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EDITORIAL COMMENT

Cancer Diagnosis, Physical Activity, and Heart Disease Risk

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Driven by increased cancer survivorship rates, the aging population, and awareness of cancer treatment-related risks, the burgeoning field of cardio-oncology has drawn attention to the interconnected nature of cancer and cardiovascular health. Physical activity is a key modifiable behavior that plays a major role in the etiology and course of disease for both conditions. Common cancer treatments, such as chemotherapy, can induce significant cardiotoxicity and physical activity-compromising side effects, including fatigue and sarcopenia.[1] Such consequences underpin the behavioral shifts occurring during cancer treatment that ultimately lead to poor adherence to inadequate physical activity, as only 10% to 30% of cancer survivors maintain activity levels during and after treatment.[2]

It is therefore important to understand how physical activity changes in cancer survivors may influence risk of heart disease, although very little research to date has addressed this. In this issue of the *JACC: CardioOncology*, the study by Jung et al[3] utilized a universal Korean medical insurance data resource to examine the associations between physical activity change before and after cancer diagnosis and myocardial infarction, heart failure, and atrial fibrillation risk in 269,943 cancer survivors. In addition to the very large sample size, other notable strengths included the detailed examination by cancer diagnosis site, and the use of Fine-Gray model to account for death as a competing risk.

The study's findings suggest a consistent association of both pre- and postdiagnosis physical activity with a reduced risk of myocardial infarction and heart failure. For atrial fibrillation, some protective associations were only evident among previously inactive participants who became active post-cancer diagnosis, a finding that was clearer once deaths within 1 year from baseline were removed. The question of whether sufficient pre-existing (ie, prediagnosis) activity alone can carry forward a reduced heart disease risk is of particular importance. The answer to this question may partly determine treatment decisions and postdiagnosis priorities, particularly for clinicians and policy makers operating in resource-scarce environments.

Compared with those survivors who remained inactive, those who were active at baseline but became inactive postdiagnosis had a 20% lower risk of myocardial infarction and 6% lower risk of heart failure. For myocardial infarction, such associations were comparable to those who remained active throughout (20%) and more pronounced than those were inactive at baseline but became active postdiagnosis (11%). For heart failure, the protective associations were more pronounced among those consistently active (16%) and those who became active postdiagnosis (13%). Based primarily on the myocardial infarction findings, the authors concluded that prediagnosis physical activity may offer some long-lasting protection against heart disease. This assertion is in poor agreement with previous literature showing that the cardioprotective effect of prediagnosis physical activity is transient as decreased physical activity over time is associated with increased cardiovascular risk.[4] Here, we provide some possibilities suggesting that this counterintuitive finding reflects less true causal associations and more the inherent limitations of the National Health Interview Survey dataset.

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First, the short follow-up, only 1 year after the date of the postdiagnosis general health screening examination, increases the likely contribution of reverse causation as a possible explanation of the finding that cancer survivors who, despite becoming inactive postdiagnosis, exhibited a 9% lower all-cause mortality, 20% lower myocardial infarction, and 6% lower heart failure risk. This explanation is supported by the sensitivity analyses (Supplemental Table 2)[3] in which excluding the first year of deaths (from prediagnosis baseline) strengthened the association of becoming active and remaining active (with all outcomes, including atrial fibrillation). Conversely, the associations of those who became inactive postdiagnosis (likely reflecting overall health fragility) were weakened.

Second, in our view, the consequences of the very short follow-up also expand to insufficient induction time (ie, the time that an exposure needs to exert its effect on a health outcome) or the physical activity reductions to manifest their deleterious effects on heart health in this case. Inversely, insufficient induction time due to short follow-up may be responsible why the post-cancer diagnosis initiation of physical activity showed lower benefits (11% lower risk of myocardial infarction) than prediagnosis physical activity (20%).

Third, the inherent limitations of physical activity self-reports (including the International Physical Activity Questionnaire used in this study) and the crude (dichotomized) exposure are also likely to have partly shaped study findings. The International Physical Activity Questionnaire only inquires about activity bouts lasting for at least 10 minutes of walking (any intensity) and moderate- or vigorous-intensity physical activity. Self-reports cannot capture information on patterns of physical activity, including shorter moderate or vigorous bouts,[5] and incidental physical activity of light intensity. Such measurement issues have very likely impacted the study's capacity to capture pre/postdiagnosis changes involving shorter activity bouts. This is a potentially critical study limitation, considering the often debilitating side effects of cancer treatments,[1] which may cause compromise the patients' ability to sustain longer bouts of activity, particularly of moderate or vigorous intensity. Therefore, the important underestimation of activity during the postdiagnosis assessment may have led to an artificial inflation of the prediagnosis activity effects.

Epidemiological studies are always reliant on the depth, breadth, and quality of the available data resource. In this sense, Jung et al made good use of this large administrative research database. However, the resource may lack essential information that further limits the causal interpretation of the study's findings. For example, the absence of adjustment for dietary factors is a critical unmeasured confounder, considering the role that diet plays[6] in both cancer risk and cardiovascular health. Also, cancer survivors are commonly subjected to multiple interventions (medications, radiotherapy, chemotherapy, etc) that occur in different combinations and at different timings. Although such therapeutic combinations can have serious adverse implications for heart health, they were unaccounted for in the study, further amplifying the risk of unmeasured confounding. Conversely, adjustment for potential mediators of the association of physical activity with heart disease (obesity, hypertension, diabetes, dyslipidemia) may have resulted in overadjustment, potentially diluting the direct effects of the exposure on study outcomes.[7]

Many of the exposure-related interpretational uncertainties outlined previously could be resolved in future cardio-oncology studies, and longitudinal cohorts in general, employing wearable device-based methods[8,9] to explore the detailed physical activity patterns of cancer survivors longitudinally. Such methods would enable future research to examine changes not only in total physical activity amounts, but also in intensity,[8] daily frequency,[10] and ways of accumulation of activity (eg, via short vs via long activity bouts),[5] all of which have important attributes for heart health. Such assessments would capture relatively complete accounts of activity, including light intensity and short bouts of moderate to vigorous intensity, which may be more accessible interventions for cancer survivors as they recover from the side effects of treatments. Future studies could also limit the influence of unmeasured confounding by capturing details on cancer stage, cancer treatments, and all key behavioral risk factors with relevance to cardiovascular disease and cancer, including valid accounts of dietary intake, and sleep. Sleep, in particular, can be captured both by self-reports[11] or by the same wearables as the ones that quantify physical activity, enabling this way the study of 24-hour behavior replacement effects[12] on cancer survivors' heart health. Importantly, capturing such information would allow the study of the interaction between cancer treatment and physical activity (eg, how much physical activity is needed to offset deleterious cardiac effects of chemotherapy and other severe cancer treatments).

Despite the inherent limitations of the data resource and the possible alternative interpretations of the study findings discussed previously, the study by Jung et al[3] is a welcome addition to the cardio-

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DECEMBER 2024:890–892

oncology literature on physical activity. However, it is likely that the study has overestimated the long-standing cardiac benefits of prediagnosis physical activity alone. In line with the authors' suggestion,[3] it is therefore important that cardiologists and cancer practitioners place emphasis on supporting patients throughout the cancer treatment journey (and beyond) to initiate and sustain adequate lifestyle physical activity and exercise levels for heart disease prevention.

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