GS1-08: Association between risk-reducing surgeries and survival in young *BRCA* carriers with breast cancer: results from an international cohort study

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Background:
In carriers of germline pathogenic/likely pathogenic variants (PVs) in *BRCA1* and/or *BRCA2* genes, cancer risk management strategies are widely recommended. While risk-reducing salpingo-oophorectomy (RRSO) has shown to improve overall survival (OS), bilateral risk-reducing mastectomy (RRM) reduces the risk of developing breast cancer (BC) but has no proven OS benefit. Very limited evidence exists on RRSO and/or RRM specifically in *BRCA* carriers with prior BC diagnosis at a young age.

Here we investigated the association between RRM and/or RRSO with survival outcomes in the largest global cohort of young *BRCA* carriers with BC.

Methods:
The BRCA BCY Collaboration (NCT03673306) is an international, multicenter, hospital-based, retrospective cohort study including women harboring germline *BRCA1* and/or *BRCA2* PVs and diagnosed between January 2000 and December 2020 with stage I-III invasive BC at the age of 40 years or younger. Patients with no information on uptake or timing of RRM and/or RRSO, or their uptake before BC diagnosis and *BRCA* healthy carriers were excluded.

Primary endpoint was OS. Disease-free survival (DFS) and BC-free interval (BCFI) were secondary endpoints. Survival endpoints were computed from BC diagnosis.

To account for potential lead time bias, in the primary analysis Cox models were used to explore the association between RRM and RRSO both included as time-dependent covariates and survival outcomes. Stratification factors were year at BC diagnosis, region/country and nodal status; OS models were also adjusted by development of distant recurrences/second primary malignancies as time-dependent covariates. In addition, sensitivity analyses were performed including a 3-year landmark analysis and a subgroup analysis including only patients tested for *BRCA* before or within 6 months from BC diagnosis.

Results:
From 109 centers in 5 continents, 5290 patients were included. Median age at BC diagnosis was 35 years (IQR 31-38). A total of 3361 (63.5%) patients were *BRCA1* carriers, 2708 (51.2%) had node-negative and 2421 (45.8%) hormone receptor-positive (HR+) BC.

A total of 2910 (55.0%) patients underwent RRM and 2782 (52.6%) RRSO. Median time from BC diagnosis to RRM was 0.8 years (IQR 0.5-2.7) and to RRSO was 3.0 years (IQR 1.3-6.8); median follow-up was 5.1 years (IQR 2.7-8.3) after RRM and 4.9 years (IQR 2.3-8.1) after RRSO.

At a median follow-up of 8.2 years (IQR, 4.7-12.8), 686 (13.0%) OS, 1923 (36.3%) DFS and 1751 (33.1%) BCFI events were observed.

RRM was associated with a significantly reduced risk of OS events (adjusted HR [aHR] 0.65, 95% CI 0.53-0.78). This association was observed irrespective of specific *BRCA* gene, age at BC diagnosis, tumor subtype, tumor size and nodal status. RRM was also associated with a significantly reduced risk of DFS (aHR 0.58, 95% CI 0.52-0.65) and BCFI (aHR 0.55, 95% CI 0.48-0.62) events.

RRSO was associated with a significantly reduced risk of OS events (aHR 0.58, 95% CI 0.48-0.71). This association was observed irrespective of age at BC diagnosis, tumor size and nodal status. A significant interaction was observed according to specific *BRCA* gene (*BRCA1* carriers: aHR 0.44, 95% CI 0.34-0.57; *BRCA2* carriers: aHR 0.85, 95% CI 0.64-1.15) and tumor subtype (triple-negative BC: aHR 0.44, 95% CI 0.33-0.58; HR+ BC: aHR 0.80, 95% CI 0.60-1.05). RRSO was also associated with a significantly reduced risk of DFS (aHR 0.68, 95% CI 0.61-0.77) and BCFI (aHR 0.65, 95% CI 0.57-0.74) events.

Sensitivity analyses provided consistent results.

Conclusions:
In this unique international cohort of *BRCA* carriers with prior BC diagnosis at a young age, RRM and RRSO were both associated with a significant improvement in OS, DFS and BCFI. These findings are critical for improving the counseling of young *BRCA* carriers with BC on cancer risk management strategies.