Impact of germline *BRCA* status on clinical outcomes of patients with HR+/HER2- early breast cancer.

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Background: Germline pathogenic variants (PVs) in the *BRCA1* and *BRCA2* (g*BRCA1/2*) genes increase the risk for breast cancer (BC) development.The prognostic significance of *gBRCA1/2* in patients with hormone receptor-positive/HER2-negative (HR+/HER2) early BC is still controversial. **Methods:** This cohort study derived from a prospectively-maintained institutional database of all consecutive patients with BC who underwent germline testing, including *BRCA1*, *BRCA2* and *PALB2*, at the European Institute of Oncology (May 2002-Jan 2024). The study population comprised patients with stage I-III HR+/HER2- (estrogen receptor expression >1%) invasive BC who underwent surgery and (neo)adjuvant treatment, as endocrine therapy (ET) +/- chemotherapy (CT) (Jan 2000-Dec 2022). Primary endpoints were distant relapse-free interval (DRFI) and invasive disease-free survival (iDFS) by STEEP 2.0. Univariate and multivariate Cox proportional-hazard models were employed for survival analyses, with left-truncated models to account for the time from BC diagnosis to germline testing. **Results:** A total of 1,730 patients were included in the analyses, with 52 (3%) *BRCA1*, 180 (10%) *BRCA2*, and 9 (0.5%) *PALB2* PV carriers. Compared to non-carriers, patients with *gBRCA1/2* and *gPALB2* PVs were younger (median age: 39 vs 42 yrs, p<.001), had advanced disease stage (stage II-III: 71% vs 58%, p<.001), higher tumor grade (G3: 54% vs 26%, p<.001) and Ki-67 expression (median: 26% vs 20%, p<.001). Patients with *gBRCA1/2* and *gPALB2* PVs were also more likely to receive neoadjuvant (13% vs 6%, p<.001) and/or adjuvant CT (56% vs 36%, p<.001) and mastectomy (56% vs 45%, p=.002). All patients received adjuvant ET, as tamoxifen or aromatase inhibitor +/- GnRH analogue. No patient received adjuvant olaparib or CDK4/6 inhibitor. At a median follow-up of 9.7 (IQR 6-13.9) years, 335 (19%) patients experienced local relapse, 316 (18%) distant metastasis, and 124 (7.2%) died due to BC. At multivariate analyses, *gBRCA2* P/LPVs were independently associated with shorter DRFI (HR 1.46, 95%CI 1.04–2.06, p=.028) and iDFS (HR 1.34, 95 CI 1.01–1.78, p=.045), regardless of stage, nodal status, (neo) adjuvant CT, type of surgery and adjuvant ET, whereas *gBRCA1* were not. Exploratory analyses showed that among 232 *gBRCA1/2* carriers, 47 (20%) and 96 (41%) were eligible for adjuvant olaparib or abemaciclib therapy per OlympiA and monarchE criteria, respectively, with 37 (16%) eligible for both therapies. Additional analyses to unravel interaction of *gBRCA* status with adjuvant treatment are underway. **Conclusions:** Patients with HR+/HER2- early BC harboring *gBRCA2* PVs had a significantly increased risk of recurrence, with a potentially distinct impact of *BRCA2* vs *BRCA1*. Only a small proportion of this population currently qualify to adjuvant treatment escalation with targeted therapies, underscoring the need of expanding the therapeutic options in this setting. Research Sponsor: None.