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Editorial

EDITORIAL

Double Trouble: Contralateral Breast Cancer Risk Management in the Modern Era

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Breast cancer survivors are at increased risk for second primary cancers compared with the general population (1,2). The most common of these second cancers is contralateral breast cancer (CBC), which is estimated to occur at a rate of 0.5% per year (3–6). CBCs are often more difficult to treat than the original cancer because of more resistant biology and inability to reuse previous effective therapy due to dose-limiting toxicities (6–8). The benefit of therapies like tamoxifen for reducing CBC risk is well established from landmark meta-analyses and observational studies (4,9–11). However, many of these studies were performed with cohorts from an earlier era of little to no use of aromatase inhibitors (AIs) and HER2-targeted therapy, absence of large meta-analyses standardizing use of polychemotherapy, and incomplete determination of breast cancer subtypes.

In this issue, Kramer et al. report on the impact of adjuvant systemic therapy on subtype-specific CBC risk in a contemporary population-based cohort of 83 144 women selected from the Netherlands Cancer Registry from 2003 to 2010 (12). This time period coincided with the widespread adoption of trastuzumab and AI therapy into clinical practice. By linking registry and nationwide pathology data, the authors classified patients into hormone receptor positive (HR+), HER2 positive (HER2+), and triple negative breast cancer subtypes. With active follow-up for CBC events through 2016 and a large sample size, the authors obtained reliable, therapy-specific and subtype-specific CBC risk estimates. Adjuvant endocrine therapy, chemotherapy, and trastuzumab combined with chemotherapy were associated with 54%, 30%, and 43% risk reductions for CBC, respectively. Because all patients who received trastuzumab received chemotherapy, the individual effect of trastuzumab on CBC risk could not be determined. However, patients receiving trastuzumab combined with endocrine therapy and chemotherapy were the least likely of all subgroups to develop CBC (hazard ratio [HR] = 0.24; 95% confidence interval [CI] = 0.17 to 0.33). These findings confirm the benefit of adjuvant systemic therapy in CBC risk reduction (9,13) and provide estimates for the magnitude of this effect in a large cohort outside the clinical trial setting.

In addition, Kramer et al. determined subtype specific estimates of CBC risk, proportion of second CBCs of each subtype, and influence of adjuvant therapy on these estimates (12). For patients with HR+HER2− first breast cancer, endocrine therapy decreased risk of ER+ CBC (HR = 0.41; 95%CI = 0.36 to 0.47) but not ER− CBC (HR = 1.32; 95%CI = 0.90 to 1.93). These findings replicate a number of observational studies and meta-analyses over the past decade showing that endocrine therapy reduces the risk of ER+ CBC but not ER− CBC (Table 1) (4,6,9,11,14). In this study, use of AIs was associated with greater CBC risk reduction than use of tamoxifen (AI: HR = 0.32; 95% CI = 0.23 to 0.44; Tam: HR = 0.48; 95% CI = 0.44 to 0.53) in agreement with the EBCTCG meta-analysis comparing AIs with tamoxifen and a recent retrospective cohort study of endocrine therapy use in community health care plan enrollees (4,15). Two limitations could affect interpretation of these risk estimates. First, duration of adjuvant therapy use was not collected. Because of emerging trends toward use of extended adjuvant endocrine therapy coupled with problems with endocrine therapy adherence (16), risk estimates could change after accounting for actual duration. Second, positive ER was defined as 10% or higher by immunohistochemistry, a difference from current ASCO-CAP guidelines where 1% or higher ER is regarded as positive. Because low ER tumors are less responsive to endocrine therapy, using a 1% cutoff for ER positivity would likely reduce the reported magnitude of risk reduction.

Mechanistically, ER+ breast tumors depend on estrogen hormone for survival and growth (17). In this study, endocrine therapy reduced but did not eliminate risk of second ER+ CBC (12). This indicates the need for better therapies targeting ER+ tumor cells. This study also has implications for understanding the cell of origin of ER− CBCs. Because ER− CBC incidence is unaffected by endocrine therapy, ER− CBCs are most likely to originate from normal breast epithelial cells that were never dependent

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Table 1. Adjuvant hormonal therapy and subsequent subtype specific CBC risk*

Study	Design	No. of CBCs	Risk of ER+ CBC (95%CI)	Risk of ER- CBC (95%CI)
Kramer et al. 2018 (12)	Population-based cohort	2816	HR = 0.41 (0.36 to 0.47)	HR = 1.32 (0.90 to 1.93)
Langballe et al. 2016 (10)	Population-based case-control	1521	RR = 0.75 (0.58 to 0.96)	RR = 0.92 (0.59 to 1.44)
Li et al. 2009 (11)	Population-based nested case-control	367	OR = 0.4 (0.2 to 0.6)	OR = 3.8 (1.0 to 14.6)
Gierarch et al. 2017 (4)	Retrospective cohort from a general community health plan	248	MRR = 0.68 (0.54 to 0.84)	MRR = 1.00 (0.69 to 1.40)
Bouchardy et al. 2011 (14)	Population-based cohort	63	SIR = 0.49 (0.31 to 0.74)	SIR = 1.00 (0.40 to 2.06)

*CBC = contralateral breast cancer; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; RR = risk ratio; OR = odds ratio; MRR = multivariable relative risk per year of use; SIR = standardized incidence ratio.

on estrogen hormone. Indeed, recent single-cell RNA-seq studies in human breast cells have identified specific luminal and basal progenitor populations that could represent initiating cells for carcinogenesis and targets for preventing ER− tumors (18–20).

Unexpectedly, Kramer et al. also found that use of taxane-containing (Tax) but not anthracycline-containing chemotherapy (Anthr) was associated with substantial CBC risk reduction (Tax: HR = 0.48; 95% CI = 0.36 to 0.62; Anthr: HR = 0.91; 95% CI = 0.77 to 1.06; Tax+Anthr: HR = 0.69; 95% CI = 0.52 to 0.91) (12). Strikingly, the 10-year risk of triple-negative CBC was higher for patients with an index triple-negative breast cancer who received adjuvant chemotherapy compared with those who did not (HR = 1.56; 95% CI = 1.00 to 2.42), and in these ER− breast cancer patients, taxane- but not anthracycline-based therapy was associated with a statistically significant reduction in CBC risk (Tax: HR = 0.36; 95% CI = 0.17 to 0.75).

The finding that taxanes reduce CBC risk whereas anthracyclines do not is provocative, but caution is warranted in overinterpreting these results because of potential unrecognized confounders. Taxane-only adjuvant chemotherapy regimens are preferred in lower risk breast cancer patients and in those who cannot tolerate anthracyclines (21). Although the authors adjusted for three variables (trastuzumab therapy, age, and stage at first breast cancer diagnosis), other clinicopathologic variables associated with lower risk could remain unaccounted for and confound their therapy-specific risk estimates. Further, this result has not been observed in other studies of CBC risk. No statistically significant differences in CBC risk between taxane- and non-taxane-treated women were reported in the EBCTCG's meta-analysis of polychemotherapy, the population-based case-control study WECARE, or the composite analysis of the US Oncology, NSABP B-46, and B-49 trials comparing TCx6 (taxane-only) vs TaxAC (taxane + anthracyline) (10,13,21). However, none of these studies compared taxanes head-to-head with a non-taxane anthracycline arm. This unexpected result requires confirmation in other populations and mechanistic studies elucidating the effects of taxane and anthracyclines on carcinogenesis at a molecular level.

In summary, Kramer and colleagues provide contemporary estimates of the influence of breast cancer subtype and adjuvant systemic therapy on CBC risk in a population of presumably largely Caucasian women with access to standardized, high-quality treatment care for their first cancer (12). In the modern era, risk estimation will be increasingly individualized. Future studies should determine whether these results hold true for ethnically diverse as well as high-risk populations, including patients with strong family history of bilateral breast cancer and patients that are BRCA1/2 mutation carriers (22,23). Therapy-specific estimates for CBC risk should not be used in isolation but must be integrated with accurate risk estimates of local recurrence and distant metastasis, especially because the risk and gravity of distant metastasis exceed those for CBC (3). Further, molecular tests—beyond the standard three receptors—are providing more accurate estimates of risk and therapy benefit in early-stage patients (24,5). At this time, a number of new therapies are being tested in the adjuvant setting. These include inhibitors of CDK4/6, mTOR and immune checkpoint pathways, anti-inflammatory agents such as aspirin, and nonpharmacologic interventions such as exercise. It is likely that future population-based studies of the kind reported by Kramer et al. will require expanded definitions of both breast cancer subtype and adjuvant therapy.

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