Variation in Cardiac Dose Explains a “Fraction” of the Disparities among Breast Cancer Patients

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Most studies on disparities in cancer have focused on differences in stage of diagnosis and access to treatment. Breast cancer death rates are highest among vulnerable populations, including African Americans, the poor, the elderly, and those living in rural settings.\textsuperscript{1} Few prior studies have look at differences in the characteristics of administered treatments as a potential explanation for observed disparities in outcomes. In medical oncology, an analysis of chemotherapy administered to breast cancer patients found African-Americans received 10% lower relative dose intensity compared to white patients.\textsuperscript{2} In this issue of the Journal, Dr. Chapman and colleagues present a novel and intricate analysis of the mediators of racial disparities among women receiving whole breast radiation therapy, using mean heart dose as the vehicle for their examination.\textsuperscript{3}

A unique and impressive strength of this study is the access to detailed radiation data across a statewide consortium, Michigan Radiation Oncology Quality Consortium (MROQC), allowing for assessment of fractionation, total dose, radiation fields and mean heart dose. Using data from 8750 women who received whole breast radiation and separately modeling right versus left-sided cases by fractionation schedule (conventional versus accelerated fractionation), the authors found that Black and Asian race were independently associated with higher mean heart dose for most laterality-fractionation groups. This difference was up to 0.42 Gy in Black women with left-sided cancers receiving conventional fractionation (2.13 Gy for Black versus 1.71 Gy for White women). The maximum difference for Asian women of 0.32 Gy was seen in the left-sided accelerated fractionation group (1.59 Gy for Asian versus 1.27 Gy for White women).

The investigators strove to disentangle the sources of this variation by creating a series of stepwise models controlling sequentially for variables based on phase of the cancer trajectory: non-modifiable factors, pre-diagnosis patient characteristics, variables for cancer workup, radiation delivery details, clustering within facilities and type of treatment facility. This sequential modelling explained greater degrees of the increase in mean heart dose for both Black and Asian patients with left-sided disease receiving accelerated fractionation and Black patients with left-sided disease receiving conventional fractionation. However, the increased cardiac dose among Black and Asian patients with right-sided breast cancers was largely unchanged with the additional variables suggesting that a different paradigm to explain cardiac dose for right-sided patients may be more appropriate.

Understanding the source of the difference in mean cardiac dose among racial groups is an important
next step. Strikingly, this study found substantially greater use of intensity modulated radiation therapy (IMRT) in Black (70.1%) relative to Asian (35.8%) and White (42.1%) patients. A recently published study, which also used data from the MROQC cohort, revealed that patients with left-sided cancers who were treated with IMRT had a greater mean heart dose for both accelerated (+19.2%) and conventional (+20.8%) fractionation schemas. Furthermore, the current study found that Asian patients had the highest likelihood of receiving internal mammary nodal (IMN) radiation (9.7%) versus Black (4.6%) and White (4.9%), despite having similar stage disease at presentation. The previous MROQC study also found that treating the IMNs increased the mean heart dose by 40.7% for conventional fractionation. Given the extent of dose modification noted with treatment of the IMNs and use of IMRT, there may be residual confounding even after controlling for radiation technique. Conducting a separate analysis among patients treated with IMRT and among patients for whom IMN radiation was included would provide more accurate assessments of the impact of race on cardiac dose. Moreover, deep inspiration breath hold (DIBH), a technique known to statistically significantly reduce heart dose for patients with left-sided cancers in the prior MROQC study, was used in only 14% of Black women versus 30-45% of Asian and White women in the present study. The authors note that this discrepancy may be explained by the complete lack of use of DIBH at two facilities which happened to treat about half of the Black patients in the entire cohort.

In this analysis, the regional contribution to variance in cardiac dose was studied using intraclass correlations and variance partitioning coefficients. Since treatment facility was added to the stepwise models after adjusting for selected radiation techniques (e.g., IMRT, DIBH), the reported facility-level variance estimates would have excluded any variance attributable to differential use of these radiation techniques. Had facility, which clearly is a strong mediator of treatment technique, been included in an earlier step, it is likely that even more variance would have been attributed to facility than what was reported. A recent analysis of disparities in breast cancer treatments and stage at diagnosis noted the stronger contribution of region in explaining variance relative to patient-level factors. Together, these findings suggest that interventions targeting healthcare systems may be essential to meaningfully address outcome disparities. Including site or healthcare systems earlier in the stepwise models may provide an indication of how much variation can be expected to be reduced with such interventions.

The authors translated excess cardiac dose noted for Asian and Black patients into a projected increase in
ischemic cardiac events and deaths by age 80 – 0.7 events and 0.3 deaths per 1000 Asian patients and 2.6 events and 1.3 deaths per 1000 Black patients. These projections add important clinical context to this study, but they should be interpreted with caution because they relied on modeling data from a study analyzing the impact of heart dose among a western European population during an era when mean heart doses were much higher than today (i.e., 6.6 Gy for left-sided cancers and 2.9 Gy for right-sided cancers). Although, these numbers underscore the great improvements that modern radiation techniques have had on reducing cardiac dose, they may not fully explain the long-term implications that will result from reducing the mean cardiac dose below contemporary standards.

Demonstrating that there may be a link between the process of administering radiation therapy and the outcome disparities experienced by historically marginalized populations is noteworthy. However, the outcome differences attributable to cardiac dose variation still represents a relatively small proportion of the excess deaths experienced by disadvantaged populations. Black patients diagnosed with breast cancer have a mortality rate of 28.0 per 100,000 women compared to White patients whose rate is 19.9. Within the US, county level-mortality variation for breast cancer is even more dramatic, with regional rates ranging from 11.2 deaths per 100,000 women to 51.6, an over 4-fold difference.

Dr. Chapman and colleagues point out many of the challenges confronted by facilities that treat disadvantaged and historically marginalized patients, including payor mix leading to lack of resources, reduced bandwidth leading to delayed uptake in technology, and even when no additional technology is required, later adoption of new research may be due to financial or social exclusion or limited time and capital for implementation. Collaborations to study adherence to guidelines and study variation in treatment, such as MROQC, are an important mechanism to help overcome these barriers. Identification of which systems and areas are most in need for intervention, and the provision of sufficient financial resources and time will be necessary to ameliorate these findings. In addition, physician decision-making surrounding the use of IMRT and IMN radiation should be explored in future studies.

In the meantime, we are confronted by the stark reality of systemic racism – only 11% of black patients in these data had no pre-existing cardiac risk factors, only 12.4% had a normal body mass index, and almost half were
current or former smokers. As Darby and colleagues noted, the detrimental effect of dose per Gray on long term cardiac outcomes is higher among patients with risk factors. The pervasive effects of racism are real. Without intentional interventions to reduce its devastation, similar to the current status of HIV, in the not too distant future it is likely that most deaths due to breast cancer will be attributable to shortcomings in the use of treatments that have been proven effective rather than to a lack of effective therapy.

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