## **RAD50 Mutations**

## Cancer Risks and General Management Recommendations

- There are currently no national consensus guidelines outlining specific clinical management recommendations for individuals who carry a *RAD50* gene mutation. Additionally, exact lifetime cancer risks associated with *RAD50* mutations are unknown at this time.
- Some studies have proposed an increased risk for breast cancer in females with a *RAD50* mutation (lifetime risk of ~24-36%).<sup>1-4</sup> However, others have found no increased risk for breast cancer.<sup>5-7</sup> Additionally, some studies have proposed an increased ovarian cancer risk in individuals with a *RAD50* mutation.<sup>8,9</sup> However, the studies are small, and data remains limited. At this time, it is unknown if individuals with *RAD50* gene mutations are at increased risk for other cancers.
- Current NCCN guidelines assert that there is insufficient evidence to make any recommendations for breast MRI, risk-reducing mastectomy (RRM), or risk-reducing salpingo-oophorectomy (RRSO) based on *RAD50* mutation status alone.<sup>10</sup> An individual's personal and family history should be considered in developing an appropriate surveillance plan.

## Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *RAD50* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- It has been proposed that individuals who inherit two pathogenic *RAD50* mutations, one from each parent, are at risk for a rare genetic condition known as Nijmegen breakage syndrome-like disorder (NBSLD).
  - NBSLD is characterized by chromosomal instability, radiosensitivity, neurodevelopmental disease, and immunodeficiency<sup>11</sup>.
  - *RAD50* genetic testing for the partner of an individual with an *RAD50* mutation may be appropriate to clarify the risk of having children with NBSLD.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks, including reproductive risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

## **References:**

- 1. Heikkinen K, Rapakko K, Karppinen SM, et al. RAD50 and NBS1 are breast cancer susceptibility genes associated with genomic instability. *Carcinogenesis.* 2006;27(8):1593-1599.
- 2. Damiola F, Pertesi M, Oliver J, et al. Rare key functional domain missense substitutions in MRE11A, RAD50, and NBN contribute to breast cancer susceptibility: results from a Breast Cancer Family Registry case-control mutation-screening study. *Breast Cancer Res.* 2014;16(3):R58.
- 3. Heikkinen K, Karppinen SM, Soini Y, Makinen M, Winqvist R. Mutation screening of Mre11 complex genes: indication of RAD50 involvement in breast and ovarian cancer susceptibility. *J Med Genet.* 2003;40(12):e131.
- 4. Tommiska J, Seal S, Renwick A, et al. Evaluation of RAD50 in familial breast cancer predisposition. *Int J Cancer*. 2006;118(11):2911-2916.
- 5. Couch FJ, Shimelis H, Hu C, et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. *JAMA Oncol.* 2017;3(9):1190-1196.
- 6. Fan C, Zhang J, Ouyang T, et al. RAD50 germline mutations are associated with poor survival in BRCA1/2negative breast cancer patients. *International journal of cancer*. 2018;143(8):1935-1942.

- 7. Shimelis H, LaDuca H, Hu C, et al. Triple-Negative Breast Cancer Risk Genes Identified by Multigene Hereditary Cancer Panel Testing. *Journal of the National Cancer Institute*. 2018;110(8):855-862.
- 8. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci U S A*. 2011;108(44):18032-18037.
- 9. Minion LE, Dolinsky JS, Chase DM, Dunlop CL, Chao EC, Monk BJ. Hereditary predisposition to ovarian cancer, looking beyond BRCA1/BRCA2. *Gynecologic oncology.* 2015;137(1):86-92.
- 10. NCCN Clinical Practice Guidelines in Oncology<sup>®</sup>: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020. 2019.
- 11. Waltes R, Kalb R, Gatei M, et al. Human RAD50 deficiency in a Nijmegen breakage syndrome-like disorder. *American journal of human genetics.* 2009;84(5):605-616.