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Cancer Survival – Time to Get Moving? Data Accumulate Suggesting a Link between Physical Activity and Cancer Survival

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Last year, a paper by Holmes et al. rocked the research community involved in cancer survivorship.¹ The paper reported a significant protective association between increased physical activity that occurred after the diagnosis of breast cancer and recurrence, cancer-related mortality, and overall mortality among a cohort of 2987 stage I-III breast cancer survivors nested within the Nurse's Health Study. This year, Meyerhardt and colleagues add to this growing body of research with findings that appear in this issue of the *Journal of Clinical Oncology*.² Their prospective study among stage III colon cancer patients also suggests a protective association of post-diagnosis physical activity on similar outcomes.

This seminal study was performed on a cohort of 832 patients participating in the NCI-sponsored Cancer and Leukemia Group B (CALGB) adjuvant therapy trial comparing weekly 5-fluorouracil (5-FU) and leucovorin to weekly irinotecan, 5-FU and leucovorin (CALGB 89803). One of this study's primary strengths is its reliance on the clinical trial framework. As such, the effects of confounding may have been minimized since the sample was comprised solely of individuals who underwent a complete surgical resection and were found to have regional lymph node metastases (no evidence of distant metastases), and who had received one of two specified chemotherapeutic regimens. In addition, physical activity assessments were specifically timed in relation to treatment course (i.e., 6 months post-therapy) and standardized methods were used for follow-up of cancer-related endpoints. Indeed, this study provides a successful example of how clinical research can augment classic epidemiologic studies to answer research questions – one approach relying on well-defined, circumscribed samples and assessing outcomes specifically in relation to disease- or treatment-course, and the other which relies on broad-based samples to obtain results that are more readily generalizable.

Findings of the Meyerhardt et al.² study found significantly lower rates of recurrence and increased disease-free survival with 18+ MET hours/week of physical activity, with data showing reductions in risk that approached 50% in both crude and adjusted analyses – associations that were durable even after the exclusion of participants who may have had underlying occult disease (i.e., those who had died or were found to have recurrences within 6-months of physical activity assessment). Associations with overall mortality were not as strong and 95% confidence intervals were much broader, however, the p for trend was still significant in adjusted analyses. From the article, it is not known whether these other causes of death were from diseases where proven associations with physical activity exist, such as cardiovascular disease, or from other causes of mortality not traditionally linked to exercise.

The findings of Meyerhardt and colleagues closely mirror those of Holmes et al. who also found a protective association between reported physical activity (using an identical questionnaire) and recurrence, breast cancer mortality and overall mortality among breast

cancer survivors participating in the Nurse's Health Study.^{1,2} Their findings also suggest reduced relative risks of approximately 50% in women who reported higher levels of physical activity, as compared to those who were sedentary, with relative risks being about 50% lower for overall mortality, as well. The stronger association with overall mortality could be attributed to an increase in power that resulted from a sample size that was almost four-fold larger than the clinical study. Another point of departure of the two studies relates to the cut points used to define quintiles of physical activity. While <3 MET hours/week was used as the designated referent to define those with sedentary lifestyles for both studies, significant benefits for breast cancer survivors were observed at 9+ MET hours/week (equivalent to roughly 4-to-5, 30-minute sessions of brisk walking per week), whereas for colon cancer patients physical activity of at least 18+ MET hours/week (equivalent to the same number of sessions, but that which is double the duration or more strenuous in nature – see Meyerhardt et al.² Table 1) was needed before significant benefit was observed. As noted by Meyerhardt et al.² these differences may be attributed to differences in patient groups, and possibly the fact that colon cancer patients were comprised of both women and men, the latter of whom reported higher levels of physical activity, in general. It is worth noting that within the Nurse's Health Study, the greatest benefits of physical activity were observed among women with stage III breast cancer, where a relative risk of breast cancer mortality of 0.36 (95% CI, 0.19–0.71) was observed among women reporting 9+ MET hours/week of physical activity. Thus, in both the Nurse's Health Study and in observational data from this controlled clinical trial,^{1,2} we see a protective association with increased physical activity and hard, cancer-specific outcomes – findings which are favorable in early stage breast cancer patients, but also among breast and colon cancer patients with later stage disease.

As clinicians, researchers and policy makers, we have long awaited such confirmatory findings. To date, our exercise interventions, as well as the current guidelines for cancer survivors,³ and what we ultimately tell our patients, is that exercise may be beneficial - guidance based largely on proven associations that exist between physical activity and specific co-morbid conditions (such as heart disease or osteoporosis) for which cancer survivors are especially prone, or associations between physical activity and other factors, such as quality of life, functional decline, fatigue, etc. Given the high-risk nature of cancer survivors and the fact that they are high healthcare utilizers who have a profound impact on the health economy at large, the benefits of exercise or a healthy diet on peripheral outcomes are still important and can not be discounted.^{4,5} Nor can we discount the several biological mechanisms which are influenced by physical activity and which may play a potent role in hindering neoplasia.^{6,7} However, what we, as clinicians or interventionists truly want to be able to say – and what cancer patients truly want to hear is the following: “through exercise you may be able to prevent progression or recurrence of your cancer.” This is where we have all stopped short, and unfortunately, this is where we all need to stop short once again.

While exceptionally valuable, it must be remembered that the findings of Meyerhardt and colleagues,² as well as those of Holmes et al.¹ are observational in nature. Therefore, cause and effect can not be assumed. Furthermore, many questions still remain regarding the effects of physical activity among cancer survivors, e.g., Is physical activity safe (especially among groups of survivors where cardiotoxicity is frequently-reported)? ...What dose is required for benefit? ...What types of exercise are most beneficial? ...Does exercise exert its effects independently of or through weight control? ...What are the characteristics of cancer patients most responsive to exercise (i.e., cancer type, stage, receptor status, etc.), and so forth. Indeed, the only way that we will be able to truly assess whether increased physical activity can reduce recurrence or deaths due to cancer is to pursue studies which lead up to and include randomized controlled clinical trials that ultimately are able to answer whether or not physical activity is beneficial for cancer control. Data from two observational studies, and possibly a third, suggest a reduced risk of recurrence of 50%.^{1,2} Such an effect parallels that of Herceptin®

(trastuzumab) for HER-2 positive breast cancer patients,^{8,9} an agent heralded by the oncologic care community and by NCI Director Andrew C. von Eschenbach, M.D. as “a major advance and turning point in eliminating suffering and death from cancer.”¹⁰

To be sure behavioral interventions are complex and have a host of barriers in that they are difficult to deliver and require careful attention to issues of adherence; however perhaps the largest barrier of all is the lack of industry funding. There is no doubt that pharma would back an agent with potential to reduce cancer recurrence by 50%, but who will back a trial that evaluates the potential benefit of sneakers and sweatpants? Would Nike “Just do it?”...perhaps. But likely, this is a research question that will fall to the shoulders of the government to support. Every 1½ minutes, another American is diagnosed with either breast or colon cancer – indeed, it is these individuals, as well as the more than 4 million survivors of these cancers,¹¹ who would benefit from the answer. It’s time to get moving!

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