Tamoxifen and Risk of Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers

BACKGROUND:

- For women in the general population, randomized controlled trials have shown that adjuvant tamoxifen treatment after a first breast cancer (BC) diagnosis halves the risk of contralateral breast cancer (CBC).
- It is uncertain if tamoxifen has any efficacy for women carrying mutations in BRCA1 or BRCA2, and it is not commonly prescribed to carriers for the purpose of BC prevention.

OBJECTIVE:

- To determine whether adjuvant tamoxifen treatment for BC is associated with reduced CBC risk for BRCA1 and/or BRCA2 mutation carriers and whether the strength of association differs according to the estrogen receptor (ER) status of the first BC

METHODS:

- *Design:* observational, retrospective and prospective cohort
- *Inclusion criteria:* pathogenic mutation in BRCA1 or BRCA2, BC diagnosed since 1970 that was not bilateral at the time of diagnosis (within 6 months of first diagnosis)
- *Exclusion criteria:* history of invasive cancers or tamoxifen use before first BC
- *Enrolled:* 2,464 women (1,583 BRCA1 and 881 BRCA2 mutation carriers) were included in combined retrospective (before cohort entry) and prospective (after cohort entry) follow-up analysis; 1,083 women (657 BRCA1 and 426 BRCA2 mutation carriers) were included in prospective follow-up only analysis
- *Drug regimens*: women were considered to have used tamoxifen if they took it for any period of time after their first BC diagnosis (dosages/durations not reported)
- *Outcome measure:* hazard ratios for CBC associated with tamoxifen use after first BC for BRCA1 and BRCA2 mutation carriers
- *Power:* not calculated; post-hoc power for prospective data analysis: 80% at $p < .05$ to detect HRs of ≤0.35

RESULTS:

- Median time since first BC diagnosis was 6.6 years; median time since cohort entry was 3.2 years
- CBC occurred in 520 women (24% of BRCA1 and 17% of BRCA mutation carriers); 100 occurred after cohort entry
- BRCA1 mutation carriers
    - Combined retrospective and prospective data: HR 0.38 (95% CI 0.27 to 0.55; $p < .001$)
    - Prospective data only: HR 0.58 (95% CI0.29 to 1.13; $p = .1$)
- BRCA2 mutation carriers
    - Combined retrospective and prospective data: HR 0.33 (95% CI 0.22 to 0.50; $p < .001$)
    - Prospective data only: HR 0.48 (95% CI 0.22 to 1.05; $p = .07$)
- Analysis by ER status of first BC
    - BRCA1 mutation carriers adjusted for ER status: HR 0.44 (95% CI 0.25 to 0.85; $p = .01$)
    - BRCA2 mutation carriers adjusted for ER status: HR 0.33 (95% CI 0.17 to 0.64; $p = .001$)
- Sensitivity analysis results similar
- The authors concluded that this study provided observational evidence that tamoxifen use for first BC might reduce the risk of CBC in BRCA1and BRCA2 mutation carriers.

STRENGTHS:

- Multi-nation study; study results could be extrapolated to a large population
- Appropriate statistical tests utilized
- Multivariate analyses and sensitivity analyses were conducted
- Results were reported for each outcome measure

LIMITATIONS:

- Relatively weak study design
- Inclusion/exclusion criteria did not address specific chemotherapy agents or radiation therapy that could affect results
- Power was not calculated prior to the investigation; post-hoc power was not sufficient for outcome measures using prospective data only; therefore, Type II error is possible
- Unknown what dosage and duration of tamoxifen therapy patients received on average, or if treatment was comparable between cohorts
- Significant potential for treatment variation since multiple countries and many years involved
- Primary and secondary outcome measures were not clearly defined
- Standardization and training did not occur among various investigators involved
- Questionnaires and frequency of follow-up varied between cohorts
- Data were self-reported by study participants
- Relatively short follow-up time after first BC diagnosis
- Prospective data only available for 44% of women
- Retrospective data analysis would have the potential to produce biased results
- Prospective data analysis excluded prevalent cancer cases
- Analysis by ER status of first BC was unclear
- Many baseline differences between tamoxifen users and nonusers could have affected results
- Compliance and adverse effects were not assessed

CONCLUSION:

- Tamoxifen may reduce the risk of CBC for BRCA1 and BRCA2 mutation carriers. However, this study had many limitations so extrapolation of results should be conservative.
- For women with BRCA1 and BRCA2 mutations, bilateral mastectomy and premenopausal bilateral salpingo-oophorectomy are associated with a reduced BC risk of >90% and approximately 50%, respectively. Further research with tamoxifen use for CBC prevention may support this drug as a noninvasive alternative for women with BRCA1 or BRCA2 mutations.
- Further investigation is required. A randomized, controlled experimental study would be ideal. Further research should focus on BRCA mutation carries with ER-negative BC, as adjuvant endocrine therapy is already the standard of care for treatment of ER-positive BC regardless of BRCA mutation status.

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