Published in final edited form as:
Breast Cancer Res Treat. 2010 July ; 122(1): 281–285. doi:10.1007/s10549-009-0601-0.

Pooled analysis indicates that the *GSTT1* deletion, *GSTM1* deletion, and *GSTP1* Ile105Val polymorphisms do not modify breast cancer risk in *BRCA1* and *BRCA2* mutation carriers

Amanda B. Spurdle,
Division of Genetics and Population Health, Queensland Institute of Medical Research, 300 Herston Rd, Herston 4006, Australia

Paul Fahey,
Division of Genetics and Population Health, Queensland Institute of Medical Research, 300 Herston Rd, Herston 4006, Australia

Xiaoqing Chen,
Division of Genetics and Population Health, Queensland Institute of Medical Research, 300 Herston Rd, Herston 4006, Australia

Lesley McGuffog,
Department of Public Health and Primary Care, Cancer Research UK Genetic Epidemiology Unit, University of Cambridge, Cambridge, UK

kConFab,
The Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer, Peter MacCallum Cancer Centre, Melbourne, Australia

Douglas Easton,
Department of Public Health and Primary Care, Cancer Research UK Genetic Epidemiology Unit, University of Cambridge, Cambridge, UK

Susan Peock,
Department of Public Health and Primary Care, Cancer Research UK Genetic Epidemiology Unit, University of Cambridge, Cambridge, UK

Margaret Cook,
Department of Public Health and Primary Care, Cancer Research UK Genetic Epidemiology Unit, University of Cambridge, Cambridge, UK

EMBRACE,
Department of Public Health and Primary Care, Cancer Research UK Genetic Epidemiology Unit, University of Cambridge, Cambridge, UK

Jacques Simard,
Cancer Genomics Laboratory, Centre Hospitalier Universitaire de Québec and Laval University, Quebec, Canada

INHERIT,
Cancer Genomics Laboratory, Centre Hospitalier Universitaire de Québec and Laval University, Quebec, Canada

Tim R. Rebbeck,

Correspondence to: Georgia Chenevix-Trench, GeorgiaT@qimr.edu.au.

University of Pennsylvania School of Medicine, Philadelphia, USA

MAGIC,
University of Pennsylvania School of Medicine, Philadelphia, USA

Antonis C. Antoniou, and
Department of Public Health and Primary Care, Cancer Research UK Genetic Epidemiology Unit, University of Cambridge, Cambridge, UK

Georgia Chenevix-Trench
Division of Genetics and Population Health, Queensland Institute of Medical Research, 300 Herston Rd, Herston 4006, Australia

Georgia Chenevix-Trench: GeorgiaT@qimr.edu.au

Abstract

The GSTP1, GSTM1, and *GSTT1* detoxification genes all have functional polymorphisms that are common in the general population. A single study of 320 *BRCA1/2* carriers previously assessed their effect in *BRCA1* or *BRCA2* mutation carriers. This study showed no evidence for altered risk of breast cancer for individuals with the *GSTT1* and *GSTM1* deletion variants, but did report that the *GSTP1* Ile105Val (rs1695) variant was associated with increased breast cancer risk in carriers. We investigated the association between these three *GST* polymorphisms and breast cancer risk using existing data from 718 women *BRCA1* and *BRCA2* mutation carriers from Australia, the UK, Canada, and the USA. Data were analyzed within a proportional hazards framework using Cox regression. There was no evidence to show that any of the polymorphisms modified disease risk for *BRCA1* or *BRCA2* carriers, and there was no evidence for heterogeneity between sites. These results support the need for replication studies to confirm or refute hypothesis-generating studies.

Keywords

GST polymorphisms; BRCA1; BRCA2; Modifier gene

Introduction

Breast cancer risk is greatly increased in female carriers of germline mutations in the *BRCA1* or *BRCA2* genes compared with the general population. However, the estimated penetrance of deleterious mutations does vary according to study ascertainment, being somewhat lower in carriers recruited via population-based studies compared to those identified in studies of multiple case families, and risks have been found to vary depending on the cancer site of the first individual that led to the family ascertainment [1–3]. It is generally accepted that genetic modifiers explain some of this difference in penetrance and, indeed, recent studies by the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) have provided evidence showing that genetic variation outside of the *BRCA1* and *BRCA2* genes can modify risk of breast cancer in carriers of pathogenic *BRCA1* and *BRCA2* mutations [4–6].

Candidate breast cancer modifier genes include those that are involved in the metabolism of carcinogens. The phase II glutathione S-transferase genes catalyze the glutathione-mediated reduction of exogenous and endogenous electrophiles with broad and overlapping substrate specificity [7,8], generally producing readily excreted water-soluble compounds. Thus, allelic variants associated with altered detoxification rates of potential carcinogens have long been postulated to confer an increased susceptibility to cancer [9]. The *GSTP1*, *GSTM1*, and *GSTT1* genes have functional polymorphisms that are frequently present in the general

population. Inherited homozygous deletions of the *GSTT1* and *GSTM1* gene lead to the complete absence of enzyme activity [10–12], whereas the *GSTP1* A313G substitution results in an isoleucine to valine amino acid substitution at position 104, which has altered specific activity and decreased heat stability [13–15].

There is conflicting evidence for a role for *GST* functional polymorphisms with risk of breast and bladder cancer, and other smoking-related cancers [16–19]. However, their effects on breast cancer risk in carriers of *BRCA1* or *BRCA2* mutations have been reported in only a single study [20]. Their analysis of 320 *BRCA1/2* carriers showed no evidence for altered risk of breast cancer for individuals with the *GSTT1* and *GSTM1* deletion variants, but did report that the *GSTP1* Ile105Val variant was associated with increased breast cancer risk (HR 1.36 ($p = 0.04$) for heterozygotes, and HR 2.00 ($P = 0.01$) for homozygotes). After stratification by gene, the effect of the *GSTP1* variant remained significant among *BRCA2* carriers only (Hazard Ratio = 3.20 (95% CI 1.26–8.09, $P = 0.01$)).

We undertook a study to collate existing data for these polymorphisms from CIMBA consortium members to assess the association of GST polymorphisms with risk of breast cancer in a larger sample set.

Subjects

The characteristics of the study samples are shown in Table 1. A total of 473 *BRCA1* and 245 *BRCA2* carriers, from four sites within CIMBA, had been genotyped for the *GSTT1* and *GSTM1* deletion polymorphisms, and the *GSTP1* Ile105Val polymorphism. All sites provided information for the *GSTT1* and *GSTM1* polymorphisms, and all except the MAGIC site provided data for the *GSTP1* missense polymorphism. The ascertainment of carriers to these four sites is described in detail elsewhere [4]. Only carriers of pathogenic mutations were included. Ethical approvals for recruitment and genotyping were obtained from the institutional review boards or ethics committees at all the sites. Written informed consent was obtained from each participant.

Molecular methods

Genotyping for the MAGIC [21], and kConFab, EMBRACE and INHERIT samples [22], was as described previously. In brief, PCR-agarose methodology was used to detect the homozygous wildtype and *GSTT1* and *GSTM1* deletion variants; ABI Prism 7700 Sequence Detection System (SDS) methodology was used for genotyping the *GSTP1* A to G Ile105Val variant (rs1695).

Statistical methods

Individuals with a first primary invasive breast cancer diagnosis were considered to be affected, while individuals with no reported breast or ovarian cancer were censored at the age of interview, or at the age of prior bilateral prophylactic mastectomy. Individuals with a first primary ovarian cancer diagnosis were censored as unaffected at the age at onset of ovarian cancer. Analyses of association between genotype and breast cancer risk were performed using Cox regression with time to breast cancer onset as the end point. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated separately for *BRCA1* and *BRCA2* carriers, and in each, study group and year of birth (categorized into subgroups 1910–1939, 1940–1949, 1950–1959, and 1960+) were included as covariates in the analysis. Secondary analyses also adjusted for ethnicity (Caucasian, other). Adjustment for other potential confounders was not considered due to the relatively small sample size of this study, which included only a limited number of CIMBA subjects with existing genotyping data. Confidence limits for the rate ratio were calculated using a robust variance approach to allow for the dependence among individuals in the same family [23]. In order to address the

problem of non-random sampling of mutation carriers with respect to the disease phenotype, we analyzed using the weighted Cox regression approach [24], where individuals were weighted such that observed breast cancer incidence rates in the study sample are consistent with established breast cancer risk estimates for *BRCA1* and *BRCA2* mutation carriers [1]. R version 2.7.0 was used for statistical analyses.

Results and Discussion

The estimated hazard ratios associated with the *GST* polymorphisms are shown in Table 2. There was no evidence for an association between any of the *GST* polymorphisms and risk in *BRCA1* or *BRCA2* mutation carriers. This included the *GSTP1* Ile105Val variant: the HR (95% CI) for this ValVal homozygote genotype was 0.89 (0.44–1.49) for *BRCA1* carriers, and 0.81 (0.40–1.65) for *BRCA2* carriers. There was no evidence for heterogeneity in the hazard ratios between studies for any of the three polymorphisms analyzed ($P \geq 0.3$). The overall findings were little different when analyses were adjusted additionally for ethnicity. For example, the HR (95% CI) for the *GSTP1* ValVal genotype was 0.92 (0.46–1.84) for *BRCA1* carriers, and 0.80 (0.39–1.65) for *BRCA2* carriers.

Although our genotyping method for *GSTM1* and *GSTT1* does not distinguish heterozygotes from wild-type homozygotes [25], our data provide no evidence for association between breast cancer risk for carriers and three *GST* common polymorphisms. Notably, the *GSTP1* 105Val variant, which was previously reported to be associated with *increased* risk of breast cancer in a small study of 90 *BRCA2* carriers [20], was associated with non-significant *reduced* risk for *BRCA2* carriers in our larger sample of 245 women with *BRCA2* mutations. Although the sample size of this study is still relatively small, there is a statistically significant difference ($P = 0.02$) between the HR for *BRCA2* in this study and that reported by Kadouri et al [20]. These results support the need for replication studies to confirm or refute hypothesis-generating studies, including analyses that use existing unpublished data collated by consortia.

References

1. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003; 72(5):1117–1130. [PubMed: 12677558]
2. Begg CB, Haile RW, Borg A, Malone KE, Concannon P, Thomas DC, Langholz B, Bernstein L, Olsen JH, Lynch CF, et al. Variation of breast cancer risk among BRCA1/2 carriers. JAMA. 2008; 299(2):194–201. [PubMed: 18182601]
3. Simchoni S, Friedman E, Kaufman B, Gershoni-Baruch R, Orr-Urtreger A, Kedar-Barnes I, Shiri-Sverdlov R, Dagan E, Tsabari S, Shohat M, et al. Familial clustering of site-specific cancer risks associated with BRCA1 and BRCA2 mutations in the Ashkenazi Jewish population. Proc Natl Acad Sci USA. 2006; 103(10):3770–3774. [PubMed: 16537453]
4. Antoniou AC, Sinilnikova OM, Simard J, Leone M, Dumont M, Neuhausen SL, Struewing JP, Stoppa-Lyonnet D, Barjhoux L, Hughes DJ, et al. RAD51 135G→C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies. Am J Hum Genet. 2007; 81(6):1186–1200. [PubMed: 17999359]
5. Antoniou AC, Spurdle AB, Sinilnikova OM, Healey S, Pooley KA, Schmutzler RK, Versmold B, Engel C, Meindl A, Arnold N, et al. Common breast cancer-predisposition alleles are associated with breast cancer risk in BRCA1 and BRCA2 mutation carriers. Am J Hum Genet. 2008; 82(4): 937–948. [PubMed: 18355772]
6. Antoniou AC, Sinilnikova OM, McGuffog L, Healey S, Nevanlinna H, Heikkinen T, Simard J, Spurdle AB, Beesley J, Chen X, et al. Common variants in LSP1, 2q35 and 8q24 and breast cancer

risk for BRCA1 and BRCA2 mutation carriers. Hum Mol Genet. 2009; 18(22):4442–4456. [PubMed: 19656774]

7. Adang AE, Meyer DJ, Brussee J, Van der Gen A, Ketterer B, Mulder GJ. Interaction of rat glutathione S-transferases 7–7 and 8–8 with gamma-glutamyl- or glycyl-modified glutathione analogues. Biochem J. 1989; 264(3):759–764. [PubMed: 2619714]
8. Hengstler JG, Arand M, Herrero ME, Oesch F. Polymorphisms of N-acetyltransferases, glutathione S-transferases, microsomal epoxide hydrolase and sulfotransferases: influence on cancer susceptibility. Recent Results Cancer Res. 1998; 154:47–85. [PubMed: 10026993]
9. Strange, RC.; Fryer, AA. The glutathione S-transferases: influence of polymorphism on cancer susceptibility. In: Vineis, P., editor. Metabolic polymorphisms and susceptibility to cancer. Vol. 148. IARC Scientific Publications; Lyon: 1999. p. 231-249.
10. Board PG. Biochemical genetics of glutathione-S-transferase in man. Am J Hum Genet. 1981; 33(1):36–43. [PubMed: 7468592]
11. Pemble S, Schroeder KR, Spencer SR, Meyer DJ, Hallier E, Bolt HM, Ketterer B, Taylor JB. Human glutathione S-transferase theta (GSTT1): cDNA cloning and the characterization of a genetic polymorphism. Biochem J. 1994; 300(Pt 1):271–276. [PubMed: 8198545]
12. Seidegard J, Vorachek WR, Pero RW, Pearson WR. Hereditary differences in the expression of the human glutathione transferase active on trans-stilbene oxide are due to a gene deletion. Proc Natl Acad Sci USA. 1988; 85(19):7293–7297. [PubMed: 3174634]
13. Ali Osman F, Akande O, Antoun G, Mao JX, Buolamwini J. Molecular cloning, characterization, and expression in Escherichia coli of full-length cDNAs of three human glutathione S-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. J Biol Chem. 1997; 272(15):10004–10012. [PubMed: 9092542]
14. Johansson AS, Stenberg G, Widersten M, Mannervik B. Structure-activity relationships and thermal stability of human glutathione transferase P1-1 governed by the H-site residue 105. J Mol Biol. 1998; 278(3):687–698. [PubMed: 9600848]
15. Zimniak P, Nanduri B, Pikula S, Bandorowicz Pikula J, Singhal SS, Srivastava SK, Awasthi S, Awasthi YC. Naturally occurring human glutathione S-transferase GSTP1-1 isoforms with isoleucine and valine in position 104 differ in enzymic properties. Eur J Biochem. 1994; 224(3): 893–899. [PubMed: 7925413]
16. Bugano DD, Conforti-Froes N, Yamaguchi NH, Baracat EC. Genetic polymorphisms, the metabolism of estrogens and breast cancer: a review. Eur J Gynaecol Oncol. 2008; 29(4):313–320. [PubMed: 18714561]
17. Garcia-Closas M, Malats N, Silverman D, Dosemeci M, Kogevinas M, Hein DW, Tardon A, Serra C, Carrato A, Garcia-Closas R, et al. NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. Lancet. 2005; 366(9486):649–659. [PubMed: 16112301]
18. Sampaio AC, Morari EC, Bufalo NE, Leite JL, Lima CS, Ward LS. Lack of influence of glutathione S-transferase genotype profile on cancer susceptibility in smokers and nonsmokers. Med Sci Monit. 2009; 15(1):CR10–CR15. [PubMed: 19114965]
19. Sergentanis TN, Economopoulos KP. GSTT1 and GSTP1 polymorphisms and breast cancer risk: a meta-analysis. Breast Cancer Res Treat. 200910.1007/s10549-009-520-0
20. Kadouri L, Kote-Jarai Z, Hubert A, Baras M, Abeliovich D, Hamburger T, Peretz T, Eeles RA. Glutathione-S-transferase M1, T1 and P1 polymorphisms, and breast cancer risk, in BRCA1/2 mutation carriers. Br J Cancer. 2008; 98(12):2006–2010. [PubMed: 18542066]
21. Kanetsky PA, Holmes R, Walker A, Najarian D, Swoyer J, Guerry D, Halpern A, Rebbeck TR. Interaction of glutathione S-transferase M1 and T1 genotypes and malignant melanoma. Cancer Epidemiol Biomarkers Prev. 2001; 10(5):509–513. [PubMed: 11352862]
22. Spurdle AB, Webb PM, Purdie DM, Chen X, Green A, Chenevix-Trench G. Polymorphisms at the glutathione S-transferase GSTM1, GSTT1 and GSTP1 loci: risk of ovarian cancer by histological subtype. Carcinogenesis. 2001; 22(1):67–72. [PubMed: 11159743]
23. Huber, PJ. The behaviour of maximum likelihood estimates under non-standard conditions. Fifth Berkeley symposium in mathematical statistics and probability; 1967; Berkeley, California: University of California Press; 1967. p. 221-233.

24. Antoniou AC, Goldgar DE, Andrieu N, Chang-Claude J, Brohet R, Rookus MA, Easton DF. A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. Genet Epidemiol. 2005; 29(1):1–11. [PubMed: 15880399]

25. Parl F. A need for true GSTM1 and GSTT1 genotyping. Cancer Epidemiol Biomarkers Prev. 2009; 18(10):2793. [PubMed: 19773452]

Appendix

kConFab—The Kathleen Cuningham Consortium for Research into Familial Breast Cancer

We wish to thank Heather Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, the heads and staff of the Family Cancer Clinics, and the Clinical Follow Up Study (funded by NHMRC grants 145684, 288704, and 454508) for their contributions to this resource, and the many families who contribute to kConFab. The kConFab is supported by grants from the National Breast Cancer Foundation, the National Health and Medical Research Council (NHMRC), and by the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia. ABS is an NHMRC Senior Research Fellow, and GC-T is an NHMRC Senior Principal Research Fellow.

Epidemiological study of BRCA1 and BRCA2 mutation carriers (EMBRACE)

DE is the PI of the study. DE, SP, and MC are funded by Cancer Research, UK Grants C1287/A10118 and C1287/A8874. EMBRACE Collaborating Centers are: Coordinating Centre, Cambridge: Susan Peock, Margaret Cook, Clare Oliver, Debra Frost; North of Scotland Regional Genetics Service, Aberdeen: Helen Gregory, Zosia Miedzybrodzka; Northern Ireland Regional Genetics Service, Belfast: Patrick Morrison; West Midlands Regional Clinical Genetics Service, Birmingham: Trevor Cole, Carole McKeown, Amy Taylor; South West Regional Genetics Service, Bristol: Alan Donaldson; East Anglian Regional Genetics Service, Cambridge: Joan Paterson; Medical Genetics Services for Wales, Cardiff: Alexandra Murray, Mark Rogers, Emma McCann; St James's Hospital, Dublin & National Centre for Medical Genetics, Dublin: John Kennedy, David Barton; South East of Scotland Regional Genetics Service, Edinburgh: Mary Porteous; Peninsula Clinical Genetics Service. Exeter: Carole Brewer, Emma Kivuva, Anne Searle, Selina Goodman; West of Scotland Regional Genetics Service, Glasgow: Rosemarie Davidson, Victoria Murday, Nicola Bradshaw, Lesley Snadden, Mark Longmuir, Catherine Watt; South East Thames Regional Genetics Service, Guys Hospital London: Louise Izatt, Gabriella Pichert, Caroline Langman. North West Thames Regional Genetics Service. Harrow: Huw Dorkins; Leicestershire Clinical Genetics Service; Leicester: Julian Barwell; Yorkshire Regional Genetics Service, Leeds: Carol Chu, Tim Bishop, Julie Miller; Merseyside & Cheshire Clinical Genetics Service. Liverpool: Ian Ellis; Manchester Regional Genetics Service, Manchester: D Gareth Evans, Fiona Lalloo, Felicity Holt; North East Thames Regional Genetics Service, NE Thames: Alison Male, Anne Robinson. Nottingham Centre for Medical Genetics, Nottingham: Carol Gardiner; Northern Clinical Genetics Service, Newcastle: Fiona Douglas, Oonagh Claber; Oxford Regional Genetics Service, Oxford: Lisa Walker, Diane McLeod; The Institute of Cancer Research and Royal Marsden NHS Foundation Trust: Ros Eeles, Susan Shanley, Nazneen Rahman, Richard Houlston, Elizabeth Bancroft, Lucia D'Mello, Elizabeth Page, Audrey Ardern-Jones, Anita Mitra; North Trent Clinical Genetics Service, Sheffield: Jackie Cook, Oliver Quarrell, Cathryn Bardsley; South West Thames Regional Genetics Service, London: Shirley Hodgson, Sheila Goff, Glen Brice, Lizzie Winchester; Wessex Clinical Genetics Service; Princess Anne Hospital, Southampton: Diana Eccles, Anneke Lucassen, Gillian Crawford,

Emma Tyler, Donna McBride. ACA is a Cancer Research UK Senior Cancer Research Fellow. CIMBA data management is supported by Cancer Research UK. The kConFab and EMBRACE genotyping was supported by an NHMRC Programme grant to GCT. MAGIC data collection and analysis was supported by R01-CA102776 to TRR.

Interdisciplinary Health Research International Team on Breast Cancer Susceptibility (INHERIT BRCAs)

Jacques Simard, Francine Durocher, Rachel Laframboise, Marie Plante, Centre Hospitalier Universitaire de Québec & Laval University, Québec, Canada; Peter Bridge, Jilian Parboosingh, Molecular Diagnostic Laboratory, Alberta Children's Hospital, Calgary, Canada; Jocelyne Chiquette, Hôpital du Saint-Sacrement, Québec, Canada; Bernard Lespérance, Hôpital du Sacré-Cœur de Montréal, Montréal, Canada. Jacques Simard- J.S. is Chairholder of the Canada Research Chair in Oncogenetics. This study was supported by the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program.

Modifiers and Genetics in Cancer (MAGIC)

This work was supported by the NIH grants R01-CA102776 and R01-CA083855 (to TRR). The MAGIC Consortium includes the following centers and individuals: Baylor- Charles A. Sammons Cancer Center (Joanne L, Blum, M.D. Ph.D.; Becky Althaus, R.N., C.G.C.; Gaby Ethington), Baylor College of Medicine (Claire Noll; Sharon Plon, M.D., Ph.D.), Beth Israel Deaconess Medical Center (Nadine Tung, M.D.), City of Hope National Medical Center (Sharon Sand; Jeffrey N. Weitzel, M.D.), Creighton University (Carrie Snyder, B.A.; Henry T. Lynch, M.D.; Patrice Watson, Ph.D.), Dana-Farber Cancer Institute (Kathryn Stoeckert; Judy E. Garber, M.D., M.P.H.), Duke University (Sydnee Crankshaw; Joellen Schildkraut, Ph.D.), Evanston Northwestern Healthcare Center for Medical Genetics (Suzanne M. O'Neill, Ph.D.; Christina Selkirk; Wendy S. Rubinstein, M.D., Ph.D.), Fox Chase Cancer Center (Mary B. Daly, M.D., Ph.D.; Andrew Godwin, Ph.D.), Queensland Institute of Medical Research (Georgia Chenevix-Trench), Georgetown University (Claudine Isaacs, M.D.), Jonsson Comprehensive Cancer Center at the University of California-Los Angeles (Joyce Seldon; Patricia A. Ganz, M.D.), Mayo Clinic College of Medicine (Linda Wadum; Fergus Couch, Ph.D.), University of Chicago (Shelly Cummings; Olufunmilayo Olopade, M.D.), University of California-Irvine (Susan L. Neuhausen, Ph.D.; Linda Steele), University of Pennsylvania Health System (Susan Domchek, M.D.; Katherine Nathanson M.D.; Tara Friebel, M.P.H.; Timothy Rebbeck, Ph.D.), University of Texas Southwestern (Gail Tomlinson, M.D.), University of Vienna (Christian Singer, M.D.), and Women's College Hospital (Steven A. Narod, M.D.).

Breast Cancer Res Treat. Author manuscript; available in PMC 2011 April 12.

Table 1

Characteristics of Study Subjects

	BRCA1		***BRCA2***		**Group TOTAL**
	n	**(% of total)**	***n***	**(% of total)**	
EMBRACE	*236*	(49.9)	*90*	(36.7)	326
KconFaB	93	(19.7)	73	(29.8)	166
Inherit	73	(15.4)	82	(33.5)	155
Magic*	71	(15.0)	0	(0.0)	71
Total	*473*		*245*		*718*
Affected with breast cancer[a]	251	(53.1)	136	(55.5)	
Affected with ovarian cancer[a]	42	(8.9)	13	(5.3)	
Unaffected[b]	180	(38.1)	96	(39.2)	

** *GSTP1* genotypes were not available for this sample set*

[a] Refers to first cancer for individuals reporting both breast and ovarian cancer. Individuals with ovarian cancer were censored as unaffected at the age of diagnosis for analysis

[b] Includes unaffected individuals censored at the age of prior bilateral mastectomy

Table 2

Association of *GSTT1*, *GSTM1*, and *GSTP1* genotypes with breast cancer risk in *BRCA1* and *BRCA2* carriers

Gene	Genotype	*BRCA1*				*BRCA2*			
		Genotype frequency	Adjusted group and year of birth			Genotype frequency	Adjusted group and year of birth		
			P	HR	(95% CI)		P	HR	(95% CI)
GSTT1	Null	0.20	0.60	0.90	(0.59–1.36)	0.14	0.71	1.13	(0.59–2.19)
GSTM1	Null	0.52	0.3	1.19	(0.84–1.67)	0.48	0.5	0.84	(0.53–1.33)
GSTP1	AG	0.47	0.82	1.05	(0.70–1.57)	0.42	0.86	1.05	(0.62–1.77)
	GG	0.10	0.74	0.89	(0.44–1.79)	0.16	0.56	0.81	(0.40–1.65)