Adequate physical activity is a cornerstone of physical health and mental well-being. Many cancer survivors who have a good prognosis are at higher risk of dying from other causes, such as cardiovascular diseases, and could possibly reap the same benefits of exercise as individuals without a cancer diagnosis. Furthermore, the physical and mental stresses of a cancer diagnosis, including side effects of treatments, present the cancer survivor with additional challenges. An increasing body of literature, including randomized trials, demonstrates the benefits of physical activity on physiological parameters, quality of life, functional status, fatigue, and depression for at least some cancers. Despite acknowledging potential risks of some specific physical activities at certain intensities for some subgroups of cancer survivors, many organizations, such as the American Cancer Society (1), the World Cancer Research Fund and the American Institute for Cancer Research (2), the American College of Sports Medicine (3), and the US Department of Health and Human Services (4), now advocate physical activity for cancer survivors. Details regarding the type, duration, and intensity of exercise will have to be tailored to the individual patient, depending on various factors such as age, physical health, specific cancer, and treatments; however, the vast majority of patients will likely benefit to some degree from physical activity.

In this issue of the Journal, Ballard-Barbash et al. (5) extensively review the potential effects of physical activity on cancer-specific and all-cause mortality. They also summarized the effect of physical activity interventions on potential intermediate biomarkers of cancer progression, such as insulin. Unlike previous reviews, which focused on functional health and quality of life, this review addresses the more provocative question of whether physical activity can actually improve cancer-specific survival. Many may accept general health benefits of physical activity for cancer survivors, but the implication of a direct anticancer effect could engender some skepticism. Given the limited success that the most potent and cleverly designed drugs have had on cancer to date, why should something as seemingly simple as walking have potent anticancer effects? We are far from having definitive answers to this question, but as reviewed by Ballard-Barbash et al. (5), perhaps, we are getting closer to an answer.

Whereas most cancer therapies to date focus on killing the tumor, physical activity may offer two complementary roles for standard cancer therapy. First, cancer-specific mortality, although generally attributed to the destructive behavior of the tumor, is also dependent on the general health of the patient. Overall health status is inherently integrated and substantially influenced by factors such as age, physical health, specific cancer, and treatments; however, the vast majority of patients will likely benefit to some degree from physical activity.

Reference

Notes
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as physical activity. For example, diabetics who develop cancer have increased overall mortality and, perhaps, cancer-specific mortality compared with nondiabetics with cancer (6), and physical activity is one of the strongest protective factors against diabetes. Even the attribution of cause of death in a cancer patient can be fraught with difficulties (7). Second, physical activity could have direct effects on the tumor that are mediated through alterations of various hormones, including insulin, insulinlike growth factor 1, estrogen, and adiponectin. Many of these hormones, and others, have been associated with cancer risk and prognosis, which indirectly supports a causal role of physical activity on cancer-specific death (8). These factors may promote or inhibit tumor cell growth, and thus directly affect tumor progression. Exercise also has immune-modulating effects, which theoretically could affect cancer development or progression.

The strongest evidence of a causal association between physical activity and cancer-specific mortality would require a randomized intervention trial. Some ongoing interventions, as described by Ballard-Barbash et al. (5), may provide important data. Currently, the best evidence is from observational studies, and the results thus far appear promising. Breast cancer has received the most study (17 studies), followed by colorectal cancer (six studies), with sporadic studies for some other cancer sites. Most studies suggest that more physically active individuals after diagnosis have better cancer-specific and all-cause survival. Beyond the general limitations of observational studies, two potential biases are of special concern in studies of cancer survivors. First, prediagnostic physical activity is likely to be correlated with postdiagnostic physical activity level, and prediagnostic physical activity could have benefits for survival. For example, tumors that develop in an environment of hyperinsulinemia, in part due to relative physical inactivity, could potentially have a worse inherent prognosis at the time of diagnosis. Thus, some statistical adjustment for prediagnostic physical activity is required to demonstrate a benefit of postdiagnostic physical activity that is independent of prediagnostic physical activity. Second, there is the potential for reverse causation, that is, subclinical metastases from cancers with a worse prognosis may limit exercise capacity. To the extent that the potential for reverse causation has been dealt with by excluding overt metastatic cases and including long lag times, physical activity has remained associated with a better prognosis. Although bias and residual confounding are difficult to rule out, the data thus far suggest that the improved cancer prognoses associated with physical activity are not entirely due to bias.

Ballard-Barbash et al. (5) have suggested various types of observational and interventional studies that can address the many remaining questions about the relationship of physical activity to cancer survival. An additional potentially valuable approach is the molecular typing of cancers, which can identify subtypes of cancers that are most sensitive or resistant to the effects of exercise. Cancers have a number of molecular abnormalities related to metabolic and energy balance–related pathways. For example, some of the effects of physical activity and obesity that are mediated through insulin and free insulinlike growth factor 1 act through phosphatidylinositol 3-kinase, which in turn phosphorylates and activates Akt (9). Phosphorylation of Akt results in cell proliferation and escape from apoptosis (10), in part by inhibiting transcription and promoting degradation of the cyclin-dependent kinase inhibitor p27 (11,12). In vitro studies demonstrate that insulin and insulinlike growth factor 1 similarly result in decreased expression of p27 (13). In rodents, p27 expression increases in a dose-dependent manner in response to energy restriction or physical activity (14–16). In one study of colon cancer patients (17), individuals with loss of p27 did not appear to benefit from physical activity, whereas those with expression of p27 had lower colon cancer–specific mortality if they were physically active. Concordantly, higher body mass index was associated with inferior survival in colon cancer patients whose tumors expressed p27 (18). Although these results need to be confirmed, they suggest that energy balance–related factors are operative for colon cancer progression primarily in cancers that express p27. Beyond providing etiological insights, the establishment of consistent, biologically coherent, and robust associations for molecular subtypes of cancer can help establish a causal association (19).

Given the promise of a role of physical activity in reducing cancer-specific mortality, future research involving observational studies, interventions, and mechanistic studies should be a high priority. Few other leads have shown as much promise as physical activity in extending the lives of cancer survivors. Many treatments may increase survival, but at a cost of quality of life; physical activity may not only extend life but may also enhance its quality. Even though direct effects of physical activity on cancer are not definitively proven, given that physical activity is generally safe, improves quality of life for cancer patients, and has numerous other health benefits, adequate physical activity should be a standard part of cancer care.

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