The Molecular Landscape of Premenopausal Versus Postmenopausal Breast Cancer in Patients Without Inherited Predisposition Mutations

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Introduction

Breast cancer in premenopausal women (preM) is frequently associated with worse prognosis compared to that in postmenopausal women (postM). There is, however, a paucity of studies characterizing molecular alterations in premenopausal patients compared to postmenopausal ones in patients with breast cancer, but without any evidence of predisposition inherited mutations. We used molecular profiling of DNA and RNA using next generation sequencing (NGS) and evaluated the molecular differences between PreM and post-M breast cancers in patient without risk of predisposition to cancer.

Methods and Materials

Case descriptions were collected by COTA, inc. This included 52 patients with breast cancer evaluated clinically at a referral cancer center (John Theurer Cancer Center, Hackensack, NJ, USA) and the DNA and RNA of their tissue samples were evaluated by Genomic Testing Cooperative using next generation sequencing (NGS) of a targeted panel of 1,408 RNA genes and 434 DNA genes. All patients were treated with standard of care therapy by subspecialized oncologists. Machine learning algorithm and Geometric Mean Naïve Bayesian (GMNB) were used to select RNA genes and distinguish between preM and postM cases. The samples were selectively enriched for 1408 cancer-associated genes. cDNA was generated from the cleaved RNA fragments using random primers during first- and second strand synthesis.

Age median (range)	52 (26-84)
Race	Asian: 4 African American: 11 White: 23 Hispanic or Latino : 8 Other or unknown :11
Stage	I : 3 II : 13 III: 14 IV: 20 Unspecified: 7
Grade	I: 2 II : 20 III: 37 IV : 4 Unspecified: 4
Tumor	T1: 10 T2: 12 T3: 14 T4: 8 Unspecified: 13
Node	N0: 14 N1: 26 N2: 4 N3: 4 Unspecified: 9
Metastasis	M0: 31 M1: 19 Unspecified: 7

Table 1. Patients' characteristics

Results

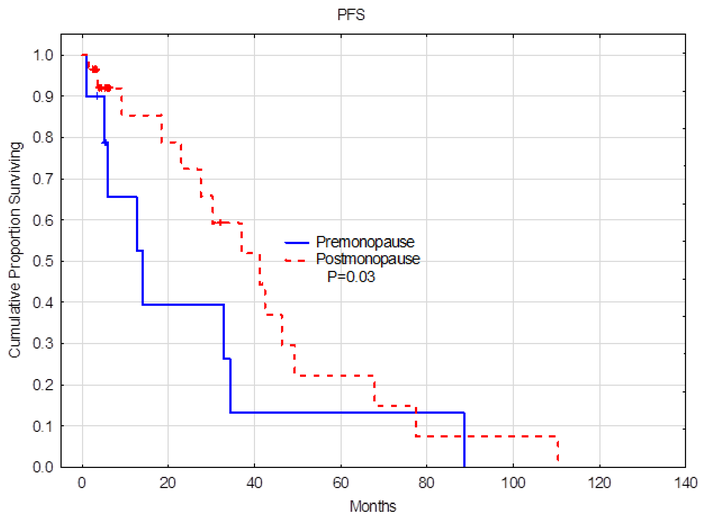

Figure 1. PreM patients showed lower cumulative survival proportion (P=0.03).

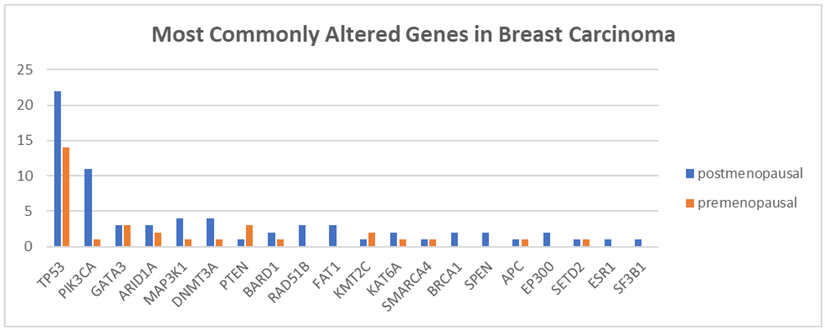

Figure 2. TP53, PIK3CA and GATA3 mutations were the most common mutations in preM and postM patients. However, PTEN mutation was more common in preM cases.

Conclusions

Together these data suggest that breast cancers in patients with no germline predisposition to cancer presenting differ biologically in preM patients as compared with postM tumors and these differences should be considered in treatment and management plans of these patients.

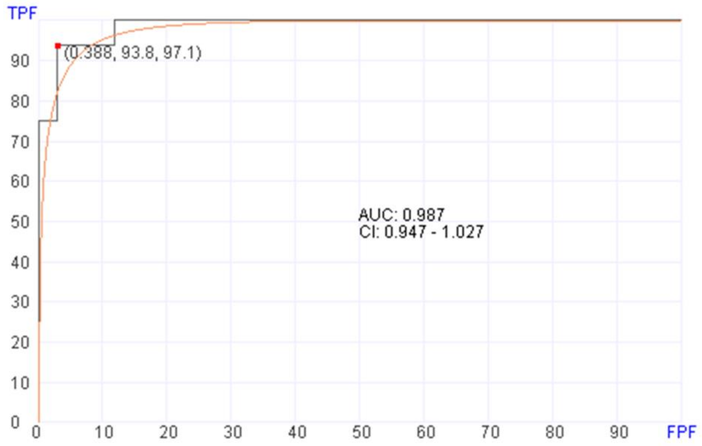

Figure 3. ROC curve for distinguishing between preM and postM cases of breast cancer. The AUC of 0.987 (95% Confidence interval of 0.947 to 1.00) is obtained using 20 genes. The 20 genes are TCF7L2, C11orf30 (EMSY), ARIH2, MLH1, IRF2BP2, FGFR1OP, NFE2L2, EPC1, SOS1, MLLT4, IL13RA2, GIT2, MAP3K1, SF3B1, ERCC4, ADD3, CHUK, FRK, REEP3 and MAP2K6.

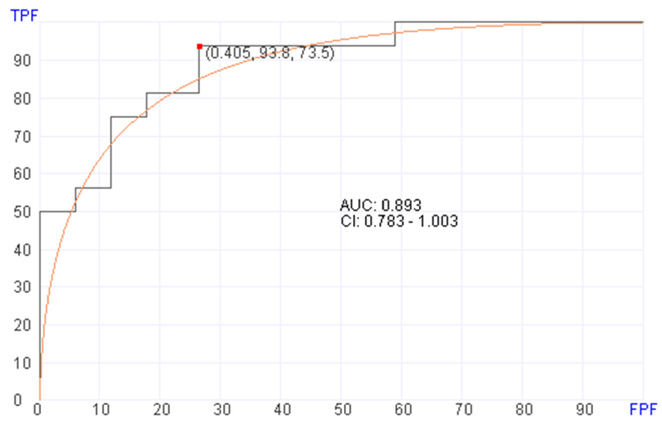

Figure 4. Leave-one-out curve showed AUC of 0.893 (95% confidence Interval of 0.783 to 1.00).