

ries, we will turn to possible responses and alternatives to corporatization that could help right the ship of U.S. health care, alleviate problems caused by this historical transformation of the system, and better leverage its positive effects.

Despite the fact that the United States leads the world in health care expenditures, American life expectancy at birth today is 4 years lower than the average life expectancy in peer countries.<sup>3</sup> Although lower-income Americans have borne the brunt of these adverse trends,<sup>4</sup> even the wealthiest quarter of Americans have life expectancies (at midlife) that are no longer than those of the least-wealthy quarter of northern and western Europeans.<sup>5</sup> As health systems and other institutions confront the social, economic, and political drivers underlying worsening U.S. population health, the extent to which the business of health care may promote or impede progress requires deeper reflection.<sup>6</sup> We hope this series will stimulate productive discussion and debate in the domains of health care, business, finance, and government and inform efforts to improve the health care system for everyone.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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## Extending Cancer Survival with Exercise — Time for Oncology to Act

Melinda L. Irwin, Ph.D., M.P.H.<sup>1</sup>

In 2006, a prospective observational study first showed that physical activity after a colon cancer diagnosis was linked to a decreased risk of recurrence and death.<sup>1</sup> Since then, numerous observational studies across various cancers have shown similar survival benefits.<sup>2</sup> However, some observers have argued that such studies could not prove causation and might reflect confounding factors, such as a higher likelihood that healthier patients would exercise or had biologically less aggressive tumors. Other observational studies have shown that physically active people have a lower risk of cancer than more sedentary people.<sup>2</sup> Preclinical research supports that exercise can slow tumor growth,<sup>3</sup> and small trials involving participants with and without cancer have shown that exercise improves metabolic,

inflammatory, and immune markers<sup>4</sup> and may improve adherence to cancer treatment.<sup>5</sup> Despite these findings and national guidelines recommending increased physical activity,<sup>6,7</sup> exercise has yet to be widely integrated into cancer care, perhaps because of a lack of definitive evidence from large randomized trials.

Oncology has reached a turning point. In this issue of the *Journal*, Courneya and colleagues present the final results from the phase 3 Colon Health and Lifelong Exercise Change (CHALLENGE) trial.<sup>8</sup> In this trial, investigators randomly assigned patients who had undergone complete resection of stage III or high-risk stage II colon cancer to receive health-education materials alone or to participate in a 3-year aerobic exercise intervention. All the patients had completed adjuvant chemo-

therapy within the previous 2 to 6 months. The primary end point was disease-free survival.

At a median follow-up of 7.9 years, the risk of disease recurrence, a new primary cancer, or death was 28% lower in the exercise group than in the health-education group, and overall mortality was lower by 37%. At 8 years, overall survival was 90.3% in the exercise group and 83.2% in the health-education group — an absolute difference in benefit of 7.1 percentage points. These remarkable findings were due to fewer recurrences of colon cancer and fewer new primary cancers, mainly of the breast, prostate, and colon.

This trial of the effects of exercise on disease-free survival in patients with colon cancer provides definitive evidence that exercise offers additional benefits to overall survival beyond surgery and chemotherapy, while also enhancing the patients' quality of life. The magnitude of benefit is similar to that of many approved cancer therapies. Ongoing trials are evaluating the effect of exercise, nutrition, and diet-induced weight loss on disease-free survival in patients with breast or ovarian cancer, studies that may help to clarify the role of these approaches across different cancer types.<sup>9,10</sup>

The 3-year, partially supervised aerobic exercise program in the trial was feasible for the patients, who had a median age of 61 years, with one third over the age of 65 years; 51% of the patients were women, and 90% had stage III colon cancer. Patients in the exercise group maintained significantly greater increases in physical activity (ranging from 1.5 to 2.5 additional hours per week), cardiorespiratory fitness, and physical function than did those in the health-education group. The primary effect of exercise was consistent across patient and treatment subgroups, which suggested that regardless of age or disease status, exercise can improve outcomes for patients with colon cancer.

Although the median body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) at enrollment was 28 and one third of the patients had a BMI of more than 30, no weight change was noted in either group over the 3-year period, which suggests that the disease-free survival benefit of exercise was independent of weight loss. Future research and clinical care for patients with cancer must include exercise interventions, given that obesity is linked to an increased risk of the development of (and death from) 13 types of cancer.<sup>11</sup> Moreover, emerg-

ing antiobesity medications show promise in reducing the risk of chronic disease but arouse concern about muscle loss.<sup>12</sup>

Despite the importance of the CHALLENGE trial, it is striking that it took 15 years to recruit 889 patients from 55 centers across six countries — averaging 59 patients per year, or about 1 patient per center annually. Although eligibility criteria were broad and applicable to most patients with stage II or III colon cancer, slow accrual probably stemmed from a limited geographic base, with 94% of the patients recruited from Canada and Australia. Moreover, many clinical-trial cooperative groups have limited infrastructure support for conducting behavioral trials, as compared with drug trials. In the United States, the National Clinical Trials Network does not provide funding for lifestyle or behavioral intervention-associated costs.

The CHALLENGE findings underscore the need to integrate exercise into cancer care. Although current guidelines already recommend physical activity before, during, and after treatment,<sup>6,7</sup> few adults — whether healthy or diagnosed with cancer — meet the recommended 2.5 hours per week of moderate-intensity activity, such as brisk walking.<sup>13</sup> Without systems-level changes, physical activity levels are unlikely to increase. Although implementation studies are needed to identify the best strategies for integrating exercise into care, we should not wait. Clinicians can refer patients to community-based exercise programs and use or adapt existing services such as cardiac rehabilitation. Trained exercise counselors should be embedded within oncology care teams, with services covered by insurance. As oncology continues to advance, exercise must become a standard part of care. The time to act is now.

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## Semaglutide and Tirzepatide to Treat Obesity

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In this issue of the *Journal*, Aronne et al.<sup>1</sup> report the results of a trial comparing tirzepatide and semaglutide, two drugs currently approved to treat obesity that consistently lead to reductions in body weight of more than 10% from baseline; the results of this trial will give guidance to physicians treating obesity. This comparison trial is notable because head-to-head comparisons of weight-loss medications in a single trial are scarce. In addition, in contrast to clinical trials that tested only the highest dose, this trial used two maximum tolerated dose options for each drug, which reflects how these medications are often used in practice. This flexibility in dose administration contrasts with the forced escalation to the maximum dose used in some previous trials of single weight-loss agents.

A strength of this trial was the fact that men made up one third of the trial cohort. In most obesity trials, women have accounted for approximately 80% of the participants, which makes it difficult to evaluate differential weight loss according to sex. In this trial, both medications led to weight loss that was approximately 6 percentage points greater among women than among men. Whether this differential weight loss was due to the stimulation of the glucagon-like peptide-1 (GLP-1) receptor, a mechanism both drugs share, is unclear, but the finding raises a question about the body constituents involved in weight loss and why these may vary according to sex.

Body composition during weight loss with

GLP-1 receptor agonists has been evaluated in substudies with the use of dual-energy x-ray absorptiometry (DXA), which measures fat accurately but does not provide a precise measure of muscle as a part of fat-free mass. Rather, DXA measures fat and bone mineral content, but the remaining body constituents (water, organs, and muscle) are combined and termed lean tissue or fat-free mass. Fat, muscle mass, and muscle strength are the most important components related to changes in body composition during weight loss. Fat-free mass consists of approximately 50% muscle, although this varies with each person.<sup>2</sup>

A study by Webster et al. in the 1980s measured total body water, total body potassium, and underwater weight among women with differing values of total body fat and determined that loss of fat-free mass during weight loss should not exceed 22%.<sup>3</sup> Because men have more muscle, a loss of more than 25% of fat-free mass is considered to be clinically excessive. Across 25 studies involving persons with overweight or obesity who were receiving GLP-1 receptor agonists to assist with weight loss, the loss of fat-free mass as measured by DXA averaged 29% of the total weight lost.<sup>2</sup> Specifically measuring muscle would be helpful to confirm whether excess muscle has been lost but would require an imaging study or a labeled creatine study (in which the conversion of creatine to creatinine is measured with the use of isotopically labeled creatine).

The forces that muscles place on the skeleton