# Literature Review of the effect of BRCA1/BRCA2 mutations on Ashkenazi Jewish Breast Cancer Patients

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BRCA 1/BRCA 2, the rare type of gene mutation, can significantly increase an adult's risk of developing breast and ovarian cancer. Not only does such mutation increases one's risk, the affected people are prone to develop cancer at a much younger age compared to the general population and are likely to be tested ER negative, which increased the difficulties of treating breast cancer. Thus, even though BRCA1/2 mutation contribute to only up to 10 percent of breast cancer, this group of patients may need preventions and special treatment to prevent recurrences.

The recommended treatment for early-stage breast cancer patients in general is breast conservation therapy (BCT) or so-called lumpectomy, which allows the patients to keep most of their breasts while trying to remove the cancer instead of a mastectomy, which removes the whole breast. Research in the 80s showed the efficacy of BCT for the general population especially for early-stage breast cancer patients.

However, the efficacy of breast conservation therapy (BCT) for BRCA1/2 mutation carriers has been discussed and examined by many professionals, but they can hardly come to a universal agreement. The controversies are represented by disagreement in mutation carrier's overall survival, breast cancer specific survival, recurrence free survival, ipsilateral recurrence rate, etc. compared with non-mutation carriers. Different studies can arrive at opposite results due to several reasons.

First, the types of patients and the properties of data available to researchers can differ; the length of study and length of follow-up can also make a difference. More importantly, the sample size for BRCA1 and especially BRCA2 carriers are relatively small, and it is possible to observe something significant by chance. This is why many review articles have suggested a large cohort study to be conducted to reach a more reliable result.

The need to address the controversy become even more important after Angelina Jollie's article about her decision to undergo a preventive mastectomy was published in New York Time. Since her mother, who combated cancer for 10 years, died at age 54, and she was found to be a

carrier of BRCA gene and had a cancer risk of 89%, she made this decision. Since then, many studies have looked at her decision's impact on general public.

1. Mark Robson, Deborah Levin, Mark Federici, Jaya Satagopan, Faina Bogolminy, Alexandra Heerdt, Patrick Borgen, Beryl McCormick, Clifford Hudis, Larry Norton, Jeff Boyd, Kenneth Offit, Breast Conservation Therapy for Invasive Breast Cancer in Ashkenazi Women With BRCA Gene Founder Mutations, *JNCI: Journal of the National Cancer Institute*, Volume 91, Issue 24, 15 December 1999, Pages 2112–2117, https://doi.org/10.1093/jnci/91.24.2112

The paper examines how effective breast conservation therapy is for women who have BRCA1/2 mutation. The effectiveness is measured by disease-free survival, dead to breast cancer risk, overall survival, contralateral breast cancer risk, and ipsilateral breast tumor recurrence. The paper first looks at if there is any difference in the characteristics of women with or without mutation. It is shown that mutation carriers tend to be diagnosed with cancer at a statistically significant earlier age than non-mutation carriers, and they have more prevalent lymph node involvement and higher likelihood of ER negative than women without mutations. However, there is no statistical difference between the two groups in tumor stage.

Robson et al. completed both univariate and multivariate survival analyses. In univariate survival analyses, risk ratios of mutation status, tumor stage, lymph node stage, and age were calculated regarding ipsilateral breast tumor recurrence (IBTR), contralateral disease (CD), distant relapse (DR), and death from breast cancer (DOBC). Those under 50 has 2.66 times the risk of IBTR than those older than 50 ($p = 0.01$). Women with mutation has 2.96 times the risk of CR than women without mutation ($p = 0.002$). Mutation status, tumor stage, and lymph node involvement can be predictive of DR, and all four variables are also predictive of DOBC. In multivariate analysis, according to cox model, age is still associated with IBTR. Both DR and DOBC are influenced by tumor stage and lymph node stage, but not mutation status.

In conclusion, this paper provides evidence against using BCT for women with mutation, because they tend to have worse disease-free survival and breast cancer-specific survival compared to the other group. Even though mutation status is not included in the

final mode, but the paper argues mutation status, which is associated with lymph node stage and probably worse biologic features, can indirectly decrease this group's survival.

2. van den Broek AJ, Schmidt MK, van 't Veer LJ, Tollenaar RAEM, van Leeuwen FE (2015) Worse Breast Cancer Prognosis of *BRCA1/BRCA2* Mutation Carriers: What's the Evidence? A Systematic Review with Meta-Analysis. PLoS ONE 10(3): e0120189. https://doi.org/10.1371/journal.pone.0120189

Van den Broek et al. conducted this meta-analysis to analyze the difference of survival probability for people with and without mutation. It reviews sixty-six studies and examines BRCA 1 and 2 separately. The result shows that in overall survival, both adjusted and unadjusted survivals were slightly worse (not significant) for both BRCA 1 and BRCA 2, thus the results for both are considered indecisive. The BRCA 1 group has worse DOBC in unadjusted outcome but slightly better DOBC in adjusted outcome, although neither is significant. The unadjusted outcome for BRCA 2 on DOBC is worse but is primarily driven by one large study, and the adjusted outcome is composed of too few studies to derive any meaningful conclusion. The metastasis free survival for both BRCA 1 and BRCA 2 compared to the mutation-free group is in decisive. The unadjusted outcome also shows that those with BRCA 1 has worse recurrence-free survival probability compared to the control group, while the adjusted outcome only consists 2 studies, making it indecisive. Only 5 studies look at BRCA 2's effect on recurrence-free survival thus making the result indecisive as well.

The paper thus concludes that it is not suitable to draw conclusion about association between BRCA1/2 mutation and cancer prognosis yet due to the indecisive and heterozygous results. However, the paper notes that there is still a tendency of worse survival outcomes for those with mutations. The conclusion of the paper demonstrates the controversies around BRCA 1/2 mutations, as the previous studies show conflicting results of the effect of mutation status on survivals. This paper does not specify which treatment the BRCA ½ mutation carriers have received, which is part of the controversy and can have a good indication of survival. However, what this paper does suggest is that, firstly, patients with BRCA1/2 mutations should not have that predisposed feeling that they are going to

have a worst survival probability. More importantly, there probably should be a standardized way that all following studies follow in order to reduce heterogeneity (don't know if this is feasible, especially with differences in what data is available, but at least in data collection in the future, specific data should be collected for study purposes and during data analysis, some common analyses should be performed to decrease heterogeneity).

3. Vallard A, Magne N, Guy J-B, Espenel S, Rancoule C, Daio P, et al. Is brest-conserving therapy adequate in BRCA 1/2 mutation carriers? The radiation oncologist's point of view. *BR J Raiol* 2019: 92: 20170657. DOI: 10.1259/bjr.20170657.

This review paper focuses on the controversies on the adequacy of breast-conserving therapy (BCT) for mutation carriers. It reviews eight previous studies' patients' local outcomes. Interestingly, even though the paper concludes that there is no difference in local relapse for mutation carriers and non-mutation carriers in short term, the Garcia-Etienne et al. with a very short follow-up demonstrates significantly higher incidence of ipsilateral breast recurrence (IBTR) for women with BRCA1/2 mutation than sporadic patients. However, according to Vallard et al., the follow-up was too short. The paper also summarizes findings from the Haffty et al. paper. Even though after a median follow-up of 12.7 years reports it reports a higher recurrence rate for mutation carriers, the limitation of this study is that the patients did not have any adjuvant therapies. Other than the two studies with limitations, all other studies conclude there is no difference between the two groups in 15 years. Therefore, despite the uncertainties with small number of studies and the controversies in their results, Vallard et al., conclude that in short term, BCT is adequate for people with mutation, while the long-term effect is not clear.

One study compares BCT to mastectomy and have found out that BRCA mutation carriers had significantly higher rate of local recurrences when they went through BCT compared to mastectomy. However, a potential limitation is that those going through mastectomy are more likely to be prescribed to adjuvant therapies, which may have caused the difference. However, further studies are still lacking and more information is needed.

In conclusion, this study acknowledges the conflicts and in consistency arisen from the previous studies, and thus it suggests a large prospective cohort.

4. Chiba, A., Hoskin, T.L., Hallberg, E.J. et al. Impact that Timing of Genetic Mutation Diagnosis has on Surgical Decision Making and Outcome for BRCA1/BRCA2 Mutation Carriers with Breast Cancer. *Ann Surg Oncol* Springer International Publishing 2016: 23: 3232-8. https://doi.org/10.1245/s10434-016-5328-7

    This study examines how knowing BRCA mutation status changes one's surgical decision. 173 patients with BRCA+ status were categorized into three groups: those who already known their BRCA status before cancer diagnosis (G1); those who know their BRCA status during cancer workshop (G2); those who only know their status after cancer surgery (G3). Compared to G2 and G3, the cancer diagnosis for G1 are much more likely to be at early breast cancer stages. Regardless of the group, those with BRCA1+ are more likely to be ER negative. In cases of patients with unilateral cancer, those in G1/G2 are much more likely to choose bilateral mastectomy (83%) while over half in G3 choose lumpectomy and later about 40 percent of them undergo UM or BM. Thus, the study argues that knowledge of BRCA+ mutation status has an important impact on surgical decision making. Patients who underwent BM had significantly reduced contralateral breast tumor recurrence.

    This article contributes to the controversy uniquely as it shows that many of patients who did not choose BM initially would choose to undergo subsequent surgeries of BM or UM after they know their BRCA status. Thus, even though some studies may show the effectiveness of BCT, many patients still will not take the risk and will prefer BM. This indicates that unless the clinical results show absolutely no difference between treatments, many people still would like to choose BM.

5. Cao, W., Xie, Y., He, Y. et al. Risk of ipsilateral breast tumor recurrence in primary invasive breast cancer following breast-conserving surgery with BRCA1 and BRCA2 mutation in China. *Breast Cancer Res Treat* (2019) 175: 749-54. https://doi.org/10.1007/s10549-019-05199-8

    This article followed 1947 patients with breast cancer in China, and 31 were BRCA1 mutation carriers and 72 were BRCA2+ carriers. When analyzing the characteristics of the two groups, those with mutations were diagnosed with breast cancer at a significantly younger age, while they are more likely to have HER negative status. The difference

between the two groups in ER status and lymph node involvement were not significantly different.

This study analyzed risk of IBTR, which is made up of true recurrence (TR) and new primary (NP). While the hazard ratio of NP for mutation group to non-mutation group is 6.39 ($p = 0.001$) indicating a significant difference in rates of NP, there is no significant difference in IBTR and TR.

This contributes to the controversy in a way that suggests the high rate of NP may lead many to decide to undergo BM to prevent a new primary, especially for patients who have been diagnosed as BC at a really early age.

6. Robson, M. E., Chappuis, P. O., Satagopan, J., Wong, N., Boyd, J., Goffin, J. R., … Foulkes, W. D. (2004). A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. *Breast cancer research: BCR*, *6*(1), R8–R17. doi:10.1186/bcr658

This study treats BRCA1 mutation carriers and BRCA2 mutation carriers separately. Looking at the difference in characteristics of those groups, BRCA1 mutation carriers are more likely to be diagnosed before age 50, diagnosed with ER negative status, and received adjuvant chemotherapy compared to all other groups.

The survival probability for the three groups are reported, and BRCA 1 has much higher ($p < 0.0001$) probability of death at 10 years compared to noncarriers, while BRCA 2 carriers' probability of death is not much different from the non-carriers ($p = 0.38$). This result indicates that when other studies conclude that mutation carriers have a higher risks than non-carriers, it is worth looking at if this stands true for both BRCA1 and BRCA2 mutation carriers or the result is skewed because sample size for BRCA1 is much larger.

When performing multivariate analysis, BRCA1 mutation status, tumor size (>2), and nodal involvement are significantly related to DOBC and overall death. Even with adjusting for adjuvant chemotherapy treatment, the BRCA1 mutation group have higher hazard in both cases. However, mutation status in multivariate analysis become insignificant in women treated with chemotherapy or tamoxifen. CR risk is much higher for mutation carriers than non-carriers. Women with tamoxifen are less likely to have IBTR and CR for both mutation group and non-mutation group.

This study provides evidence for mixed result for mutation carriers undergoing BCT, and even with adjuvant chemotherapy or tamoxifen, the mutation group is still at a disadvantage compared to no mutation group.

7. Pierce, L.J., Phillips, KA., Griffith, K.A. et al. Breast Cancer Res Treat (2010) 121: 389. https://doi.org/10.1007/s10549-010-0894-z

This study compares breast conservation therapy (BCT) with mastectomy (M) for BRCA+ mutation carriers. It first examines local and regional failures, and concludes that patients undergoing BCT has significantly increase in local failure cumulative incidence estimates than patients undergoing M (HR = 4.5, $p < 0.0001$). In multivariate analysis, surgical option is the only factor associating significantly with local failures. However, in analyses of distant failures, contralateral breast cancers, DOBC, and overall survival, the two groups were not different in all of them. This study thus become particularly controversial, as it not only contradicts the general notion that patients undergoing BCT more likely tend to develop contralateral breast cancer, but also the difference in local failures with only 8.2 and 8.9 years follow up for the two groups respectively seem to be much higher than reported in other journals.

The other three articles are on the Angelina Jolie effect.