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Response

Response to Schoormans

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Psychosocial stress is a biologically significant cardiovascular risk factor (1) and an enormous burden in cancer survivors (2). We appreciate the comments by Dr Schoormans and acknowledge that work continues to be done to precisely stratify which breast cancer survivors may have an elevated risk of cardiovascular disease, as well as to better understand the mechanisms underlying this elevated risk. As the number of breast cancer survivors increases, the long-term negative effects of cancer and/or cancer treatment have become a substantial public health concern. Fatigue, pain, lymphedema, bowel and sleep disturbances, nausea and vomiting, anorexia, body image concerns, infertility, emotional distress, depression, and anxiety are common among cancer patients and survivors (2). Many of these stresses occur during therapy but continue well into survivorship years after initial treatment.

Although observational studies suggest that psychosocial stress is associated with higher rates of cardiovascular complications in cancer survivors (3), the mechanism of this association has not been elucidated. In clinical studies, endothelial dysfunction is present early on in breast cancer survivors, suggesting an increased risk of cardiovascular disease (4). Other studies suggest an elevated risk of cardiovascular disease exists even prior to starting any treatment (5), suggesting that cancer-associated inflammation and/or psychosocial stress may increase cardiovascular risk prior to any actual cancer treatment. The exact mechanism, is not clear, however, whether this is inflammatory in nature as suggested by other cardiovascular researchers or related to estrogen depletion or a different mechanism such as the premature aging phenotype.

To fill this gap, we have developed a clinically relevant mouse model of chemotherapy-induced latent cardiotoxicity that is exacerbated by psychosocial stress as a "second hit." In this model, chemotherapy-treated mice manifested exaggerated myocardial fibrosis and increased gene expression of pro-inflammatory and pro-fibrotic cytokines in response to chronic psychosocial stress. Neither chemotherapy nor psychosocial stress alone was sufficient to cause clinically significant myocardial damage (6).

Because recent studies have shown that both chemotherapy and psychosocial stress induce a premature aging phenotype (7), we further hypothesized that stress exacerbates chemotherapy-induced cardiovascular aging to increase the risk of overt cardiovascular complications. This hypothesis is currently being tested in a National Institutes of Health–National Heart, Lung, and Blood Institute–funded project (1R01HL151740). We look forward to learning these results, in an effort to better understand both the mechanisms related to this cardiovascular risk and the potential for targeted interventions, particularly because anti-inflammatory medications and senolytic therapy (or senotherapeutics) are now being tested.

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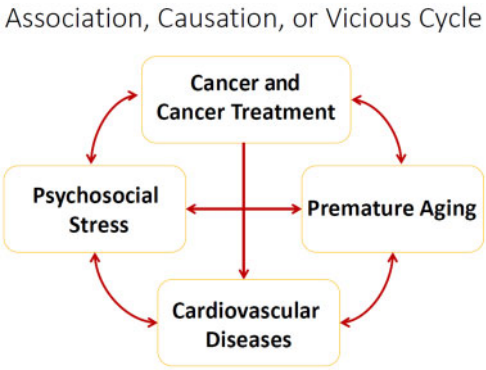

Figure 1. The interplay between cancer, aging, stress, and cardiovascular diseases: Is it association, causation, or a vicious cycle?

Notes

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Author contributions: Dr. Blaes and Dr. Zordoky were involved in the writing and research supporting this piece. Dr. Konety reviewed the concepts and writing.

Data Availability

Data is available upon request to the corresponding author.

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