ABSTRACT

Several groups have studied the molecular pathology of inherited breast cancer. By combining several such studies, we show in this study that somatic TP53 abnormalities are more common in breast cancer associated with BRCA1 or BRCA2 germ-line mutations than in sporadic breast cancers (odds ratio, 2.8; \( P = 0.0003 \)). Then, we compared the spectrum of TP53 mutations for breast cancers in the IARC TP53 mutation database with the 82 mutations reported in BRCA1/2-associated breast cancers. The spectrum differed significantly both in distribution (\( P < 10^{-5} \)) and in base changes (\( P = 0.025 \)). Mutations at A:T bp were more common in BRCA1/2-associated tumors and strand bias suggesting DNA repair abnormalities was found. Changes were common at TP53 codons that are not mutation hotspots. Structural modeling showed that most of these p53 non-hotspot amino acids characterized in breast tumors isolated from patients with deficient BRCA1/2 function are distributed in a region of the protein on the opposite side of the p53 DNA-binding surface. Our results suggest that BRCA1/2 mutations influence the type and distribution of TP53 mutations seen in breast cancer.

INTRODUCTION

Germ-line mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 are associated with an increased risk for breast cancer (1). The clinicopathological features of breast cancer associated with BRCA1/2 germ-line mutations differ from those seen in sporadic breast cancer (2, 3). In several studies (4), the tumor suppressor gene TP53 was more commonly altered in BRCA1/2-related breast cancer than in non-BRCA1/2-related breast cancer, as measured either by immunohistochemistry or mutation analysis. Notably, many of the mutations observed in BRCA1/2-related breast cancer have not been reported previously in the IARC TP53 mutation database.4

Differences in mutation spectrum may be explained by either alterations in mutagenesis or differences in selection of cells containing the resultant mutations; e.g., altered mutagenesis could be attributable to abnormal BRCA1 or BRCA2 function (perhaps because of changes in DNA damage or repair patterns). Alternatively, the p53 mutants observed may result in a greater selection advantage in BRCA1/2-deficient cells than in BRCA1/2 wild-type cells. These mechanisms are not mutually exclusive. Evidence that links BRCA1 and BRCA2 to DNA repair supports the first hypothesis. BRCA1 and BRCA2 are thought to be involved in DNA repair through transcription-coupled and homologous recombination mechanisms (5). BRCA1 associates with and is phosphorylated by the kinase ATM, which regulates cell cycle arrest after DNA damage (6). Both BRCA1 and BRCA2 associate with Rad51, the mammalian homologue of the Escherichia coli RecA protein, which is essential for double-strand break repair through homologous recombination (7). BRCA1 has been shown recently (8) to be part of a large complex that includes essential DNA damage repair proteins, such as MSH2, MSH6, MLH1, ATM, and BLM. This BRCA1-containing complex may serve as a sensor of DNA damage and could be implicated in DNA repair mechanisms. BRCA1 also is known to interact with the COOH termini of p53 via two interaction sites, one each in the NH2 and COOH termini of BRCA1, and stimulates p53-mediated transcription (9–11). In addition, in a conditional knockout model of Brca1 in mouse mammary tissue, Xu et al. (12) showed that development of tumors occurred after a long latency and was associated with genetic instability. When the same experiment was repeated on a Trp53+/− background, Brca1-associated tumorigenesis was clearly accelerated and four of five tumors showed loss or partial loss of the wild-type Trp53 allele (12).

Using computational methods of mutational spectrum analysis and structural modeling, we examined the distribution of TP53 mutations in breast cancer associated with BRCA1/2 germ-line mutations. We compared the TP53 mutation spectrum between BRCA1/2-associated and other breast tumors and studied the structural context of the novel mutations relative to their reported functional consequences. Using the same methods, we also studied the limited number of ovarian cancers associated with BRCA1/2 germ-line mutations that have been analyzed for TP53 mutations.

MATERIALS AND METHODS

Literature Review. Publications identified through Medline between 1976 and December 1999 were reviewed including the following search terms: hereditary breast cancer, ovarian cancer, TP53, p53, BRCA1, BRCA2, and related articles. We included 12 studies providing information on the association between p53 immunostaining or TP53 mutation status and breast cancer with characterized BRCA1 or BRCA2 germ-line mutations. There are three similar studies for ovarian cancer, but only one has published the exact TP53 mutations identified (13), so we have restricted our analysis here to that study. TP53 Mutation Database Analyses. The IARC version of the TP53 somatic mutation database was used. For comparison of mutational spectrum, the April 1999 version of the database was used.5 For spectrum comparison using the method of Cariello et al. (14), an earlier version of the database was used (15). The two versions do not differ significantly with regard to mutation distribution and spectrum (data not shown). For the spectral analyses, we included only mutations that have known DNA sequence changes.

Structural Analysis. Rendering and visualization of the p53 structure (Protein Data Bank structure 1TSR; Ref. 16) was performed on a Silicon Graphics workstation with the InsightII molecular modeling environment program (Molecular Simulations Inc., San Diego, California). Amino acids in the p53 structure were designated buried, partially exposed, or exposed as reported previously (17).

Statistical Analyses. Studies of BRCA1/2-associated breast cancer with TP53p53 information were pooled, and the Mantel-Haenszel test was used to compare the frequency of TP53p53 abnormalities in BRCA1/2 mutation carriers versus noncarriers. Comparisons of mutation spectra were performed using the
program of Cariello et al. (14). Briefly, the program compares two p53 mutational spectra and generates a P describing the likelihood that the observed differences could have arisen from similar spectra by chance alone using a Monte Carlo method. A Pearson χ² test was used to compare TP53 mutation types found in the IARC database with those described in BRCA1/2-related tumors. The two-way classification of mutation frequency data according to the source of the tumor (breast tumors from the IARC database or BRCA1/2-associated breast tumors) and mutation type [G:C→CG, G:C→TA; G:C→AT (CpG), G:C→AT (non-CpG), A:T→TA, A:T→GC, A:T→CG, deletions + insertions, and complex/tandem mutations] was analyzed first with a Pearson χ² test for independence of the row and column classification factors using MINITAB (Minitab, Inc.). Then, we used random sampling of the multiple hypergeometric distribution (StatXact 4 for Windows, 1998; Cytel Software Corporation). Mutations were also pooled into three categories (G:C mutations, A:T mutations, and insertion/deletion/complex/tandem mutations) for analysis using an exact permutation test. In both cases, the results were essentially the same as those obtained using the Pearson χ² test. The probability that the spatial distribution of BRCA1/2-associated substitution mutations in the p53 DNA-binding domain is the same as that of all of the p53 substitution mutations in the IARC database was tested using nonparametric bootstrap analysis. A high-resolution structure of the p53 DNA-binding domain was used to map codons associated with mutation database entries to the α-carbon Cartesian coordinates of the associated amino acids. Spatial averages of α-carbon positions were determined for the two samples (which consisted of 7396 α-carbons associated with p53 mutations from the IARC database and 62 α-carbons associated with p53 mutations in tumors from BRCA1/2 mutation carriers), and the distance between the two averages was calculated. The significance of the difference in the spatial averages was assessed by pooling the samples and drawing, with replacement, 100,000 pairs of samples. One element of each pair contained 7,396 coordinates and the other contained 62 coordinates. The P was calculated as

\[
P = \frac{M}{N} \pm 1.96 \sqrt{\frac{(1 - P)}{N} + \frac{1}{2N}}
\]

where \(N\) is the number of sample bootstrap replicates (100,000) and \(M\) is the number of replicates for which the difference between the spatial averages was greater than that of the original samples (110).

**RESULTS**

To determine whether the distribution and types of mutations in TP53 were significantly different between breast cancer associated with BRCA1/2 germ-line mutations and nonhereditary breast cancer (i.e., the majority of mutations in the IARC database), we collated all of the published data on TP53 alterations. BRCA1/2-related breast cancers were significantly more likely to overexpress p53 than non-BRCA1/2-related breast cancer (pooled OR\(^a\), 2.6; 95% CI, 1.8–3.7; \(P < 0.0001\)) and to carry TP53 mutations (OR, 2.8; 95% CI, 1.6–4.7; \(P = 0.0003\); Table 1; Refs. 18–21). To evaluate these ORs, we only included studies that were followed the same method (pooled OR\(^a\), 2.6; 95% CI, 1.8–3.7; \(P = 0.0003\)) and to carry TP53 mutations (OR, 2.8; 95% CI, 1.6–4.7; \(P = 0.0003\); Table 1; Refs. 18–21). To evaluate these ORs, we only included studies that were followed the same method.

### Table 1: TP53 mutations in BRCA1/2-related and non-BRCA1/2-related breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>BRCA1/2 mut + (%)(^b)</th>
<th>BRCA1/2 mut − (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crook et al. (18)</td>
<td>33 of 50 (66)</td>
<td>7 of 20 (35)</td>
</tr>
<tr>
<td>Goretzdoit et al. (19)</td>
<td>10 of 34 (29)</td>
<td>62 of 368 (17)</td>
</tr>
<tr>
<td>Armes et al. (20)</td>
<td>3 of 19 (16)</td>
<td>3 of 21 (14)</td>
</tr>
<tr>
<td>Phillips et al. (21)</td>
<td>10 of 13 (76)</td>
<td>10 of 33 (30)</td>
</tr>
</tbody>
</table>

\(\chi^2\) test. Studies that reported TP53 mutations among BRCA1/2 mutation carriers but not concomitantly in a control population are not reported here.

From a reanalysis of the two published studies (22, 23), overexpression of p53 is also more frequent in ovarian cancer associated with BRCA1/2 germ-line mutations than in its sporadic counterpart (pooled OR, 2.3; 95% CI, 1.2–4.3; \(P = 0.02\)). However, from analysis of a third study (13), of the 26 codons that were individually mutated in BRCA1/2-related ovarian cancer, only one of the mutations has not been observed previously in ovarian cancer, and four have not been reported for any human cancer. All five of these new mutations were frameshifts. The difference in the distribution of previously reported and novel mutations in breast and ovarian cancer is significant (\(P = 0.008\)). Notably, all of the 18 missense mutations seen in BRCA1/2-related ovarian cancer have been seen previously in nonhereditary ovarian cancer, whereas for hereditary breast cancer, 19 of 58 separate missense mutations have not been reported in nonhereditary breast cancer. This difference is statistically significant (\(P = 0.004\)).

We used the Monte Carlo method of Cariello et al. (14) to compare the spectrum of the 82 TP53 mutations in breast cancer associated with BRCA1/2 germ-line mutations with the spectrum of TP53 mutations reported in breast cancers in the IARC database (Fig. 1). We found significant differences in the codon distribution (\(P < 1 \times 10^{-6}\)) and type of nucleotide change (\(P = 0.025\)) for TP53 mutations in BRCA1/2-related breast cancer compared with breast cancer in the IARC database (Table 2). Thirty eight percent of all of the TP53 mutations found in breast cancer occurring in BRCA1/2 mutation carriers were at A:T bp; this compared with 25% for all of the TP53 mutations in breast cancer in the IARC database (\(P = 0.1; \chi^2\) test). When mutations were pooled into three categories (mutations at G:C bp, A:T bp, and insertion/deletion/complex/tandem mutations), there was a significant difference between the sample sets (\(P = 0.03; \chi^2\) test). When the 82 mutations were divided into nine categories of mutations and assessed separately (rather than in three groups), the difference was of borderline significance (\(P = 0.12\)). The Ps for Monte Carlo simulations and exact Ps were almost identical. The A:T to G:C and A:T to T:A mutations demonstrated a strand bias; i.e., 88% of A:T to G:C mutations were T>C rather than A>G, and 80% of A:T to T:A mutations were T>A rather than A>T. This contrasted with 35% T>C and 56% T>A among breast cancer mutations in the IARC database. We have hypothesized previously (24) that bias toward the nontranscribed strand represented damage from an exogenous carcinogen that was not properly repaired. In the current observation, the T was on the nontranscribed strand. This imbalance at A:T bp suggests that thymine lesions might be inefficiently repaired in cells with altered BRCA1 or BRCA2.

BRCA1 and BRCA2 are thought to interact (25) and probably have interrelated functions, but to address the possibility that the effect we observed is limited to TP53 mutations occurring in either BRCA1 or BRCA2 mutation carriers alone, we repeated the analyses separately for the 44 BRCA1 mutation carriers and the 29 BRCA2 mutation carriers. No significant difference between breast cancers associated with BRCA1 or BRCA2 germ-line mutations was noted for codon usage or type of nucleotide change. In particular, one TP53 tandem CC>TT mutation was associated with each BRCA gene, and there were no significant differences in the frequencies of silent mutations, of mutations at A:T bp, and in strand bias (data not shown).

The location of the TP53 mutations provides clues to functional motifs

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\(^a\) Avail at http://metalab.unc.edu/dnam/mainpage.html.

\(^b\) The abbreviations used are: OR, odds ratio; CI, confidence interval.
of the protein. Walker et al. (17) previously defined 73 codons that were mutation hotspots in TP53 by determining whether the number of mutations at each codon exceeded the amount expected from a random binomial distribution. These 73 hotspots accounted for 88% of TP53 missense mutations in all of the cancers and 82% in all of the breast cancers (499 of 610 missense mutations in the IARC database). Thus, only 18% of all of the TP53 missense mutations occurred at non-hotspots. However, in breast cancer associated with BRCA1/2 germ-line mutations, 33% (19 of 58) of the observed missense mutations occur at 15 different non-hotspot codons, a significantly increased proportion of non-hotspot sites (33% versus 18%; \( P = 0.01; \chi^2 \) test; Fig. 2). It is possible that mutations at these codons are not selected in non-BRCA1/2-related tumors because under normal circumstances they do not abrogate p53 wild-type function. Thus, we analyzed the existing functional data from these non-hotspot mutants in the context of p53 structure. The transactivation, apoptosis-promoting, growth-suppressing, and transformation-suppressing activities of several BRCA1/2-associated p53 mutants have been tested recently (26). Our previous work would predict that the mutations at hotspot codons would likely abrogate wild-type p53 function, but mutations at non-hotspot codons would not. Thus, we analyzed the functional data relative to hotspot status as defined previously (17).

Six of the tested mutants are at non-hotspot codons. Three of them (T150I, G199R, and R202S) retained function similar to wild type in multiple transactivation, apoptosis, and growth suppression assays, although none could reduce ras- or E7-induced transformation as effectively as wild type. This contrasts with the results from nine mutants at hotspot codons, which were tested recently (26). Two of the other three BRCA1/2-associated non-hotspot mutants (P144P and S240R) lost wild-type function in most assays, although their suppression of transformation was similar to the aforementioned non-hotspot mutants. The sixth non-hotspot mutant (P219H) displayed intermediate p21 transactivation, growth suppression, and transformation activity but mutant function in apoptosis and other transactivation assays. Thus, non-hotspot mutants can be distinguished on functional grounds from hotspot mutants. This could imply a particular role for non-hotspot mutants in BRCA1/2-related breast carcinogenesis.

We used molecular modeling to define the structural context of the novel p53 mutations seen in breast cancer associated with BRCA1/2 germ-line mutations. The 15 non-hotspot amino acids at which missense mutations have been described in BRCA1/2-associated tumors were modeled using the solved p53 crystal structure (16), using the program InsightII. Only 6 of these 15 amino acids (40%) lay within the p53 loops, helices, \( \beta \)-sheets, or DNA contact areas. By comparison, 82% of the 73 TP53 mutation hotspots fell within one of these motifs (17). Using a nonparametric bootstrap method, we determined the probability that the spatial distribution of BRCA1/2-associated substitution mutations in the p53 DNA-binding domain is the same as that of all of the p53 substitution mutations in the IARC database. The distributions were found to be different (\( P = 0.0017 \pm 0.0007 \)). Then, we repeated these analyses for breast tumors associated with BRCA1 (\( n = 44 \)) and BRCA2 germ-line mutations (\( n = 29 \)) separately, and there was no suggestion that this difference was attributable to either BRCA1-related or BRCA2-related tumors alone (23% of TP53 mutations in BRCA1-associated cancers were at non-hotspot codons versus 28% in BRCA2-related cancers). With regard to ovarian cancer associated with BRCA1/2 germ-line mutations, because all of the missense mutations seen in BRCA1/2-related ovarian cancer have been reported previously to occur in ovarian cancer,7 the distribution of TP53 mutations in ovarian cancers from mutation carriers will not differ from that seen in noncarriers.

Ten of the 15 non-hotspot amino acids clustered in one region of p53, on the opposite side of the protein from the DNA-binding surface (Fig. 3, A–C). Seven of these mutations are in exposed amino acids and when mutated would alter the surface topography of p53 in this region, possibly interfering with binding to another protein or p53 dimerization. These amino acids form no side-chain hydrogen bonds. Because the “back” of one p53 monomer abuts the “front” of its dimeric partner (Fig. 3, D–E), this region of p53 is completely exposed on the “front” dimeric partner and can interact with another protein. For the other p53 molecule, this region faces the p53-p53 interface, although most of the mutated residues are still exposed (Fig. 3, D–E). It is unlikely that these mutations significantly affect p53 dimerization, because disrupting the p53 dimer would likely alter DNA binding and transactivation, and this loss of function would be likely to be selected frequently in tumors. Therefore, it is possible that the existence of these non-hotspot missense mutations in BRCA1/2-related breast cancer is the result of selection. Moreover, the presence of these altered amino acids on the non-DNA-binding side of the p53 molecule could represent an interaction surface for another, unknown protein.

<table>
<thead>
<tr>
<th>Table 2 TP53 mutation spectrum in BRCA1/2-related and non-BRCA1/2-related breast cancer*</th>
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<tr>
<td></td>
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<tr>
<td>Hotspots</td>
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<tr>
<td>Silent</td>
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<tr>
<td>A:T base pairs</td>
</tr>
<tr>
<td>Tandem CC &gt; TT</td>
</tr>
<tr>
<td>Multiple substitutions</td>
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<tr>
<td>Strand bias</td>
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</table>

* All of the differences are statistically significant; see text.

7 Available at http://www.iarc.fr/p53/Homepage.htm.
DISCUSSION

Our analysis of TP53 mutations in hereditary and nonhereditary breast cancer suggests that both the spectrum and the structural distribution of these mutations differ between the two groups of cancers. It is possible that this is accounted for by genomic mechanisms, such as impaired DNA repair of certain classes of mutations or by selection for specific regions in p53 that have a role in breast carcinogenesis in BRCA1/2 mutation carriers. These hypotheses are not mutually exclusive but would imply a different causal mechanism in each case. Further study of the TP53 mutation spectrum in BRCA1/2-associated breast cancer suggests that DNA repair abnormalities may contribute to mutagenesis in these tumors (Table 2). As noted by Crook et al. (18), multiple point mutations frequently occurred in the same tumor, pointing toward a repair defect. These authors also identified two tandem CC/TG mutations in BRCA1/2-associated tumors, one associated with BRCA1 and the other with BRCA2. These mutations are rare and usually are found in skin tumors, where they result from failure to repair the photoproducts created by UV light. Even among skin tumors, tandem mutations are uncommon except in tumors from persons with xeroderma pigmentosum, who have impaired nucleotide excision repair (24). Only 57 CC>TG tandem mutations are reported in the IARC database of over 10,000 TP53 mutations; 51 are in skin tumors. Of the six CC>TG mutations in other tumors, five are in either breast or ovarian cancer: two in the BRCA1/2-associated tumors mentioned above, a third in a breast cancer of unknown BRCA1/2 status, and two in ovarian cancers, also of unknown BRCA1/2 status. It is intriguing that the two CC>TG mutations are found among only 82 BRCA1/2-associated TP53 mutations, raising the possibility that the other CC>TG mutations in the breast and ovarian cancer databases may also be in BRCA1/2-associated tumors. Taken together, the mutation spectrum data support the hypothesis that impaired DNA repair functions in tumors associated with BRCA1/2 germ-line mutations may contribute to mutations important in breast tumorigenesis (27). Additional studies of repair of these DNA lesions in cells with BRCA1 or BRCA2 abnormalities are warranted.

Thus, the functional significance of p53 abnormalities found in breast cancers may depend on the BRCA1/2 mutation status. An explanation for our observations could be that in the absence of BRCA1 or BRCA2 abnormalities, a subset of p53 mutations is insufficient to provide the developing tumor with a growth advantage. The presence of an abnormal BRCA1/2-mediated pathway could promote, in BRCA1/2-associated breast tumors, selection of this subset of p53 mutants that otherwise would not confer a growth advantage. Additional clinical, biochemical, and computer modeling studies will be required to explore the BRCA1/2-p53-related carcinogenic pathways.

An interesting parallel is seen in colorectal cancer. Germ-line mutations in mismatch repair genes result in microsatellite unstable (MSI) cancers. These MSI cancers, with or without germ-line mismatch repair gene mutations, have a significantly lower frequency of TP53 mutations than microsatellite stable colorectal cancers (28). Therefore, the presence of a germ-line (or early somatic) mutation in a cancer predisposition gene can determine the subsequent mutation profile of the tumors that occur. BRCA1 has been shown recently (8) to form a complex with the DNA mismatch repair proteins MSH2, MSH6, and MLH1, and it was proposed that BRCA1 plays a role in transcription-coupled repair through this mechanism. Nevertheless, MSI, the general hallmark of DNA mismatch repair deficiency, has been rarely seen in familial or hereditary breast cancer (18, 29). Thus, even if defects in mismatch repair are important in the pathogenesis of breast tumors occurring in germ-line BRCA1/2 mutation carriers, the mechanism of repair deficiency does not involve genome-wide MSI.
Our findings suggest that not only the mutation profile but also the type and distribution of mutations within a given gene can be influenced by inherited susceptibility at another locus. Therefore, it will be interesting to find out whether nonhereditary breast cancers with low levels of BRCA1 protein (30) will also be associated with an unusual spectrum of TP53 mutations.

Our analysis of TP53 mutations in ovarian cancer associated with BRCA1/2 germline mutations is limited by the small number of tumors that have been studied but thus far indicates that, in contrast to what is observed in breast cancer, the mutational profile of TP53 in BRCA1/2-related ovarian cancer does not appear to differ significantly from that observed in nonhereditary ovarian cancer. This conclusion is supported by the comments in Ramus et al. (23) where, although precise mutation data are not provided, the authors state that the position and type of 24 TP53 mutations in 43 BRCA1/2-related ovarian cancers did not differ from the 10 TP53 mutations observed in 33 nonhereditary cases.

As shown in Fig. 3, A–E, the novel non-hotspot mutations seen in breast cancer associated with BRCA1/2 germline mutations are centered on the non-DNA-binding side of the p53 molecule. Four of the six mutated amino acids that are in recognized p53 β-sheets (Q144, L145, V197, and P219 in sheets S3, S5, and S7) are buried in the p53 core close to this anti-DNA region and might affect the folding of this region or of the p53 core. This structural feature may help explain why mutants Q144P and P219H cause loss of wild-type function, although they are not hotspots (L145P and V197L were not tested; Ref. 26). Only three of the non-hotspot mutations (M133I, M169I, and S240R) appeared to cause the usual changes in p53 structure associated with loss of growth suppression, i.e., alterations of the folded core structure of p53 or direct interaction with DNA. That three of these mutants on the anti-DNA surface (T150I, G199R, and R202S) do not change wild-type p53 function in vitro, as discussed above, is consistent with the fact that they are not commonly found in cancers. Their occurrence in BRCA1/2-associated breast cancer suggests that a more subtle change in p53 structure and function might confer a growth or transformation advantage in this context. Thus, the BRCA1/2-associated non-hotspot TP53 mutations appear to be spatially clustered and might represent a region of p53 that physically interacts with an unknown protein. These mutations have not become hotspots because, by themselves, they have not been selected on the basis of transforming functions. However, alterations in the affected
region might alter cell growth in the context of mutated or absent BRCA protein. For future studies, our structural modeling suggests that the non-DNA-binding site of p53 could exhibit functional importance by providing sites for interactions with other proteins, which may alter the function of p53. In one study, certain TP53 mutations were associated with a poorer outcome (31). Studies to examine the prognostic significance of the non-hotspot mutations that we have studied here will be of interest. Interestingly, Alsnor et al. (32) recently showed that breast cancer carrying TP53 missense mutations located outside of the conserved or structural regions (corresponding to most of the non-hotspot mutations in this series) were associated with a significantly better prognosis, when compared with tumors with TP53 mutations in conserved or structural domains.

Differences in mutation spectrum may be explained either by altered mutagenesis attributable to changes in DNA damage and repair patterns or by altered selection of the resulting mutants. The concepts of differential growth regulation in different tissues and variability in immune surveillance might also play a role in the carcinogenesis of hereditary breast and ovarian cancers. These hypotheses are not mutually exclusive, and all of them can be tested. Our preliminary data demonstrate how computational studies contribute to the interpretation of functional studies by showing: (a) that the TP53 mutation spectrum in BRCA1/2-related breast cancer differs from the spectrum in nonhereditary cases; (b) that silent, tandem, and multiple mutations are common; and (c) that novel mutations cluster in an unexpected region of p53. Our results provide provocative preliminary evidence that both altered mutagenesis and selection are involved in BRCA1/2-associated carcinogenesis and support additional studies in both of these areas.

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TP53 Mutations in Breast Cancer Associated with BRCA1 or BRCA2 Germ-line Mutations: Distinctive Spectrum and Structural Distribution

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