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Exercise is the Drug

New research at Duke University is studying how exercise might be used during and after cancer treatment.

By Chris Cooper

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Courtesy of Duke Marketing and Communications

Oliver Glass is a former CrossFit Games athlete, qualifying on the CrossFit Local team in 2010 and the CrossFit Raleigh team in 2011. He currently trains at CrossFit Raleigh in North Carolina in the evenings. In the daytime, he's a cancer researcher.

"I've been doing CrossFit competitively for five years," Glass said. "I've been doing cancer research since 2001. I know CrossFit has done so much for my life, and along the way I've met so many people that have been dealing with cancer treatment and finding CrossFit. They've done so well, and I thought, 'There's a conversation I'd like to start.'"

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While working on vaccines for breast cancer at Duke University in 2008, Glass found the work of Dr. Lee Jones, who was beginning to study the clinical use of exercise on cancer patients.

"He was trying to understand what was going on biologically in these people," Glass said. "He wanted to see what kind of biological markers exercise would kick up—whether it was helpful or harmful during treatment."

Jones' work has been published in the scientific press and widely cited by popular media since 2008. While other cancer researchers were focusing on important drugs and delivery systems, Jones wondered if exercise could help a patient absorb the drugs better or survive longer after chemotherapy.

To date, research has largely focused on the remediation of problems caused by cancer treatments. For example, early mortality from heart disease is common in those who have undergone chemotherapy because the treatment is damaging to cardiac muscle. Exercise is used after

cessation of chemotherapy to rehabilitate the cardiovascular system, but it has never been studied as an adjunct to the cancer therapy itself. In other words, no one knows how soon is too soon to start exercising after a cancer diagnosis. And no one knows whether exercising during cancer treatment is helpful, harmful or neutral.

Because so much data exists for exercise related to heart disease, Glass says aerobic-type workouts are often prescribed for patients after they recover from chemotherapy. But that may not be the best solution for everyone.

"Right now we've been using therapies for cardio diseases in cancer patients," he said. "But in the future it may be proven that mixed-modal training, like CrossFit, elicits the greatest effects. We just don't know yet."

The Long Road to Understanding

Jones began his quest 10 years ago, and his research has encouraged oncologists to prescribe exercise after chemotherapy.



Courtesy of Duke Marketing and Communications

Glass analyzes blood samples and tumor biopsies of cancer patients who exercise during and after treatment.



Shawn Rocco

An athlete and cancer researcher, Glass decided to start researching how CrossFit might help patients undergoing treatment for cancer.

"A good analogy is the way that exercise and cardiac rehab has taken off. Fifty years ago, you have a heart attack, and it's six weeks of bed rest. They thought they'd kill you if you exercised after a heart attack. But really, you improve their risk of having a secondary event," Jones said. "That's where we are with cancer right now. Oncologists tell you to rest and take it easy. To them, exercise is counterintuitive."

The outcomes are important: the right exercise prescription at the right time could reverse damage done to organs by radiation and chemotherapy, extending a survivor's lifetime by up to 20 years. While the potential upside lends urgency to the situation, Jones said the first step was to study whether exercise is actually safe for patients undergoing radiation or chemotherapy.

"There have probably been about 85 studies that have looked at the role of exercise in those diagnosed with cancer," Jones said. "We're finally to the point where we're

publishing exercise guidelines for cancer patients. But we're not close to a point where exercise is a part of cancer rehabilitation. Part of my job is to create the evidence base to convince governments and insurance companies to cover it."

To build that case, Jones and his team will have to study both general and specific effects of exercise via several studies (see below).

"We have seven big studies on the go (at Duke), all funded by the National Institute of Health," Jones said.

Jones added: "The first thing you want to do is treat cancer, but now that the survival rate is higher, we need to be concerned about what's going to happen in 20 years' time. That's where CrossFit might be extremely beneficial: not just effective to help the side effects but lowering recurrence rates and reducing risks of noncompeting causes of mortality—a triple threat."

Glass' job is to take blood samples and tumor biopsies from the exercisers in Jones' studies and perform "translational research," taking the data from the lab bench to the patient's bedside.

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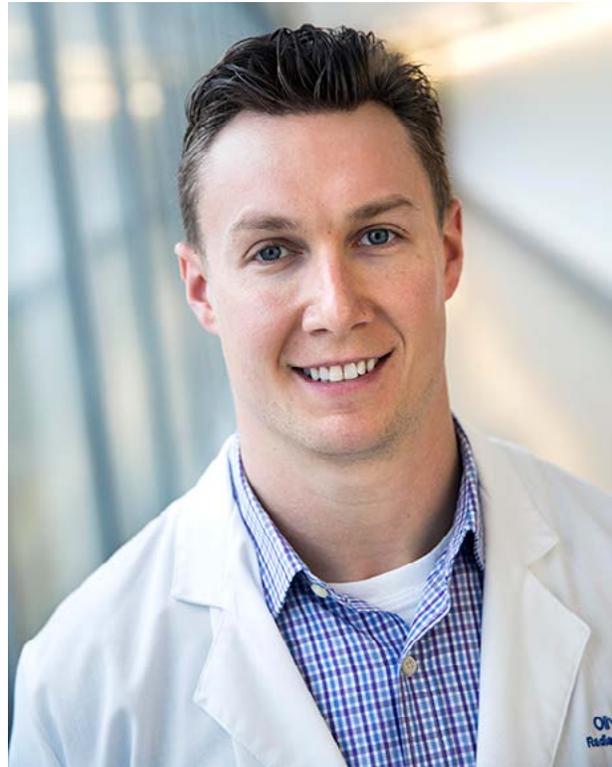
"How does a given marker correlate to better outcomes? Each could be different for those undergoing treatment or survivors or those at risk," Glass said. "In patients undergoing treatment, maybe we can just increase the delivery of chemotherapy drugs through increased blood-vessel growth. Maybe exercise can normalize blood vessels in tumors so the drugs can do their job better. Resistance training is going to elicit a different response than general fitness or endurance-type stuff. Maybe we can even tailor the exercise prescription to target the effects we need in each patient."

Jones' lab at Duke is seeking answers to the many questions with an array of clinical trials lasting from 12 weeks to five years. Though Jones will leave Duke in early 2014 to launch an exercise oncology program at Memorial Sloan-Kettering Cancer Center, the Duke lab will continue these investigations without him.

Six Studies on Exercise and Cancer at Duke University

1. Lungevity is a randomized, controlled trial on lung-cancer survivors who have already completed therapy. Researchers are testing for optimal types of exercise to improve peak VO_2 in survivors of lung-cancer surgery. A 16-week trial comprised four groups: aerobic only, strength only, aerobic and strength combined, and control (no exercise). When aerobic and strength work are combined on the same day, the resistance component is done on stationary exercise equipment.

Many researchers choose to use weight machines instead of free weights because of replicability: Peter's leg press is the same as Paul's leg press, with a very shallow learning curve.



Oliver Glass

Courtesy of Duke Marketing and Communications



Dr. Lee Jones

Courtesy of Duke Marketing and Communications

2. Excite is a trial of 174 women who have completed therapy for early stage breast cancer. Participants are organized into three groups: 60-70 percent of baseline VO_2 consistently, 50-100 percent (interval training) of baseline VO_2 and a control.

"We take the approach we use to training athletes and apply it to cancer to get optimal improvement in fitness," Jones said. "Patients certainly enjoy it a lot more, but is it more efficacious than what we've been doing for the last 30 years?"

Jones' goal in this trial is to find the optimal exercise prescription. Over 16 weeks, the first group will use the same exercise intensity without change; the second will vary the intensity between 50 and 100 percent of max VO_2 . This interval training may have secondary benefits: if patients enjoy it more, they'll be encouraged to complete their workouts.

3. In a trial involving women with metastatic breast cancer, each participant has been previously treated for cancer, and it's come back; survival outcomes are forecast at only 24-36 months.

"These women have been treated before, so now the treatment is more aggressive, and they have a tumor burden at the same time, so they're sicker," Jones said. "We've shown that exercise is safe and advantageous in early stage diagnosis. Can we exercise these individuals the same way?"

The primary outcome metric will be safety and feasibility.

"We're measuring fitness, quality of life, fatigue—but those are secondary outcomes," said Jones. "If adverse events, or side effects, happen to 20 percent or more of the women, we'll deem that exercise isn't safe in this population."



Courtesy of Duke Marketing and Communications

Jones wants to know when cancer patients can start exercising, and he believes sooner is better than later. He's currently testing his hypothesis.

Due to the risks involved, patients are free to drop out of this study at any time. As in all of Jones' research, potential risks and benefits are explained to every participant. Consent forms can be up to 15 pages long, with every minute detail explained, from the randomization process to the possible side effects.

4. A trial of 160 women newly diagnosed with breast cancer seeks to answer the question, "When should we start exercising?" Jones believes that sooner is better.

"If you talk to most oncologists, their response will be to wait until after therapy because you'll be tired," Jones said. "But I think, from some of our data, if you don't exercise during therapy, you'll take big hit to the cardiovascular system. Knowing this, I believe that if you're diagnosed with cancer, you need to start exercise right away. But that's just my belief. We have no data to back that up yet. So these women have been diagnosed and had surgery but haven't started chemotherapy yet."

"I believe that if you're diagnosed with cancer, you need to start exercise right away."

—Dr. Lee Jones

Participants are split four ways: exercise during chemo but not afterward, no exercise during chemo but exercise immediately afterward, exercise during and after chemo, and no exercise at all (the current standard prescription).

All the exercise done in this trial is aerobic to eliminate as many potential variables as possible. Patients will remain in the study group between six and 12 months, depending on the length of their chemotherapy treatment, which varies between individuals.

5. Another trial focuses on men with early stage prostate cancer who have just completed surgery.

"What we're interested in is that their greatest risk of dying is from cardiovascular disease, not prostate cancer," Jones said. "Erectile dysfunction is an important cardiovascular

risk factor; we think it's an early marker of cardiovascular disease. We're interested in erectile function and its improvement through exercise."

Fifty men have just completed six months' exercise training after surgery for prostate cancer, and the results could alter the current prescription for hormonal supplementation typically given to prostate-cancer patients.

"Already, we have research showing that people who have had prostate cancer go into androgen deprivation, which reduces circulating testosterone to near-castrate levels," Jones said. "So you lose all the secondary effects of testosterone: preserving muscle mass, maintaining energy levels. And then you get insulin resistance and a 50 percent increase in new-onset diabetes, which develops into cardiovascular disease."

The male subjects are given three sessions of guided aerobic exercise each week, as well as two prescribed "home workouts" that are self-guided.

"Most of the men choose walking as their aerobic activity," Jones said.

This trial will last six months.

6. A sixth study is a trial on breast-cancer prevention.



Positive research results at Duke could mean cancer institutes would start creating gyms for their patients.

"We know that certain women are at a higher risk because they're overweight or have a family history. If you see abnormalities in mammography, you can do a biopsy," Jones said. "Some of the normal breast epithelial cells look atypical: now they have a fivefold higher risk of breast cancer, with no effective form of therapy. So you can do a mastectomy or lumpectomy, but that's radical because you don't know if the cells are going to be cancerous or not. They might, but it's not 100 percent certain to happen.

"So we use different types of exercise and follow them over time to see if the cells change. Can exercise reverse the characteristics of those cells? Can you take someone who's high risk and convert them to low risk? We have a study on mice that suggests there's a dose-response effect to exercise. Can we identify the dose most efficacious at modulating these cells?"

In this six-month intervention, Jones' team will compare different doses of exercise—100 minutes per week, 150 minutes per week or 300 minutes per week—in an attempt to determine if more exercise is better. Is there a dose-response relationship between breast-cancer risk and movement?

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—Dr. Lee Jones

Jones is also leading pilot studies on patients with brain tumors and patients who have had bone-marrow transplantation and bladder cancer. Those trials are in the early stages.

"We're just doing exercise testing to see what they can tolerate now. We don't know those things yet," Jones said.

Cancers Are Different

Because cancer can affect so many different parts of the body, a one-size-fits-all exercise prescription for cancer patients is unlikely.

"You don't treat a breast-cancer patient like a brain-cancer patient. They're very different," Jones said. "You have to work through the logical progressions to understand what cardio is like in these individuals, then how to do the research. That's why I think exercise oncology is so interesting: every time you go to a new cancer type, it's like starting a new area of research.

"On top of that, you have new treatments coming in all the time. It's changed remarkably over the last eight years. If we showed exercise is effective using a method of chemotherapy eight years ago, it may no longer be relevant. It may no longer work with the new therapy. It's a very dynamic field, constantly changing, and that makes it very interesting and challenging."

Though the research takes time, and every angle has to be considered, Jones believes that exercise therapy is the way of the future for cancer patients.

"Over the next five to 10 years, you're going to see all big cancer institutes having fitness facilities in their institutes. You can imagine the potential for that. That's a huge network. CrossFit makes a lot of sense in that kind of partnership.

"Think of how many cancer survivors will be in North America then: 25 million by 2020. Every year adds hundreds of thousands of individuals who will need exercise rehab. The beautiful thing about this is we're talking about the beginning. Exercise isn't a part of standard care yet but coming on the horizon. It's going to be the standard of care, (with) lots of opportunities for novel partnerships. You go into hospitals now, they have chain restaurants. Soon, you're going to see fitness centers."

Upon diagnosis, the first question asked by most cancer patients is, "What can I do?" For many, feeling a lack of control over their own fate is depressing. Providing a self-guided form of treatment like exercise could help a cancer patient regain a sense of control and perhaps even hope. It might also significantly increase quality of life and health after cancer treatment.

Oncologists will no doubt be awaiting the results of the studies at Duke University to see exactly how they can use exercise to fight cancer.



About the author

Chris Cooper is a staff writer for CrossFit. His gym, CrossFit Catalyst, aims to combine various rehabilitation modalities into CrossFit programming, including for cancer patients.