10.1007/s10549-008-9963-y . hal-00486703

HAL Id: hal-00486703

<https://hal.science/hal-00486703>

Submitted on 26 May 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Evidences for association of the *CASP8* -652 6N del promoter polymorphism with age at diagnosis in familial breast cancer cases

Giovanna De Vecchi · Paolo Verderio · Sara Pizzamiglio ·
Siranoush Manoukian · Monica Barile · Stefano Fortuzzi ·
Fernando Ravagnani · Marco A. Pierotti · Paolo Radice ·
Paolo Peterlongo

Received: 28 February 2008 / Accepted: 29 February 2008 / Published online: 16 March 2008
© Springer Science+Business Media, LLC. 2008

To the Editor,

Recently, a study conducted in Chinese individuals reported that a 6-nucleotide deletion in the promoter of the *CASP8* gene (the -652 6N del; rs3834129) was strongly associated with decreased cancer risk in several types of cancers including breast cancer (BC) [1]. Here, we studied the effect of this polymorphism in a series of 580 Italian familial BC index cases and 406 controls. The cases were

originally ascertained through the Genetic Services of Fondazione IRCCS Istituto Nazionale Tumori (INT) or Istituto Oncologico Europeo (IEO) in Milan, as eligible for mutation analysis in *BRCA* genes based on criteria including family history and age at cancer diagnosis [2]. All the females affected with BC as the first diagnosed cancer (median age: 43; range: 21–80), who tested negative for *BRCA* disease-causing mutations, were included in this study. The controls were Italian female blood donors who were ≥ 45 years at the blood draw (median age, 54; range, 45–71) recruited at INT. The genotyping was performed comparing the length of PCR fragments of the normal and the deleted allele with a size marker using Denaturing High-Performance Liquid Chromatography (assay and primer sequences are available upon request).

In cases and controls, common homozygous (nor/nor), heterozygous (nor/del) and rare homozygous (del/del) were 162 (27.9%), 301 (51.9%) and 117 (20.2%); and 106 (26.1%), 206 (50.7%) and 94 (23.2%), respectively, consistent with Hardy-Weinberg equilibrium. By logistic regression analysis adjusted for age [3], we observed that the odds ratio (OR) for heterozygous and rare homozygous compared with common homozygous was 1.05 (95% confidence interval (CI) = 0.74–1.49) and 1.09 (95% CI = 0.71–1.67), respectively, and the per-allele OR was 0.96 (95% CI = 0.78–1.18). These results provided no evidence for association between the -652 6N del polymorphism and familial BC unlinked to *BRCA* genes, confirming the findings obtained in German, English and Polish individuals [4, 5]. We pursued the study of the -652 6N del polymorphism. Of interest was the investigation of the association between the polymorphism and age at BC diagnosis in cases. The three genotypes were collapsed into two: (del/del), and (nor/–) by aggregating common homozygous and heterozygous cases; the age at diagnosis

G. De Vecchi · P. Radice · P. Peterlongo
IFOM, Fondazione Istituto FIRC di Oncologia Molecolare,
Milan, Italy

G. De Vecchi · P. Radice (✉) · P. Peterlongo
Unit of Genetic Susceptibility to Cancer, Department
of Experimental Oncology, Fondazione IRCCS Istituto
Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy
e-mail: paolo.radice@istitutotumori.mi.it

P. Verderio · S. Pizzamiglio
Unit of Medical Statistics and Biometry, Fondazione IRCCS
Istituto Nazionale dei Tumori, Milan, Italy

S. Manoukian
Medical Genetics Service, Fondazione IRCCS Istituto Nazionale
dei Tumori, Milan, Italy

M. Barile
Division of Cancer Prevention and Genetics, Istituto Europeo di
Oncologia, Milan, Italy

S. Fortuzzi
Cogentech, Consortium for Genomic Technologies, Milan, Italy

F. Ravagnani
Immunohematology and Transfusion Medicine Service,
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

M. A. Pierotti
Scientific Direction, Fondazione IRCCS Istituto Nazionale dei
Tumori, Milan, Italy

Table 1 Association of genotypes of the *CASP8* -652 6N del polymorphism with age at breast cancer diagnosis in 580 familial breast cancer index cases

Age at diagnosis	N	del/del (%)	not/– (%)	OR ^b	95% CI ^c	P-value
≤35 ^a	173	22 (12.7)	151 (87.3)	1.00		
36–43	120	27 (22.5)	93 (77.5)	1.99	1.07–3.70	0.03
44–50	148	34 (23.0)	114 (77.0)	2.05	2.14–3.69	0.02
>50	139	34 (24.5)	105 (75.5)	2.22	1.23–4.01	0.01

^a Reference group^b OR, Odds ratio^c CI, Confidence interval

was categorized into four classes according to the pertinent age centiles (25th: 35; 50th: 43; 75th: 50). We assessed the associations between each age class and genotype by the logistic regression model considering as reference group the cases with younger age at diagnosis. We observed a statistically significant association between these two variables (Table 1). In particular, our results suggested an increasing trend of the del/del genotype with later age at BC diagnosis (trend test *P*-value = 0.01).

In conclusion, our results confirmed those obtained in previous Europeans studies. Nevertheless, we observed that the -652 6N del polymorphism of *CASP8* was associated with age at diagnosis in familial BC cases. Thus, we suggest that this polymorphism may have an effect in

postponing the BC onset in predisposed individuals. To our knowledge, this is the first study that investigated this latter aspect; consequently, our results should be taken with caution and further analyses are necessary to clarify the effect of this polymorphism on BC.

Acknowledgements This work was supported by Fondazione Italiana per la Ricerca sul Cancro (FIRC; Special Project 'Hereditary tumors'); Associazione Italiana per la Ricerca sul Cancro (AIRC; Grant number 4017); Ministero dell'Università e Ricerca (MiUR; Grant number: RBLA03BETH); and Istituto Superiore di Sanità (ISS, Grant number: 526D/41).

References

1. Sun T, Gao Y, Tan W et al (2007) A six-nucleotide insertion-deletion polymorphism in the *CASP8* promoter is associated with susceptibility to multiple cancers. *Nat Genet* 39:605–613
2. Manoukian S, Peissel B, Pensotti V et al (2007) Germline mutations of TP53 and BRCA2 genes in breast cancer/sarcoma families. *Eur J Cancer* 43:601–606
3. Hosmer Jr DW, Lemeshow S (1989) *Applied logistic regression*. John Wiley & Sons, New York
4. Frank B, Rigas SH, Bermejo JL et al (2007) The *CASP8* -652 6N del promoter polymorphism and breast cancer risk: a multicenter study. *Breast Cancer Res Treat*. doi:10.1007/s10549-007-9752-z
5. Cybulski C, Wokołorczyk D, Gliniewicz B et al (2007) A six-nucleotide deletion in the *CASP8* promoter is not associated with a susceptibility to breast and prostate cancers in the Polish population. *Breast Cancer Res Treat*. doi:10.1007/s10549-007-9864-5