Concordance of Genomic Alterations between Primary and Recurrent Breast Cancer

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Abstract
There is growing interest in delivering genomically informed cancer therapy. Our aim was to determine the concordance of genomic alterations between primary and recurrent breast cancer. Targeted next-generation sequencing was performed on formalin-fixed paraffin-embedded (FFPE) samples, profiling 3,320 exons of 182 cancer-related genes plus 37 introns from 14 genes often rearranged in cancer. Point mutations, indels, copy-number alterations (CNA), and select rearrangements were assessed in 74 tumors from 43 patients (36 primary and 38 recurrence/metastases). Alterations potentially targetable with established or investigational therapeutics were considered “actionable.” Alterations were detected in 55 genes (mean 3.95 alterations/sample, range 1–12), including mutations in PIK3CA, TP53, ARID1A, PTEN, AKT1, NFI, FBXW7, and FGFR3 and amplifications in MCL1, CCND1, FGFR1, MYC, IGF1R, MDM2, MDM4, AKT3, CDK4, and AKT2. In 33 matched primary and recurrent tumors, 97 of 112 (86.6%) somatic mutations were concordant. Of identified CNAs, 136 of 159 (85.5%) were concordant: 37 (23.3%) were concordant, but below the reporting threshold in one of the matched samples, and 23 (14.5%) discordant. There was an increased frequency of CDK4/MDM2 amplifications in recurrences, as well as gains and losses of other actionable alterations. Forty of 43 (93%) patients had actionable alterations that could inform targeted treatment options. In conclusion, deep genomic profiling of cancer-related genes reveals potentially actionable alterations in most patients with breast cancer. Overall there was high concordance between primary and recurrent tumors. Analysis of recurrent tumors before treatment may provide additional insights, as both gains and losses of targets are observed. Mol Cancer Ther; 13(5); 1382–9. ©2014 AACR.

Introduction
Opportunities to use genomic information to guide cancer therapy are rapidly emerging. Genomic alterations have been associated with drug sensitivity and resistance. For example, amplification of HER2 predicts responses to HER2-targeted therapy in patients with breast cancer. Emerging results suggest that other alterations, such as PIK3CA mutations, may modulate sensitivity to established therapies such as trastuzumab and endocrine therapy as well as to investigational agents and over-the-counter medications (1–4). Therefore, genomic characterization of breast cancer tumors may identify aberrations that can be pursued as potential therapeutic targets.

In patients with metastatic cancer biomarkers are often assessed in archived primary tumor specimens. However, recurrent breast tumors may differ from primary tumors on the molecular level, and tumors may also evolve with treatment. In previous studies, we and others showed discordances between primary and metastatic tumors in standard-of-care markers estrogen receptor (ER), progesterone receptor (PR), and HER2 (5, 6) as well as other markers such as PIK3CA (7, 8). Differences in standard biomarkers between primary and metastatic tumors have been associated with differences in outcomes; thus, comparisons of primary and metastatic or recurrent tumors may help optimize patient management (5, 6). The goal of this study was to conduct a comprehensive, next-generation sequencing–based analysis comparing alterations in cancer-related genes in patients with recurrent or metastatic breast cancer with alterations in such genes in patients with primary breast cancer.

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Patients and Methods

Identification of patient samples
Paraffin blocks from formalin-fixed primary breast cancer specimens and/or biopsy specimens of recurrent or metastatic tumors were obtained at the Hospital Clínico Universitario de Valencia (Valencia, Spain). All histologic diagnoses were verified by breast pathologists. Clinicopathologic information was obtained by a retrospective review of patient records. Patients were selected on the basis of sample availability. The Institutional Review Boards of The University of Texas MD Anderson Cancer Center and Hospital Clínico Universitario de Valencia approved the study.

Immunohistochemistry and FISH
ER, PR, and HER2 protein expression levels in the samples were determined by immunohistochemistry (IHC) in a central laboratory (Hospital Clínico Universitario de Valencia). HER2 copy numbers were determined by FISH if the HER2 IHC staining score was 2+ or if HER2 IHC findings for the primary tumor sample and the recurrent or metastatic tumor sample from the same patient were discordant. IHC for ER (clone SP1; Ventana Medical Systems) and PR (clone 1E2; Ventana) was performed on 3-μm-thick formalin-fixed paraffin-embedded (FFPE) sections with a BenchMark XT instrument (Ventana). Tumors with moderate intensity nuclear staining of 1% or higher or an Allred score ≥3 were considered positive for ER and/or PR (9, 10). IHC for HER2 was performed with anti-HER-2 antibody (4B5; Ventana). HER2 positivity was defined as 3+ on IHC (strong complete membranous staining in at least 30% of cells) and/or HER2 gene amplification (HER2 copy number/CEP-17 copy-number ratio greater than 2.2 by FISH), as determined by the HER2 FISH pharmDx assay (Dako, Inc.). PTEN IHC was performed with anti-human PTEN antibody (clone 6H2.1; Dako). PTEN staining results in normal epithelium and stroma served as internal positive controls and were quantified as staining intensity × the percentage of positive cells. Staining intensity was scored as follows: 0, negative; 1, weak; 2, moderate; 3, strong. The percentage of positive cells was scored as follows: 0, <1%; 1, 1%–10%; 2, 11%–50%; 3, 51%–80%; 4, >80% positive cells.

Genomic profiling
We performed comprehensive genome profiling on FFPE samples by using a targeted next-generation sequencing (NGS) assay in a Clinical Laboratory Improvement Amendments certified laboratory (Foundation Medicine, Inc.). After breast cancer nuclear cellularity of at least 70% was confirmed by hematoxylin and eosin staining, 50-μm-thick FFPE sections were prepared. At least 50 ng and up to 200 ng of extracted DNA was sheared to approximately 100 to 400 bp by sonication, followed by end repair, deoxyadenylic acid (dA) addition and ligation of indexed, Illumina sequencing adapters. Genomic libraries were prepared and captured for 3,230 exons in 182 cancer-related genes plus 57 introns from 14 genes often rearranged in cancer (Supplementary Table S1), and the genes were sequenced to an average depth of 380× uniquely mapped reads. The full coding region was sequenced. The coverage is listed in Supplementary Table S2.

Paired end were sequenced (49 × 49 cycles) with the HiSeq2000 system (Illumina). Sequence data were mapped to the reference human genome (hg19) with BWA alignment software (11) and processed with the publicly available SAMtools (12) software packages Picard (http://picard.sourceforge.net and GATK; ref. 13). Genomic base substitutions and indels were detected with custom tools optimized for mutation calling in heterogeneous tumor samples, on the basis of statistical modeling of sequence quality scores and local sequence assembly. Base substitution detection was performed using a Bayesian methodology, which allows detection of novel somatic mutations at low mutant allele frequency (MAF) and increased sensitivity for mutations at hotspot sites (11) through the incorporation of tissue-specific prior expectations:

\[ P(\text{Frequency of mutation } R) = P(\text{Read data } R) \times (1 - P(\text{mutation} R)) P(F = 0) P(F = 0), \]

where \( P(R | F) \) is evaluated with a multinomial distribution of the observed allele counts using empirically observed error rates and \( P(F = 0) \) is the prior expectation of mutation in the tumor type. Novel mutations causing premature stop codons (nonsense mutations), novel frameshift mutations, and novel mutations affecting splicesites (−2 to +2) were considered to be likely functional truncation mutations of tumor suppressor genes. Genes significantly enriched in truncation mutations in cancer genome surveys were considered to be tumor suppressor genes (13).

To detect indels, de novo local assembly in each targeted exon was performed using the de-Bruijn approach (12). Candidate calls were filtered using a series of quality metrics, including strand bias, read location bias, and a custom database of sequencing artifacts derived from normal controls. Germline DNA was not available therefore, somatic alterations were determined computationally. Germline alterations were identified and filtered using dbSNP (version 135; ref. 13) and subsequently annotated for known and likely somatic mutations using the Catalogue of Somatic Mutations in Cancer (COSMIC) database (version 62).

Detection of copy-number alterations (CNA) was performed by obtaining a log-ratio profile of the sample by normalizing the sequence coverage obtained at all exons against a process-matched normal control. The profile was segmented and interpreted using allele frequencies of approximately 1,800 additional genome-wide single-nucleotide polymorphisms (SNP) to estimate tumor purity and copy number based on established methods (14–16) by fitting parameters of the equation

\[ \log_{10} \text{seg}_l \sim \log_{10} \text{seg}_l + \log_{10} \text{seg}_l \times \log_{10} \text{seg}_l + \log_{10} \text{seg}_l \times \text{tumor ploidy} + \log_{10} \text{seg}_l , \]

where \( \log_{10} \text{seg}_l \), \( \log_{10} \text{seg}_l \), and \( \log_{10} \text{seg}_l \) are the log ratios and copy

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numbers at each segment and sample purity, respectively. Focal amplifications are called at segments with ≥6 copies and homozygous deletions at 0 copies, in samples with purity >20%. This threshold (≥6 copies) is referred to as the "reporting threshold" in the results and discussion. Genomic rearrangements were detected by clustering chimeric reads mapping to targeted introns.

Variations were filtered by using the dbSNP archive (http://www.ncbi.nlm.nih.gov/projects/SNP/) and a custom artifact database and then annotated for known and likely somatic mutations by using the COSMIC (13). The mutations for each gene in our series were compared with the mutation frequency in the breast cancer data recently published in The Cancer Genome Atlas (TCGA) as a descriptive analysis (14).

Altered genes deemed targetable with established or investigational therapeutics on the basis of a literature review and a search of clinicaltrials.gov were considered actionable.

The median disease-free survival times from diagnosis and from surgery were performed using the R package "survival." The Fisher exact test was used to study the number of matched recurrences.

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Results

Patient and sample characteristics

The study cohort consisted of 43 patients who had both primary and recurrent/metastatic tumor tissue available. The median age at breast cancer diagnosis was 48 years (range, 30–83). At presentation, 3 patients had a stage I disease, 22 had stage II, 17 had stage III tumor, and one had stage IV disease. Thirty-six patients received adjuvant chemotherapy. Five patients whose primary tumor was analyzed had received neoadjuvant chemotherapy, and another patient had adjuvant letrozole. None of the patients received HER2-targeted therapy.

Forty-one patients developed a metachronous locoregional or distant recurrence after receiving treatment for primary breast cancer. The median disease-free survival times for these patients were 39 months from diagnosis and 36.5 months from surgery. In addition, one patient (patient 211) had distant metastases at diagnosis, and another patient had axillary metastasis only (sample 147M) without subsequent locoregional or systemic relapse.

From the 43 patients, 74 breast tumors were profiled, including 36 primary breast tumors, one synchronous metastatic lymph node, 9 locoregional recurrences (LRR), and 28 distant metastases (Supplementary Table S3). Fifty samples were hormone receptor (HR)-positive, 16 samples were HER2-positive and eight were triple negative. Thirty-three of 43 patients had both primary tumor samples and recurrent or metastatic tumor samples available: one patient had samples for a synchronous primary tumor and metastasis, and 32 patients had samples of primary tumors with samples of subsequent recurrent tumors, including 16 distant metastases, 7 LRR, and one set of two matched recurrences.

In addition, three unmatched primary tumor samples, one unmatched lymph node metastasis sample, and eight unmatched recurrence samples (three from 1 patient) were analyzed. These samples were included because little is known about the spectrum of genomic alterations in patients with metastatic or recurrent breast cancer.

Genomic alterations

Among the 74 samples, we identified alterations in 55 genes. Every sample tested had at least one alteration (mean 3.95; range, 1–12). Genomic alterations were classified as known somatic alterations (i.e., those previously reported in COSMIC), novel truncations of tumor suppressor genes likely to be functional, or whole-gene CNAs. The alterations found are listed in Supplementary Table S2; genes altered in the primary tumors are listed in Fig. 1A, and genes altered in recurrent or metastatic tumors are listed in Fig. 1B. One primary tumor (132P) was profiled twice, and is included as a single sample in calculations below.

The most common alterations observed are shown in Fig. 2. Mutations were identified in a wide variety of cancer-related genes, including PIK3CA, TP53, ARID1A, PTEN, AKT1, NF1, FBXW7, and FGFR3. Focally amplified genes (≥6 copies) included MCL1, CCND1, FGFR1, MYC, IGF1R, MDM2, MDM4, AKT3, CDK4, and AKT2.

TP53 alterations were significantly associated with tumor subtype and were found in 87.5% of triple-negative (ER-, PR-, and HER2-negative) samples, 68.8% of HER2-positive samples, and 18.2% of HR-positive samples (P = 0.0028). PIK3CA alterations were found in 12.5% of triple-negative samples, 37.5% of HER2-positive samples, and 44% of HR-positive samples (P = 0.4358).

HER2 amplification was detected by NGS in 12 (30%) of the 43 samples. Eleven (92%) of the 12 samples that were HER2-positive by IHC had HER2 copy-number gains by NGS. In addition, a HER2 copy-number gain was identified by NGS in one HER2-negative (1+IHC score) sample that had not been tested by FISH. Unfortunately, no additional tumor sample was available for validation of amplification by FISH. Three patients with HER2 amplification also had a RARA (retinoic acid receptor alpha) rearrangement. In 3 (25%) of the patients with HER2 amplification, a chromosomal breakpoint within the RARA gene was identified.

PTEN IHC was performed on the samples, including seven samples with PTEN mutations. Six (86%) of the seven samples with PTEN mutations had a complete lack of PTEN expression as determined by IHC (immunoreactive score = 0), and one had low expression (immunoreactive score = 4). Of the 18 samples that had complete loss of PTEN, seven (39%) had PTEN mutations.
**Comparison of primary tumors and recurrent/metastatic tumors**

To look for evidence of molecular evolution, we compared genomic alterations in matched primary tumor samples and recurrent/metastatic tumor samples from 33 patients. Two recurrent tumor samples were available for one patient. The adjuvant systemic treatments received by these patients are listed in Supplementary Table S4. Overall mutations in primary and recurrent/metastatic tumors were highly concordant. Upon unsupervised hierarchical clustering of samples based on genomic alterations, 26 pairs of samples out of 33 paired samples clustered together. Thus, paired samples are more likely to cluster together ($P = 0.001728$).

In the 33 matched primary recurrent/metastatic tumor pairs, 97 (86.6%) of the 112 somatic mutations detected were concordant. Ninety-nine (62.3%) of 159 CNAs reported were concordant, 37 (23.3%) were concordant but below the reporting threshold in one of the matched samples, and 23 (14.5%) were discordant. Three (37.5%) of eight primary tumor–LRR pairs had at least one genomic discordance, and 18 (72%) of 25 primary tumor–metastasis pairs had at least one genomic discordance ($P = 0.1057$).

One HER2-positive tumor had acquired a detectable PIK3CA amplification in two separate recurrences. Four HR-positive tumors, one HER2-positive tumor, and one triple-negative tumor had acquired detectable CDK4 and MDM2 amplifications in recurrences, whereas one HR-positive tumor had lost amplifications of CDK4 and MDM2. The copy-number changes are summarized in Supplementary Fig. S1.

The degree of genomic concordance between primary and recurrent tumor samples from the same patients is shown in Supplementary Fig. S1, whereas discordances are summarized in Fig. 3. Of note, two HR-positive patients that had PIK3CA mutation in the primary tumor did not have a detectable PIK3CA mutation in the recurrent tumor. Both of these alterations were at low allelic frequency in the primary tumor (0.10 in 39P and 0.02 in 79P). In addition, three recurrent tumor samples from 1 patient had a PIK3CA H1047R mutation, and 1 of the 3 had an additional PIK3CA mutation, R93Q. Because R93Q is not a known mutation in recurrent breast cancer, it may have been a passenger mutation in this tumor.

Genomic alterations that are targets of approved or investigational drugs were classified as potentially actionable. Overall, 40 (93%) of the 43 patients had potentially actionable genomic alterations, including HER2 amplifications (Supplementary Table S5). Excluding HER2 as a target in patients in whom HER2 was known to be amplified, in 37 (86%) of the 43 patients, comprehensive genomic profiling detected new potentially actionable alterations that had not been previously identified by standard-of-care testing. The targets identified included PIK3CA mutations and amplification (targeted by PI3K (phosphoinositide 3-kinase) pathway inhibitors), AKT1 mutations and AKT2 and AKT3 amplifications (targeted by Akt inhibitors), CDK4 amplification (targeted by CDK4 inhibitors), and MDM2 amplification (targeting by Mdm2 inhibitors). In addition, alterations that lead to activation of downstream pathways that could potentially be targeted by investigational agents were also identified: PTEN mutations (targeted by PI3K, Akt, and mTOR inhibitors), PIK3CA alterations (targeted by Akt and mTOR inhibitors), Akt alterations (targeted by mTOR inhibitors), and BRCAl and BRCAl2 mutations (targeted by PARP inhibitors and platinum agents). The majority of actionable targets were conserved between primary and recurrent/metastatic tumors. However, some gains (PIK3CA, PTEN, CDK4, MDM2, HER3, and AKT3) and losses (PIK3CA, FGFR3, and MDM2) of detectable alterations were detected.

**Discussion**

We performed deep NGS of known cancer-related genes to determine the spectrum of genomic alterations in metastatic or recurrent breast cancer and to compare those alterations with alterations in primary tumors. Genomic alterations were detected in all samples, with potentially actionable alterations in $>90\%$ of patients. Both gains and losses of potential targets were observed in recurrent/metastatic tumors relative to primary tumors. However, genomic alterations in recurrent/metastatic tumors were highly concordant with those in primary tumors.

The ability to perform NGS on small FFPE samples such as core biopsies in a Clinical Laboratory Improvement Amendments setting creates the opportunity to comprehensively characterize cancer-relevant genes and personalize therapy. Notably, we identified genomic aberrations in all samples studied. In addition to genes previously reported to be frequently mutated in breast cancer—AKTI, CDH1, PIK3CA, PTEN, TP53, RB1, and MAP2K4—we detected novel mutations recently reported by TCGA and Ellis and colleagues: RUNXI and NF1 (14, 15).

NGS allowed identification of multiple CNAs, including HER2 gains. This suggests that targeted exome sequencing should be considered as an alternate strategy for HER2 assessment. NGS can also detect HER2 mutations, which have recently been identified in connection with potential benefits of anti-HER2 agents (17). In addition to oncogenes widely recognized to be amplified in breast cancer, such as HER2, FGFR, CCND1, MYC, MDM2, and CDK4, we found copy-number gains in the antiapoptosis gene MCL1 in almost a third of the samples. MCL1 has recently been reported to be amplified in multiple cancer types, including breast cancer (18). An MCL1 copy-number gain may influence sensitivity of a tumor to standard chemotherapeutic agents (19). Because cancer cells with an MCL1 amplification are dependent on MCL1 for survival, MCL1 inhibitors are now being actively pursued (18). Thus, MCL1 may be an important therapeutic target in metastatic breast cancer.
Figure 1. Genomic alterations in primary (A) and metastatic or recurrent (B) tumors. Each column represents a single tumor sample. The total number of alterations in a sample is indicated at the bottom of each column. Each row represents an individual gene. Bar graphs on the right summarize the types of alterations seen for each gene.
Almost all patients had at least one alteration potentially targetable with the U.S. Food and Drug Administration–approved or investigational therapeutics. This finding indicates that routine genomic profiling may be instrumental for individualized pathway-directed therapy. Over the next few years, evidence needed to routinely deliver genomically informed personalized therapy will likely be amassed. Except for HER2, level I evidence (randomized controlled trials) linking potentially actionable genomic markers with investigational options for breast cancer is currently lacking. However, on the basis of preclinical data, some clinical trials have already been initiated with genomics-based selection of targets, such as PIK3CA for PI3K inhibitors; PIK3CA, AKT, and PTEN for AKT inhibitors; FGFR amplification for FGFR (fibroblast growth factor receptor) inhibitors; and BRCA for PARP inhibitors. Even in the absence of level I evidence, the matching of patients to clinical trials of drugs that are likely to target each patient’s specific tumor’s molecular aberrations holds significant promise. Moreover, alterations that we did not consider actionable in this analysis may be sensitive to certain targeted therapeutics (e.g., MYC and CDK inhibitors), and novel therapies directed at other targets such as TP53 are rapidly evolving (20).

Our study has several limitations. As many institutions do not routinely biopsy metastatic disease, it has been very challenging to find matched sets of primary and metastatic/recurrent disease. Thus, this cohort represents a unique resource. However, the cohort is still small in size, represents tumors of various subtypes, and the

![Figure 2. Comparison of genomic alterations in primary or metastatic or recurrent samples. A, unsupervised clustering of primary and metastatic or recurrent samples. B, most common genomic alterations (mutations and copy-number changes) in primary and metastatic tumors in our series.](image)

![Figure 3. Discordant genomic alterations. Mutations are represented in blue, copy-number changes in red. P, alterations found in primary tumor samples but not in matched recurrent/metastatic tumor samples. M, alterations found in recurrent/metastatic tumor samples but not in matched primary tumor samples.](image)
metastatic sites were biopsied at various time points throughout disease course. The samples were collected as standard of practice, and, thus, the lack of standardized adjuvant therapy is another limitation of the study. Furthermore, as patients were chosen based on sample availability, there may be some inherent biases in patient selection. Furthermore, alterations potentially targetable with established or investigational therapeutics were considered “actionable.” However, currently only HER2 is an established therapeutic target, and patients with other potentially actionable alterations may not have access to investigational agents targeting their genomic alterations, and even if they do, these investigational therapies may not be effective.

Although the recognition of genomic evolution of tumors during disease progression and treatment is increasing (21–24), our study has demonstrated a high concordance between primary and recurrent/metastatic tumors. Therefore, analysis of archived primary tumor samples may be sufficient for therapeutic decision making for most patients. Alterations acquired in metastases, such CDK4 and MDM2 amplifications, may give unique insights into the mechanisms of metastases and drug resistance. Whether these alterations drive disease progression and survival and, therefore, represent suitable therapeutic targets for treatment of metastatic breast cancer or for adjuvant therapy aimed at preventing a relapse warrants further study. However, as both gains and losses of potential therapeutic targets were observed in recurrences and metastases, repeat biopsy and genomic profiling of recurrent or metastatic tumors should be considered when feasible and when a change in biology is clinically evident.

Disclosure of Potential Conflicts of Interest
G.M. Frampton has ownership interest (including patents) in Foundation Medicine. R. Yelensky has ownership interest (including patents) in Foundation Medicine. J. Ferrer-Lozano has ownership interest (including patents) in Foundation Medicine. F. Meric-Bernstam has ownership interest (including patents) in Foundation Medicine. G.B. Mills has ownership interest (including patents) in Foundation Medicine. S. Cronin has ownership interest (including patents) in Foundation Medicine. V.A. Miller has ownership interest (including patents) in Foundation Medicine. J.S. Ross has ownership interest (including patents) in Foundation Medicine. J. Ferrer-Lozano has ownership interest (including patents) in Foundation Medicine. P.J. Stephens has ownership interest (including patents) in Foundation Medicine. J.S. Ross has ownership interest (including patents) in Foundation Medicine. F. Meric-Bernstam has ownership interest (including patents) in Foundation Medicine. J. Ferrer-Lozano has ownership interest (including patents) in Foundation Medicine. P.J. Stephens has ownership interest (including patents) in Foundation Medicine. G.B. Mills has ownership interest (including patents) in Foundation Medicine. J.S. Ross has ownership interest (including patents) in Foundation Medicine. J. Ferrer-Lozano has ownership interest (including patents) in Foundation Medicine. P.J. Stephens has ownership interest (including patents) in Foundation Medicine. G.B. Mills has ownership interest (including patents) in Foundation Medicine.

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