Do MDM2 SNP309 and TP53 R72P Interact in Breast Cancer Susceptibility? A Large Pooled Series from the Breast Cancer Association Consortium


Abstract

Association studies in large series of breast cancer patients can be used to identify single-nucleotide polymorphisms (SNP) contributing to breast cancer susceptibility. Previous studies have suggested associations between variants in TP53 (R72P) and MDM2 (SNP309) and cancer risk. Data from molecular studies suggest a functional interaction between these genes. We therefore investigated the effect of TP53 R72P and MDM2 SNP309 on breast cancer risk and age at onset of breast cancer in a pooled series of 5,191 cases and 3,834 controls from the Breast Cancer Association Consortium (BCAC). Breast cancer risk was not found to be associated with the combined variant alleles [odds ratio (OR), 1.00; 95% confidence interval (95% CI), 0.81–1.23]. Estimated ORs were 1.01 (95% CI, 0.93–1.09) per MDM2 SNP309 allele and 0.98 (95% CI, 0.91–1.04) for TP53 R72P. Although we did find evidence for a 4-year earlier age at onset for carriers of both variant alleles in one of the breast cancer patient series of the BCAC (the German series), we were not able to confirm this effect in the pooled analysis. Even so, carriers of both variant alleles did not have different risk estimates for bilateral or estrogen receptor–positive breast cancer. In conclusion, in this large collaborative study, we did not find an association of MDM2 SNP309 and TP53 R72P, separately or in interaction, with breast cancer. This suggests that any effect of these two variant alleles would be very small and possibly confined to subgroups that were not assessed in our present study. [Cancer Res 2007;67(19):9584–90]

Introduction

Highly penetrant variant alleles of BRCA1 and BRCA2 explain about 2% to 4% of breast cancers in the general female population (1). The remainder of breast cancer susceptibility is likely to be due to multiple susceptibility alleles conferring low to moderate risks (1–4). Rare variants in ATM, CHEK2 (1, 5, 6), BRIP1 (7), and PALB2 (8) confer an ∼2-fold risk of breast cancer, and the coding variant CASP8 D302H is associated with a reduced risk of breast cancer (9). These variants, however, only account for a minority of the hereditary component of breast cancer. Association studies in large series of patients, such as the Breast Cancer Association Consortium (BCAC; refs. 3, 9), have been able to identify single-nucleotide polymorphisms (SNP) contributing to breast cancer susceptibility. Genes that have a function in DNA damage response, such as TP53 and its key regulator MDM2 (10), are strong candidates for breast cancer susceptibility genes.

MDM2 is overexpressed in various cancers and there are indications that this leads to a worse prognosis at least in some cancers (11). One polymorphism in the promoter region of MDM2, SNP309 (T>G change at nucleotide 309 in the first intron; rs2279744), has been reported to be associated with earlier (>10 years) onset of breast cancer in Li-Fraumeni patients (12–14) as well as with earlier onset of sporadic soft tissue sarcoma (12) and (female) colon cancer (15, 16) and with risk for gastric carcinoma (17). SNP309 leads to increased expression of the Mdm2 mRNA and attenuated function of the p53 protein (12). To date, however, no evidence for an association between SNP309 and breast cancer outside of Li-Fraumeni patients has been found. One large study in African-Americans and Whites in North Carolina (n = 2,037; ref. 18) and several small studies in Chinese (n = 366; ref. 19), German non-BRCA1/2 familial (n = 549; ref. 20), British (n = 351; ref. 21), Baltimore (n = 293; ref. 22), and Turkish (n = 223; ref. 23) breast cancer cases found no evidence for an increased risk of breast cancer. However, it has been suggested that SNP309 could alter effects of hormones such as estrogen on the MDM2 promoter in the context of breast tumorigenesis (16, 24, 25) and that SNP309 may be specifically associated with the early age at onset in estrogen receptor–positive tumors (25).

TP53 is frequently somatically mutated in breast tumors, whereas germ-line mutations in TP53, which are present in <1% of the general breast cancer population (26), are the major cause of the Li-Fraumeni syndrome (14). A coding variant of TP53, R72P (G>C change at nucleotide 215 in the first exon; rs1042522), has been associated with an increased risk for human papillomavirus–related cervical cancer and several other cancer types in some studies (lung, prostate, ovary, and skin), but the results have been inconsistent (26, 27). Earlier age of onset for...
colorectal cancer in TP53 R72P variant carriers was reported in a small study of hereditary nonpolyposis colorectal cancer patients (28). A pooled analysis by the BCAC found no evidence of an increased risk of breast cancer associated with R72P (3). However, the TP53 Pro variant has been reported to lead to worse survival in breast cancer patients (29) and other cancers (27), which may be related to its different apoptotic and DNA repair potential (30, 31). In addition, there is some evidence that it may be associated with earlier onset of breast cancer in BRCA1 or BRCA2 mutation carriers (29, 32, 33).

Earlier, we confirmed the finding of Bond et al. (12) that MDM2 SNP309 is associated with earlier age at onset of breast cancer in Li-Fraumeni patients with a TP53 germ-line mutation (14). However, we found no associations with age at onset in cancer patients with a Li-Fraumeni-like family history but no TP53 mutation (14). This raises the possibility that, although there may be no effect of variant alleles of TP53 and MDM2 on their own, in combination they may lead to an increased risk of cancer or earlier age at onset. A combination of variant alleles in TP53 R72P (Pro/Pro) and MDM2 SNP309 (GG and TG) was reported to modify the age of onset in Li-Fraumeni patients (13), and a suggestion for such an effect was seen in colorectal cancer (34). In addition, preliminary data from a German study suggested that TP53 R72P and MDM2 SNP309 may modulate the age at onset of breast cancer (35). We therefore investigated the combined effects of TP53 R72P and MDM2 SNP309 on breast cancer risk and the age at onset in breast cancer patients in a large pooled series of cases and controls from the BCAC. We also examined specifically the association of these polymorphisms with bilateral breast cancer and estrogen receptor–positive breast cancer.

### Materials and Methods

#### Subjects
Breast cancer cases from five European studies within the BCAC, together with healthy controls from the same studies, were included in this analysis (Table 1). Three of the studies [Hannover Breast Cancer Study (HaBCS), Amsterdam Breast Cancer Study (ABCS), and British Breast Cancer (BBC)] specifically ascertained cases based on bilaterality. All breast cancers were invasive, except 13 cases in HaBCS and 23 cases in ABCS. All contributing groups included data on family history of breast cancer cases (data missing for 11% of the cases); some additional data on tumor grade and estrogen receptor–positive breast cancer.

#### Genotyping
Genotyping assays were done by each group separately (see Table 1 for assay description). Primer (and probe) sequences are available from the authors on request. The samples included had previously shown good call rates and concordance when genotyped in duplicate (3, 9).

### Table 1. Characteristics of the studies and genotyping assays

<table>
<thead>
<tr>
<th>Contributing groups and studies</th>
<th>Design</th>
<th>Description of case subjects and ascertainment (age range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland: HeBCS (40)</td>
<td>Hospital-based case-control study</td>
<td>Consecutive incident cases from the Department of Oncology, Helsinki University Central Hospital, 1997 to 1998 (22–96 y)</td>
</tr>
<tr>
<td>Germany: HaBCS and bilateral breast cancer patients (41, 42)</td>
<td>Hospital-based case-control studies</td>
<td>Case patients who received radiotherapy for breast cancer at Hannover Medical School between 1997 and 2003 (27–91 y)</td>
</tr>
<tr>
<td>Netherlands: ABCS (a) Bilateral Breast Cancer Study (43); (b) unselected series of breast cancer patients &lt;30 y of age (44)</td>
<td>(a) Case-case study; (b) hospital-based consecutive cases; healthy blood bank controls</td>
<td>(a) Prevalent bilateral breast cancer cases ages &lt;50 y at diagnosis of first breast cancer from two hospitals, 1966 to 2000 (22–51 y); (b) all operable breast cancer patients ages &lt;50 y diagnosed 1974 to 1994 in four Dutch hospitals (Amsterdam and Leiden; 23–50 y)</td>
</tr>
<tr>
<td>United Kingdom, Cambridge: SEARCH (45)</td>
<td>Population-based case-control study</td>
<td>Two groups of case patients (prevalent and incident) identified through East Anglian Cancer Registry; patients diagnosed before age 55 y in 1991 to 1996 and still alive when study started in 1996 and patients diagnosed before age 70 y since 1996 (25–65 y)</td>
</tr>
<tr>
<td>United Kingdom, London: BBC (46, 47)</td>
<td>Population-based case-control study</td>
<td>Cases with two primary breast cancers and “moderate risk” unilateral cases ascertained through English and Scottish Cancer Registries: (a) two primaries-breast cancer cases who developed a first primary before age 65 y in 1971 or later and who subsequently developed a second primary (26–65 y); (b) for a subset of cases with two primaries, matched unilateral cases, diagnosed before age 65 y with at least one first-degree relative with breast cancer diagnosed before age 70 y, were selected; all cases reported being Caucasian (27–64 y)</td>
</tr>
</tbody>
</table>

**Abbreviations:** MOG, Mammography Oestrogens and Growth factors; RCT, randomized clinical trial.

*KBioscience (http://www.kbioscience.co.uk); Taqman, Applied Biosystems (http://www2.appliedbiosystems.com); Illumina (http://www.illumina.com).
controls than published earlier. The subset of bilateral cases in ABCS was analyzed for MDM2 only.

**Statistical methods.** Deviations from the genotype frequencies in the controls from those expected under Hardy-Weinberg equilibrium were evaluated by a $\chi^2$ test (1 degree of freedom) for each study group separately. Breast cancer risks for each SNP were estimated as odds ratios (OR) for the rare homozygote, the heterozygote, and per-allele (each copy of rare allele) with the common homozygote as the referent category. Combined OR estimates across all studies were obtained using logistic regression by including study as a categorical covariate. Differences in mean and median among groups of common allele homozygotes, heterozygotes, and rare allele homozygotes were tested by ANOVA and Student’s $t$-test, respectively. All statistical tests were two sided. All analyses were done using Statistical Package for the Social Sciences (SPSS, Inc.).

**Results**

In total, 5,836 breast cancer cases (4,827 unilateral, 1,009 bilateral) and 4,673 controls were genotyped for MDM2 SNP309 and 8,345 cases (7,579 unilaterals, 766 bilaterals) and 6,849 controls were genotyped for TP53 R72P (Table 2). There was no evidence for deviation from the Hardy-Weinberg equilibrium for any of the individual control series, except for SNP309 in the SEARCH study ($P = 0.004$ for overall genotype distribution) where there was a shortage of heterozygotes (959 observed, 1,021 expected).

The ORs associated with MDM2 SNP309 heterozygotes and GG homozygotes, compared with TT homozygotes, were 1.04 [95% confidence interval (CI), 0.95–1.13] and 0.90 (95% CI, 0.80–1.02), respectively (per-allele OR, 1.01; 95% CI, 0.93–1.09). The corresponding ORs for TP53 R72P were 0.98 (95% CI, 0.91–1.05) for heterozygotes and 0.97 (95% CI, 0.86–1.11) in homozygotes (per-allele OR, 0.98; 95% CI, 0.91–1.04). Thus, there was no evidence of an association with either SNP in the combined data set. No evidence for an association with breast cancer was detected for either SNP in any individual study (Table 2). The borderline significant effect of the TG genotype in the SEARCH study was no longer apparent if the frequency in the cases was compared with the expected Hardy-Weinberg frequency in the controls. ORs were similar when restricted to unilateral and bilateral cases (Table 2). There was no indication for heterogeneity among contributing groups for MDM2 SNP309 ($P < 0.01$), which was found to be attributable to the series from Finland ($P = 0.99$ after excluding this group).

Table 3 summarizes the ORs for combined genotypes at TP53 R72P and MDM2 SNP309. In the pooled series, 4.5% of cases and 8.2% of controls were carriers of variant alleles of both SNPs [i.e., TP53 R72P CC (Pro/Pro) and MDM2 SNP309 GG or TG]. There was no evidence of a difference in the frequency of these combined genotypes between cases and controls. The median and mean ages at onset of the first breast cancer did not differ significantly between the different genotypes in MDM2 (median ages, 49, 49, and 50 years for genotypes TT, TG, and GG, respectively) or TP53 (median ages, 49, 50, and 50 years for GG, GC, and CC). Evidence for a slightly younger median age at onset for the combined MDM2 TG/GG TP53 CC genotype carriers was initially found in the HaBCS study (4 years younger; Table 3; ref. 35). However, in the pooled

## Table 1. Characteristics of the studies and genotyping assays (Cont’d)

<table>
<thead>
<tr>
<th>Description of control subjects and ascertainment (age range)</th>
<th>Participation rates</th>
<th>Genotyping platform(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A random sample of 28% of all females blood donors (breast cancer-free), recruited from the same geographic region in Southern Finland (18–65 y) in 2003</td>
<td>79% of the case subjects; for 82% of the control subjects DNA was available</td>
<td>BFLP (MDM2 SNP309); Amplifluor fluorescent genotyping (KBioscience; TP53 R72P)</td>
</tr>
<tr>
<td>Anonymous random blood donors at Hannover medical School (44–81 y)</td>
<td>Approximately 80% of case subjects and 50% of control subjects contacted agreed to give a blood sample</td>
<td>Restriction enzyme-based assays</td>
</tr>
<tr>
<td>Healthy, Dutch blood bank controls (female and male; Leiden)</td>
<td>(a) 80% of all patients invited to participate; (b) all patients with paraffin-embedded tissue blocks available (normal tissue) from the pathology archives and successful DNA isolation (75–85%)</td>
<td>Taqman</td>
</tr>
<tr>
<td>Selected from the European Prospective Investigation of Cancer, Norfolk cohort study of 25,000 individuals (45–74 y), based in the same geographic region as case subjects</td>
<td>64% of eligible case subjects and 41% of invited control subjects provided a blood sample</td>
<td>Taqman</td>
</tr>
<tr>
<td>(a) BBC—a friend, sister-in-law, or daughter-in-law of case patients (24–81 y); (b) MOG—additional controls were selected from a cohort of healthy women participating in a RCT of mammographic screening. These controls were frequency matched to cases on geographic area of residence (48–51 y); all controls reported being Caucasian</td>
<td>(a) BBC: 68% of case subjects and 76% of control subjects gave a blood sample; (b) MOG: 82% gave a blood sample</td>
<td>BFLP (MDM2 SNP309); Illumina, Golden Gate assay (TP53 R72P)</td>
</tr>
</tbody>
</table>
data set, after excluding the hypothesis-generating study, this effect was no longer apparent (Table 3; Fig. 1). In addition, there was no evidence for an association of breast cancer with the same combination of both SNPs (MDM2 TG/GG TP53 CC): OR, 1.00 (95% CI, 0.81–1.23; Table 3); this OR was similar for unilateral (1.01; 95% CI, 0.81–1.27) and bilateral breast cancer (0.95; 95% CI, 0.62–1.45). There was no indication for heterogeneity in the OR among contributing groups (P = 0.84).

OR estimates did not differ with family history of breast cancer [pooled data, per-allele OR for breast cancers with or without a family history, respectively, in MDM2 were 1.10 (95% CI, 0.94–1.29) and 1.00 (95% CI, 0.91–1.08) and in TP53 were 0.97 (95% CI, 0.84–1.12) and 0.98 (95% CI, 0.91–1.05)]. Risk estimates did also not differ with respect to estrogen receptor status [per-allele OR for estrogen-negative and estrogen-positive breast cancers in MDM2 were 1.01 (95% CI, 0.84–1.21) and 1.07 (95% CI, 0.96–1.20), respectively, and in TP53 were 0.99 (95% CI, 0.85–1.15) and 1.05 (95% CI, 0.96–1.15), respectively] or tumor grade (data not shown). Furthermore, risk estimates of combined variant alleles of MDM2 TG/GG and TP53 CC did also not differ with regard to family history of breast cancer [with and without: OR, 1.03 (95% CI, 0.70–1.53) and 0.96 (95% CI, 0.77–1.20), respectively] or with estrogen receptor status [negative and positive: OR, 1.09 (95% CI, 0.70–1.70) and 1.13 (95% CI, 0.85–1.49)].

Discussion

We found no increased risk of breast cancer (unilateral or bilateral) or of earlier age at onset in the general population for carriers of the MDM2 SNP309 variant allele. We had already shown that if there was any association of TP53 R72P with breast cancer, it must be very weak (the upper 95% CI for rare homozygotes was 1.15 and for heterozygotes was 1.04; ref. 3). We have now shown that the same is true for MDM2 SNP309. This finding, in a very large study, confirms some earlier publications (18–23).

If anything, we found some evidence of a protective effect of the GG genotype of MDM2 (GG versus TG/TT: OR, 0.88; 95% CI, 0.79–0.99; P = 0.02; see Table 3); however, this would no longer be significant after adjusting for multiple testing. In addition, this protective effect seemed to be most apparent in the TP53 CC genotype (Table 3), which might suggest an interaction. However,
this interaction was not found to be significant in a model including an interaction term for both SNPs (data not shown). Such an effect would probably only be expected if Mdm2 preferentially ubiquitinated the p53 Pro variant protein for degradation; as far as we know, this has not been reported. In addition, both the effect of the MDM2 GG genotype and the results in Table 3 were no longer significant after exclusion of the SEARCH study.

The general lack of evidence for effects of individual SNPs in association studies probably reflects that in fact only a small proportion of SNPs are associated with disease but also that most studies are underpowered to detect small effects (3, 9). However, it may also be that gene-gene and gene-environment interactions are of more importance than main effects (2). A plausible pair of candidates for a gene-gene interaction is TP53 and MDM2 based on their functions, known functional interaction, data in Li-Fraumeni patients (13), and preliminary data in German breast cancer patients (35). We investigated the interaction between these two SNPs in a large series of breast cancer patients, but we found that individuals with the presumed risk phenotype (i.e., CC in TP53 and GG or TG in MDM2) do not have a detectably increased risk of breast cancer. Although we pooled large numbers of cases and controls, it should be noted that we still had limited power to detect small interaction effects (\( f_{80\%} \) power to detect interactions with an OR of >1.8, assuming an OR of 1.1 for both SNP309 and R72P; refs. 36, 37). It may also be that any or both of these SNPs (SNP309 and R72P) will have an effect in breast cancer only in interaction with other SNPs. After an initial stratification by genotype of the German hospital-based breast cancer series, we found evidence for an earlier age at onset but only for carriers of the putative risk MDM2 GT/TT and TP53 CC genotype (35). However, this finding could not be confirmed when this analysis was extended to the combined data set. Hence, the earlier age of onset in the German group is likely due to chance, although it might reflect differences in genetic background or environmental factors of that specific population.

The mean age of the German patients was higher than that in the pooled data set (Fig. 1). However, stratified analyses for age did not reveal earlier age at onset for any genotype specifically in the older age groups, neither within the German data set nor in the pooled data (data not shown). Although we found evidence for heterogeneity among contributing groups for MDM2 SNP309, which was attributable to the series from Finland, we did not consider this a

Table 3. Risk estimates and age at onset of breast cancer (case-control comparison) of pooled data in combined variant alleles of MDM2 SNP309 and TP53 R72P

<table>
<thead>
<tr>
<th>TP53 R72P*</th>
<th>MDM2 SNP309</th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>OR (95% CI)</th>
<th>Age at onset first breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HaBCS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>GG</td>
<td>TT</td>
<td>1,127 (21.7)</td>
<td>806 (21.0)</td>
<td>Reference</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>1,294 (24.9)</td>
<td>925 (24.1)</td>
<td>0.99 (0.88–1.13)</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>376 (7.2)</td>
<td>293 (7.6)</td>
<td>0.91 (0.76–1.10)</td>
<td>56.5</td>
</tr>
<tr>
<td>GC</td>
<td>TT</td>
<td>789 (15.2)</td>
<td>627 (16.4)</td>
<td>0.89 (0.77–1.02)</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>945 (18.2)</td>
<td>656 (17.1)</td>
<td>1.02 (0.89–1.17)</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>274 (5.3)</td>
<td>240 (6.3)</td>
<td>0.78 (0.64–0.96)</td>
<td>56</td>
</tr>
<tr>
<td>CC</td>
<td>TT</td>
<td>157 (3.0)</td>
<td>113 (2.9)</td>
<td>0.94 (0.72–1.23)</td>
<td>58.5</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>189 (3.6)</td>
<td>132 (3.4)</td>
<td>1.04 (0.81–1.34)</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>40 (0.8)</td>
<td>42 (1.1)</td>
<td>0.68 (0.43–1.08)</td>
<td>51</td>
</tr>
<tr>
<td>GG or GC</td>
<td>TT</td>
<td>4,962 (95.6)</td>
<td>3,660 (95.5)</td>
<td>Reference</td>
<td>57</td>
</tr>
<tr>
<td>CC</td>
<td>TG or GG</td>
<td>229 (4.4)</td>
<td>174 (4.5)</td>
<td>1.00 (0.81–1.23)</td>
<td>53</td>
</tr>
</tbody>
</table>

*GG = Arg/Arg, GC = Arg/Pro, CC = Pro/Pro.
† Pooled data presented here exclude HaBCS.
‡ P = 0.07.
reason for exclusion of these data. The ORs for SNP309 of Finland were in the range of the other groups and the higher proportion of MDM2 SNP309 G allele carriers may be due to the specific genetic background of the Finnish population, as the frequency distribution (converted 51 years) versus 4% (of 72; ref. 39). Although it remains possible that the SNP309 only acts in synergy with a particular genetic background, in two additional series of familial breast cancer cases of the Netherlands Cancer Institute (Netherlands), namely, one randomly selected case per BRCA1 family (n = 95) and one randomly selected case ages <50 years per non-BRCA1/2 family (n = 244), SNP309 was not associated with earlier age at onset of breast cancer.10

In summary, in this large collaborative study, we did not find an indication for either an increase in risk or an earlier age at onset of breast cancer in carriers of either MDM2 SNP309 or TP53 R72P alone or in combination. This suggests that any effect of these two variants would be very small and, if present, confined to subgroups that were not separately assessed in our present study.

References

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