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BRCA-mutation Carriers With a History of Early-onset Breast Cancer May Benefit From Risk-reducing Surgery

SAN ANTONIO – Patients with germline BRCA mutations who were diagnosed with breast cancer at or before age 40 and who underwent a bilateral risk-reducing mastectomy (RRM) and/or a risk-reducing salpingo-oophorectomy (RRSO) had lower rates of recurrence, secondary breast and/or ovarian malignancies, and death than those who did not undergo these surgeries, according to results presented at the San Antonio Breast Cancer Symposium (SABCS), held December 10-13, 2024.

“The benefits of RRM and RRSO have been shown for BRCA-mutation carriers without a prior history of cancer, but their impact for BRCA-mutation carriers with a history of early-onset breast cancer is less clear,” said presenter Matteo Lambertini, MD, PhD, an associate professor of medical oncology and consultant in medical oncology at the University of Genova-IRCCS Policlinico San Martino Hospital in Genoa, Italy.

Both RRM and RRSO can adversely affect a patient’s quality of life and RRSO also leads to infertility and early menopause, which can be particularly difficult for BRCA carriers with prior breast cancer since they are not eligible for the hormone replacement therapies that help mitigate menopause symptoms, Lambertini explained. “Considering the unique traits and needs of this younger population, and their high risk for secondary malignancies, it is critical to understand how risk-reducing surgeries affect patient outcomes so that the risks and benefits of these procedures can be carefully weighed,” he said.

To study the association between RRM and/or RRSO and survival outcomes, Lambertini and colleagues conducted an analysis of the BRCA BCY Collaboration study, an international, multicenter, retrospective cohort study of patients with germline pathogenic or likely pathogenic variants of BRCA who were diagnosed with stage 1-3 breast cancer at the age of 40 or younger between January 2000 and December 2020.

The analysis included 5,290 patients from 109 institutions across five continents. Among these patients, 3,888 underwent at least one risk-reducing surgery: 2,910 underwent RRM, 2,782 underwent RRSO, and 1,804 opted for both RRM and RRSO. The remaining 1,402 patients did not undergo either surgery.

The researchers found that undergoing RRM and/or RRSO was associated with improved outcomes after a median follow-up of 8.2 years.

Specifically, patients who had a RRM had a 35% lower risk of death and a 42% lower risk of breast cancer recurrence or a second primary malignancy. The improved outcomes were observed regardless of whether the germline BRCA mutation was present in the BRCA1 or BRCA2 gene.

Patients who underwent a RRSO had a 42% lower risk of death and a 32% lower risk of breast cancer recurrence or second primary malignancy. The benefit of RRSO on overall survival varied by the BRCA gene that was mutated, with a greater survival benefit for patients with germline mutations in BRCA1 than in BRCA2 (56% vs. 15% lower risk of death, respectively). When examining by breast cancer subtype, the researchers found that RRSO had the greatest survival benefit for patients with triple-negative breast cancer (56% lower risk of death), followed by hormone receptor-positive breast cancer (20% lower risk of death).

Overall survival was similar between patients who underwent both surgeries and those who had only one surgery.

“This global study provides the first evidence that risk-reducing surgeries improve survival outcomes among young BRCA-mutation carriers with a prior history of early-onset breast cancer,” said Lambertini. “We believe that our findings are critical for improving the counseling of BRCA-mutation carriers with early-onset breast cancer on cancer-risk management strategies.”

Limitations of the study include its retrospective design and the inclusion of patients from different health care systems with different resources and guidelines. In addition, the analysis includes patients treated over a period of 20 years, during which recommendations for germline BRCA testing and for risk-reducing surgeries have evolved. Further, the results may have been biased if patients perceived to have better prognosis were more likely to have risk-reducing surgeries recommended to them.

The study was supported by the Italian Association for Cancer Research (AIRC) and the European Society for Medical Oncology (ESMO). Lambertini reports advisory roles for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Exact Sciences, Pierre Fabre, and Menarini; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Menarini, and AstraZeneca; travel grants from Gilead, Daiichi Sankyo, and Roche; and research funding to his institution from Gilead.

Abstract

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

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, 5292 patients were included. Median age at BC diagnosis was 35 years (IQR 31-38). A total of 3364 (63.6%) patients were BRCA1 carriers, 2723 (51.5%) had node-negative and 2422 (45.8%) hormone receptor-positive (HR+) BC. A total of 2911 (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), 691 (13.0%) OS, 1928 (36.3%) DFS and 1753 (33.0%) BCFI events were observed. RRM was associated with a significantly reduced risk of OS events (adjusted HR [aHR] 0.64, 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 0.47-0.70). 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 0.63-1.14) and tumor subtype (triple-negative BC: aHR 0.43, 95% CI 0.32-0.58; HR+ BC: aHR 0.80, 95% CI 0.61-1.06). 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.

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