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Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer.

Couch FJ[1], Hart SN[2], Sharma P[2], Toland AE[2], Wang X[2], Miron P[2], Olson JE[2], Godwin AK[2], Pankratz VS[2], Olswold C[2], Slettedahl S[2], Hallberg E[2], Guidugli L[2], Davila JI[2], Beckmann MW[2], Janni W[2], Rack B[2], Ekici AB[2], Slamon DJ[2], Konstantopoulou I[2], Fostira F[2], Vratimos A[2], Fountzilas G[2], Pelttari LM[2], Tapper WJ[2], Durcan L[2], Cross SS[2], Pilarski R[2], Shapiro CL[2], Klemp J[2], Yao S[2], Garber J[2], Cox A[2], Brauch H[2], Ambrosone C[2], Nevanlinna H[2], Yannoukakos D[2], Slager SL[2], Vachon CM[2], Eccles DM[2], Fasching PA[2].

bstract

PURPOSE:

Recent advances in DNA sequencing have led to the development of breast cancer susceptibility gene panels for germline genetic testing of patients. We assessed the frequency of mutations in 17 predisposition genes, including BRCA1 and BRCA2, in a large cohort of patients with triple-negative breast cancer (TNBC) unselected for family history of breast or ovarian cancer to determine the utility of germline genetic testing for those with TNBC.

PATIENTS AND METHODS:

Patients with TNBC (N = 1,824) unselected for family history of breast or ovarian cancer were recruited through 12 studies, and germline DNA was sequenced to identify mutations.

RESULTS:

Deleterious mutations were identified in 14.6% of all patients. Of these, 11.2% had mutations in the BRCA1 (8.5%) and BRCA2 (2.7%) genes. Deleterious mutations in 15 other predisposition genes were detected in 3.7% of patients, with the majority observed in genes involved in homologous recombination, including PALB2 (1.2%) and BARD1, RAD51D, RAD51C, and BRIP1 (0.3% to 0.5%). Patients with TNBC with mutations were diagnosed at an earlier age ($P < .001$) and had higher-grade tumors ($P = .01$) than those without mutations.

CONCLUSION:

Deleterious mutations in predisposition genes are present at high frequency in patients with TNBC unselected for family history of cancer. Mutation prevalence estimates suggest that patients with TNBC, regardless of age at diagnosis or family history of cancer, should be considered for germline genetic testing of BRCA1 and BRCA2. Although mutations in other predisposition genes are observed among patients with TNBC, better cancer risk estimates are needed before these mutations are used for clinical risk assessment in relatives.