Prevalence of Estrogen Receptor Alpha (ESR1) Somatic Mutations in Breast Cancer

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Abstract

Estrogen receptor–positive breast tumors, which initially respond effectively to endocrine therapy, progress due to acquired endocrine therapy resistance, including genomic alterations in estrogen receptor alpha (ESR1). A recent study has suggested that there is a sufficient number of preexisting ESR1 mutations acting as an intrinsic resistance mechanism to warrant primary screening. We determined the incidence of de novo ESR1 mutations in hormone-positive treatment-naïve primary breast tumors using 12 publicly available international datasets in the cBioPortal. The prevalence of mutation was statistically significantly lower in treatment-naïve primary tumors (n = 6 of 3682, 0.16%) than in metastatic (n = 156 of 1089, 14.3%, 2-sided P < .001) or previously treated primary tumors (n = 11 of 92, 12.0%, 2-sided P < .001). Pathogenic ESR1 mutations are a common mechanism of acquired but not intrinsic resistance to endocrine therapy and may not warrant universal testing of primary breast cancer populations.

Approximately 70%-80% of breast cancers are estrogen receptor (ER) positive, which respond effectively to endocrine therapy. However, breast tumors have been shown to progress due to acquired endocrine therapy resistance, including genomic alterations in estrogen receptor alpha (ESR1) (1). ESR1 mutations are common in metastatic and endocrine-resistant disease and are associated with a more aggressive clinical course. Recently, Dahlgren et al. (2) also showed that pathogenic mutations in ESR1 may be a biomarker of intrinsic resistance to endocrine therapy in primary breast cancer patients. The authors analyzed 3217 patients enrolled in the multicenter Sweden Cancerome Analysis Network - Breast (SCAN-B) Initiative, which is the largest prospective population-based cohort of primary breast tumor patients undergoing routine RNA sequencing. ESR1 pathogenic mutations occurred in 1.1% of ER-positive tumors and were associated with poorer relapse-free and overall survival after endocrine therapy. Although ESR1 mutations were recently described as a mechanism of acquired resistance to endocrine therapy, this is the first study, to our knowledge, to identify preexisting ESR1 mutations as a biomarker of intrinsic resistance in the adjuvant setting. The authors conclude that if their results are replicated, ESR1 screening should be considered in ER-positive primary breast cancer. We therefore sought to validate their results using publicly available international datasets in the cBioPortal (3).

All publicly available breast and pan-cancer databases in cBioPortal were queried for clinically and genomically annotated data. Primary and metastatic breast tumor samples were included in our analysis if information on hormone status was available. Putative driver (pathogenic) mutations versus variants of unknown significance were defined via OncoKB and Cancer Hotspots annotations. Treatment status was included when available. The prevalence of ESR1 mutations was compared between groups using Fisher’s exact test. Continuous variables were compared by the Wilcoxon test. Tests of statistical significance were 2-sided, and P values less than .05 were considered statistically significant. Statistical analyses were conducted using the cBioPortal website and RStudio Version 1.4.1106 (RStudio, Inc) software.

We surveyed 7103 primary or metastatic breast tumors from 6882 patients in 12 studies, including 4863 hormone-positive samples derived from 4727 patients (Table 1) (4-13). In the Metastatic Breast Cancer Project (7), pathogenic ESR1 mutations were more common in hormone-positive metastatic versus primary tumors (13.2% vs 2.5% [5 of 38 vs 4 of 161], P = .01) and pretreated versus treatment-naïve tumors (11.1% vs 0% [4 of 36 vs 0...
Table 1. Frequency of pathogenic ESR1 mutations in hormone-positive tumors

| Study Description | No. of patients | Age < 50, % | HER2+, % | Grade 1–2, % | Stage I-II, % | No. of samples | Variant allele frequency threshold | ESR1-mutant, No. | ESR1-mutant, % |
|-------------------|----------------|-------------|----------|-------------|--------------|---------------|----------------------------------|----------------|----------------|
| Primary breast cancer, treatment-naïve | | | | | | | | | |
| MBC project, ESMO Open, 2018 (7) | United States | 63 | 73.0 | 27.6 | 66.7 | 32.3 | 69 | 0.01 | 0 | 0 |
| MSKCC, Cancer Cell, 2018 (4) | United States, prospective | 739 | 38.6 | 7.6 | 51.1 | 69.7 | 756 | 0.02 | 4 | 0.53 |
| TCGA, Cell, 2018 (6) | International, retrospective/prospective | 659 | 29.1 | 30.1 | — | 73.1 | 659 | 0.03 | 2 | 0.30 |
| METABRIC, Nature, 2012 (9) | United Kingdom/Canada | 1844 | 17.8 | 7.4 | 61.0 | 92.5 | 1844 | None | 0 | 0 |
| SMC, Nature Comm, 2018 (12) | Korea, prospective | 131 | 87.0 | 21.4 | — | 66.4 | 131 | — | 0 | 0 |
| Broad, Nature, 2012 (8) | Vietnam/Mexico | 58 | 51.7 | 16.1 | 74.3 | 81.0 | 58 | Other | 0 | 0 |
| Sanger, Nature, 2012 (11) | United Kingdom | 81 | 39.5 | 30.9 | 56.8 | 81 | — | — | 0 | 0 |
| CPTAC, Cell, 2020 (5) | International, prospective | 83 | 22.9 | 9.0 | — | 66.7 | 83 | 0.01 | 0 | 0 |
| Total | | 3659 | 28.6 | 13.5 | 58.6 | 79.5 | 3682 | 6 | 0.16 |
| Metastatic breast cancer | | | | | | | | | |
| MBC project, ESMO Open, 2018 (7) | United States | 32 | 85.0 | 35.5 | 52.6 | 33.3 | 38 | 0.01 | 5 | 13.6 |
| MSKCC, Cancer Cell, 2018 (4) | United States, prospective | 788 | 53.5 | 11.9 | 28.8 | 51.7 | 877 | 0.02 | 132 | 15.1 |
| INSERM, PLoS Med, 2016 (13) | France, prospective | 143 | — | 0.0 | — | 143 | — | 0.1 | 16 | 11.2 |
| China Pan-cancer (3) | China | 31 | 51.6 | — | — | 31 | — | 3 | 9.7 |
| Total | | 994 | 54.2 | 12.9 | 29.5 | 51.3 | 1089 | 6 | 156 | 14.3 |
| Primary breast cancer, previously-treated | | | | | | | | | |
| MBC project, ESMO Open, 2018 (7) | United States | 27 | 44.4 | 18.5 | 58.3 | 24.0 | 28 | 0.01 | 2 | 7.1 |
| MSKCC, Cancer Cell, 2018 (4) | United States, prospective | 47 | 53.2 | 9.1 | 55.9 | 10.6 | 47 | 0.02 | 9 | 19.1 |
| China Pan-cancer (3) | China | 17 | 70.6 | — | — | 6.7 | 17 | — | 0 | 0 |
| Total | | 91 | 53.8 | 12.7 | 56.9 | 14.8 | 92 | 11 | 12.0 |

*aAll datasets are publicly available on cBioportal. Hormone-positive samples were identified from 7103 samples from 6882 patients in 12 studies. The MET500 (Nature, 2017) and ICGC (Nature, 2020) datasets lacked information on hormone status and were excluded.

*bTreatment status not specified.

*Patients were 88% premenopausal and 95% treatment naïve.

*Patients received a median of 3 previous lines of therapy (range 1–15).

*Patients pooled from genomic screening for SAFIR01 (Lancet Oncol., 2014), SAFIR02 (Nature Med., 2021), SHIVA (Lancet Oncol., 2015), and MOSCATO (Cancer Discovery, 2014) prospective trials. A total 84% received prior endocrine therapy.

*All patients received previous endocrine therapy.

*No threshold was used for mutations that were present/confirmed in the COSMIC database. Variants were removed if present in the normal tissue pool.

*Mutations were identified if statistically above noise and not present in normal tissue pool.

*Mutations identified in exons 380 (n = 3), 536 (n = 1), 537 (n = 1), and 538 (n = 1).

*Mutations identified in exons 380 (n = 22), 422 (deletion, n = 3), 463 (n = 1), 536 (n = 8), 537 (n = 66), and 538 (n = 63).

*Mutations identified in exons 380 (n = 2), 463 (n = 1), 536 (n = 1), 537 (n = 5), and 538 (n = 2).

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of 80], \( P = .008 \), consistent with previous reports (4,13). Additionally, median times from diagnosis to sample collection and metastatic diagnosis were longer in ESR1 mutant tumors (100 vs 1 months, \( P = .001 \) and 68 vs 2 months, \( P = .04 \), respectively), suggesting a dose-response relationship between endocrine therapy exposure and the development of ESR1 pathogenic mutations.

Across all studies, there were 6 tumors with pathogenic ESR1 mutations identified among 3682 hormone-positive treatment-naïve primary breast tumors. The prevalence of mutation was statistically significantly lower in treatment-naïve primary tumors (\( n = 6, 0.16\% \)) than in metastatic (\( n = 156 \) of 1089, 14.3%, \( P < .001 \)) or previously treated primary tumors (\( n = 11 \) of 92, 12.0%, \( P < .001 \)). Of the 4 hormone-positive treatment-naïve primary breast tumors with ESR1 mutations identified in the MSKCC dataset, follow-up times were shorter than 7 months and there were no progressions, distant recurrences, or deaths, precluding meaningful interrogation of the prognostic impact of preexisting ESR1 mutations. Two additional patients with ESR1 mutant tumors in the TCGA database were followed-up for 13 and 50 months, respectively, without progressions, recurrences, or deaths. Two patients in the China Pan-cancer dataset with ESR1 mutant treatment-naïve primary tumors were excluded because of unknown hormone status. In a sensitivity analysis, including these 2 tumors with unknown hormone status would increase the prevalence of ESR1 mutations to 0.21% in hormone-positive treatment-naïve primary tumors.

These data provide evidence that pathogenic ESR1 mutations are a common mechanism of acquired but not intrinsic resistance to endocrine therapy. Differences in prevalence may be attributed to sequencing methodology and vary within populations. Additional studies are necessary to determine if the incidence is sufficient to warrant universal testing of primary breast cancer populations.

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Data Availability

Data is available as cited in the cBioPortal.

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