“Exercise and Cancer Development and Progression" (Lee Jones, PhD) [#143]

Brad Power
May 14, 2025

“There's no randomized data suggesting that exercise lowers the risk of any form of cancer.” – Lee Jones, PhD

“When we measured individuals going through standard chemotherapy, we found that fitness could decline anywhere from 5% to 20% over a period of three months. If you talk to anybody who's been through chemotherapy, they will tell you, ‘I feel like there's been a significant detriment.’ And people say, ‘Well, that's expected.’ Typically, you see a 10% decline in somebody's fitness level over a decade; your fitness will decline 1% per year. You see 10 to 15 years of aging in just three to six months of chemotherapy. We started to describe this model of accelerated physiological aging.” – Lee Jones, PhD

“I work on thinking from a biological perspective, a translational perspective, how exercise can influence cancer. That's either from a prevention standpoint, or in individuals with cancer, asking fundamental questions, such as, ‘Can we prevent it in the first place?’ ‘Can we slow it down?’ Or, ‘Can we prevent it from coming back?’” – Lee Jones, PhD

Meeting Summary

While medical researchers have made significant advances in cancer therapies, these are far from perfect and complementary approaches are needed that are non-toxic and may also help lower your risk of progression and improve your outcomes. Exercise is an intervention you can use to control or offset your cancer and the side effects of therapies. You may wonder which exercise and other lifestyle approaches you should adopt after your cancer diagnosis that are grounded in scientific research.

Lee Jones, Director, Exercise-Oncology Program, Member and Attending Physiologist, Department of Medicine, Memorial Sloan Kettering Cancer Center, and Professor, Weill Cornell Medical College, is uniquely qualified to talk about the latest research on exercise and cancer development and progression. His academic career has focused on a near patient translational approach on the effects and mechanisms of highly controlled exercise in health and disease with an emphasis on cancer. His team was among the first to adopt traditional and molecular epidemiological approaches to investigate the link between post-diagnosis exercise and clinical outcomes in patients with cancer. Building on these efforts, they leveraged established as well as novel mouse model systems to uncover whether and how exercise alters tumor growth kinetics and biology at the cellular and molecular level. They have translated these efforts to the clinic, conducting some of the first prospective clinical trials investigating the tolerability, safety, and efficacy of exercise therapy across the entire cancer trajectory (i.e., prevention to advanced disease). Adhering to a rigorous translational development pipeline, they are conducting the first ever phase 1 trials to evaluate the tolerability and tissue / tumor biological efficacy of exercise therapy in persons with and at-risk of cancer. To enhance conduct of these trials, they have

pioneered a decentralized, patient-centric approach called the Digital Platform for Exercise (DPEx) which permits all study procedures to be conducted remotely inpatient’s homes.

Why is exercise important for cancer patients?

- **Mitigate treatment side effects**: can help prevent the significant decline in fitness during cancer treatment; you can lose 5-20% of your fitness in just three months of chemotherapy.
- **Counteract accelerated aging**: can help slow or reverse the process of rapid physiological aging – feeling like you’ve aged 10 years in just a few months.
- **Slow cancer progression**: can influence cancer progression, potentially preventing recurrence or slowing cancer growth, according to emerging research.
- **Improve overall physical function**: can help maintain muscle mass, strength, and cardiovascular health during and after treatment.
- **Support your immune system**: can enhance immune surveillance, potentially helping the body detect and control damaged or mutated cells.
- **Improve therapy response**: can improve response to certain cancer therapies.

What is the emerging scientific evidence connecting exercise and outcomes for cancer patients, including potential benefits?

- **Observational studies** suggest exercise may lower risk of 13 different cancer types, potentially reduce cancer mortality (especially in breast and colorectal cancers), and mitigate physiological aging during and after cancer treatment.
- **Current research** focuses on understanding exercise as a potential cancer treatment strategy, in addition to a symptom control intervention.
- **Ongoing phase three trials** (studies that test safety and how well a new treatment works compared with a standard treatment) are investigating exercise's impact on cancer recurrence and overall survival. There is no randomized data suggesting that exercise lowers the risk of any form of cancer.
- **Preliminary research** shows promising findings, e.g., in a prostate cancer study, 225 minutes of weekly exercise was feasible (i.e., achieved good compliance) and showed promising biological activity in tumor markers.
- **Challenges** remain: more rigorous research is needed to definitively prove exercise's anti-cancer effects, treating it more like a "drug" with careful dosing and patient selection.

What is general advice on exercise?

- Aim for 225 minutes of exercise per week, spread across 5 days. (This is only for prostate cancer. We don’t know if it applies to other tumor types yet.)
- Personalize your prescription of exercise based on your fitness level and what your target is: body composition vs. fitness vs. cancer control. There is overlap, but the goal is to match your prescription with your goal and not just “one size fits all”.
- Consult with qualified exercise physiologists or oncology teams to develop a personalized exercise plan

How should you personalize your exercise?

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- Consider your current treatment stage, cancer type, physiological capacity, and potential risk of over-training to create a precise, adaptable exercise plan. Vary intensities and session lengths within the same week. In the future you will also base your exercise prescription on other characteristics, such as treatment type, tumor biology, etc
- Conduct a cardiopulmonary exercise test to determine your baseline fitness level
- Monitor your compliance and physiological adaptation and modify your program based on your progress; focus on finding your "sweet spot" of exercise dosage

How can you learn more?

- Reach out to Lee Jones for discussions and questions and to get links to his papers at lee.jonesphd@gmail.com
- Review previous Cancer Patient Lab discussion on exercise, including:
    - “Exercise to Boost Your Immune System to Fight Cancer” (Dr. Tom Incledon) [#49]
    - Adding Exercise for Everyday Life and Developing a Medical Device to Personalize Cancer Treatment (Cathy Skinner) [#47]
    - “Exercise as a Countermeasure to Hormone Deprivation Therapy Side Effects and for Bone and Mental Health” (Kerri Winters-Stone) [#48]

For the video recording of this conversation, please see here.

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Meeting Notes

KEYWORDS

Exercise oncology, cancer treatment, exercise physiology, fitness decline, biological aging, exercise trials, phase three trials, exercise prescription, cancer recurrence, exercise benefits, resistance training, aerobic training, inflammation, hormesis, exercise compliance.

SPEAKERS

Lee Jones (79%), Cindy Ness (5%), Brad Power (5%), Richard Anders (4%), Roger Royse (2%), Chris Apfel (2%), Alexander Lalov (1%), Rick Davis (1%), Jim Ward (1%)

CHAT CONTRIBUTORS

Robb Owen, Alane Watkins, Roger Royse, Se, Alexander Lalov, David Plunkett, Cindy Ness, Rick Davis, Jim Ward, Chris Apfel, Richard Anders

SUMMARY

Lee Jones, a PhD researcher on exercise and cancer, discussed his career trajectory and current research at Memorial Sloan Kettering. He highlighted the lack of evidence in the early 1990s on the feasibility and benefits of exercise in cancer patients, leading to his first studies in colorectal, breast, prostate, and lung cancers. Jones emphasized the importance of rigorous exercise trial design, including phase one studies to identify optimal doses and feasibility. His recent work found that 225 minutes of exercise per week was the most effective dose for prostate cancer patients, with higher doses showing no additional benefits. Jones also discussed the challenges and benefits of a decentralized exercise trial model.

OUTLINE

Introducing Lee Jones

- Lee Jones, a PhD researcher on exercise and cancer.
- His journey has been from the UK to Canada to the US.
- His early career was in Edmonton, Alberta, where he worked with Kerry Courneya on the first studies in exercise for individuals with cancer.
- He moved to Duke University in North Carolina, where he started his lab and received grants for his research.
- He joined Memorial Sloan Kettering (MSK) in 2014, where he established the exercise oncology program with a team of 32-33 people.
- He recently accepted a new position at City of Hope in East LA, starting on July 5, where he will start a new research program in exercise oncology.

Initial Research and Findings

- His initial focus was on behavioral exercise intervention, studying how to initiate and maintain exercise in individuals with cancer.

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- There was a lack of evidence in the early 1990s to suggest that exercise was feasible or beneficial for individuals with cancer.
- His first studies in colorectal, breast, prostate, and lung cancers showed the feasibility and tolerability of exercise during and after therapy.
- He became interested in the physiological adaptations and consequences of cancer and cancer treatment, using exercise physiology tools to measure organ function during stress.

Impact of Cancer Treatment on Fitness

- There is a significant decline in fitness levels during cancer treatment, with a 5-20% decline in fitness over three months.
- There is accelerated physiological aging, where individuals feel like they have aged 10 years in just three to six months of chemotherapy.
- His research aimed to recover fitness levels to pre-treatment baselines and prevent dysfunction during treatment.
- You need to understand the optimal dose and timing of exercise to mitigate the physiological side effects of cancer treatment.

Transition to Exercise as Cancer Treatment

- He shifted focus to whether exercise can influence cancer outcomes, either as a prevention or treatment strategy.
- His current research at MSK aims to understand how exercise can affect cancer progression and response to treatment.
- Rigorous development of exercise interventions is important, from discovery epidemiology to definitive clinical trials.

Challenges in Exercise Research

- There are challenges in designing and conducting phase three trials of exercise in cancer, including the lack of evidence and the need for a rigorous development framework.
- Ongoing phase three trials are few, such as the Challenge Trial in colorectal cancer and the Interval Trial in metastatic prostate cancer.
- It’s important to understand the right dose and patient selection for exercise interventions.

Decentralized Exercise Trials

- A decentralized approach to exercise trials, using technology to deliver exercise prescriptions and monitor compliance, is better.
- The decentralized approach to exercise trials involves sending treadmills and other equipment to patients' homes.
- The approach allows for more efficient recruitment and longer trial durations, beyond the typical 12-15 weeks.
- The non-linear exercise prescription includes different intensities and durations to elicit specific physiological responses.
- The approach has been used in various cancer settings, including high-risk individuals and those with cancer.

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Phase One Trial in Prostate Cancer

- There was a phase one trial in localized prostate cancer, which aimed to identify the optimal dose of exercise for anti-tumor activity.
- The trial recruited 53 non-exercising men scheduled for surgery, who were assigned to six different exercise doses ranging from 90 to 450 minutes per week.
- The trial found that 225 minutes of exercise per week was the recommended phase two dose, based on feasibility and biological activity.
- The results showed that higher doses did not provide additional benefits, and 225 minutes was deemed the optimal dose.

Discussion on Exercise Prescription

- Exercise prescriptions should be tailored to each patient's physiological response.
- A non-linear approach to exercise is needed, which includes different intensities and durations.
- He offered to provide more detailed guidance on exercise prescriptions and to review individual cases.
- You should understand the right dose and patient selection for exercise interventions.

Aging, the Use of Oxygen, and the Impact of Exercise on Cytokines and Natural Killer Cells

- There are challenges in measuring biological aging
- Fitness is important as an integrative measurement.
- The use of biomarkers in current studies are important for understanding the physiological effects of exercise.
- Rigorous development and testing of exercise interventions is needed to prove their efficacy.

Invitation to Discuss

- Dr. Jones encouraged participants to reach out to him for further discussions and to stay informed about his research.

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TRANSCRIPT

Brad Power
This is the Cancer Patient Lab, and our weekly webinar series.

We're honored to have Lee Jones with us, who's beaming to us from San Diego, where he's in transition, I gather, moving between things. He's with Memorial Sloan Kettering, and he's a PhD researcher on exercise and cancer, and he's going to share with us some of his research findings before we get started.

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Lee Jones 1:13
When I first started in this research area, which is probably 25 years ago, this area of exercising and cancer didn't exist. I don't know how much you know about my background, but you can probably hear by my accent that I'm not originally from San Diego or New York. I'm originally from the UK. That's where I did my undergrad. I then moved to Canada to do all my graduate training, first in northern Ontario, before moving to Edmonton, Alberta, at the University of Alberta. That is important in my career trajectory because I started working with somebody named Kerry Courneya there. Kerry was a young professor at the time, and was just starting some of the very first studies about exercise in individuals with cancer, specifically colorectal cancers as it happened. I was his first PhD student, which meant that I was doing everything. I was the clinical coordinator. I was the exercise physiologist. I was the person doing all the exercise prescriptions and every session with individuals undergoing treatment or afterwards. That was an amazing experience for me. With that, I did my PhD and post doctoral fellowship there in Edmonton.

My first job was at Duke University in North Carolina. My wife and I drove down from Edmonton, Alberta, to North Carolina. It took us about five days, which was a lot of fun. It was about minus 32 degrees when we left Edmonton, and then we were golfing on New Years Day in Raleigh or Durham, North Carolina. I thought “What have we been doing all this time?” We should have moved here years ago.

I was at Duke for about 10 years. Then I started my lab there. We got a few grants, which we were fortunate to get. Then I was recruited to Memorial Sloan Kettering (MSK) in 2014. There I started this new program of research that we call exercise oncology. There, I'm in the Department of Medicine. We have a team of about 32-33 people, all of whom are completely dedicated to research and exercise in cancer of which I'll talk a little bit about today.As I was just saying to Brad, I've actually just accepted a new offer for a new position at City of Hope in East LA, and I'll be moving there on July 5th. Leaving MSK after 11 years is going to be sad, but I'm

excited about this new beginning. There, I'll be starting this new research program again in exercise oncology.

To talk more about my career path and how I first got started in this area of exercise in cancer, Kerry Courneya was a behavioral exercise interventionist, which means that he was very interested in the motivational aspects of exercise. For example, how do individuals get interested in exercise in the first place? How do they initiate exercise, and then once they do start exercising, how do you keep them on it? How do you improve compliance and adherence to exercise prescriptions? That's where we started.

The problem with that was that there was no evidence to suggest that exercise was actually feasible or beneficial with individuals with cancer. This is when I first started my PhD in 1998. I think we found three studies at that time that looked at the role of exercise. There was no background, foundation, or evidence to suggest exercise was beneficial in the first place.

As a result, we started some of the very first trials. In fact, I think the first trials performed in colorectal, breast, prostate, and lung cancer were all done in Edmonton, Alberta, believe it or not. We started performing those first studies looking at feasibility and tolerability of exercise, both during and after therapy. As my PhD continued, I started to get more interested and went back to my exercise physiology roots, to the questions of “What are the fundamental physiologic adaptations that occur in individuals with cancer?” and “What are some of the physiological consequences of cancer and cancer treatment?” When I went down to Duke, my area of work was characterizing what treatment was doing to the human body using exercise physiology tools.

As many of you will know, when you go through different oncology treatments, they will measure things like your lung function using PFTs, or they'll look at your heart, doing echocardiograms. But all these tests have been done when your body is at rest. The body has a lot of reserve capacity at rest, and so you don't typically see very much injury or dysfunction when these tests are done at rest. From an exercise physiology perspective, we always think about looking at organ function that's working together, so integrative organ function, but during stress, the stress, in this case, is exercise. As a result, we've done a lot of exercise stress and cardiopulmonary exercise testing to measure and quantify the impact of different therapies on the whole body, as opposed to looking at individual organ function. That's where we started our work in this area. We found all these significant detriments in things like exercise capacity as individuals are going through treatment.

Just to put that into context, when we measured individuals going through standard chemotherapy, we found that fitness could decline anywhere from 5% to 20% over a period of three months. If you talk to anybody who's been through chemotherapy, they will tell you “I feel like there's been a significant detriment.” People will say, “Well, that's expected.” Typically, you see a 10% decline in somebody's fitness level over a decade. Your fitness will decline 1% per year. You see 10 to 15 years of aging in just three to six months of chemotherapy. We first started to describe this cancer treatment as a model of accelerated physiological aging. Again–

people who've been through therapy will tell you this–they feel like they've aged 10 years. We were the first group to quantify that was true.

On the basis of that, we said, “We need to do something about this.” We started the first exercise studies, first in individuals who completed their therapy to see if we can recover them back to their pretreatment baseline, if you will, and then exercising individuals during their treatment to see if we can prevent the dysfunction in the first place. I spent the first 15 years of my career doing that type of research, such as looking at the optimal dose and looking during treatment and after treatment in various types of solid tumors.

But then, when I moved to Memorial Sloan Kettering, I wanted to start a new line of research that I felt that complemented this, such as looking at exercise to mitigate the physiological side effects. One fascinating question that the individuals in our trials would ask me all the time is “I’m feeling less fatigued, stronger, and better, and I’m exercising, but what's happening to my cancer?”

I'd say, “What do you mean?”

They’d say, “Well, I'm in better shape now. Does that mean that there's less chance of my cancer coming back? Does that mean I've slowed my cancer down? Does that mean I'm responding better to my treatments?”

I’d say, “I don't know. Nobody's asked that question before.” So, when I went to Memorial, this is where I felt that the research gaps were. Could we now start thinking about exercise as a form of treatment of cancer itself? If so, how does it work? What are the right doses? Does it have an effect or not?

I've been in this field of cancer research now for a long time, but what I specifically work on now is thinking from biological and translational perspectives, as well as how exercise can actually influence cancer. That's either from a prevention standpoint or, in individuals with cancer, asking fundamental questions such as, “Can we prevent it in the first place? Can we slow it down? Can we prevent it from coming back?”

Those are the questions that I'm focused on.

Brad Power 10:39
I'm sure if you give a pause, questions will come. Anybody have any right off the top?

Chris Apfel 10:46
What would be the objective measurement of aging as a result of chemotherapy?

Lee Jones 10:56
There’s various measures that are looking at biological aging, and there's many different people who are using epigenetic clocks to look at that. We've been thinking about it from a physiologic

aging perspective, and the way that we measured that is by performing these tests called cardiopulmonary exercise tests. A cardiopulmonary exercise test is like a fancy stress test. If you've ever had a stress test while walking on a treadmill, they'll look at how long it takes for your heart rate to get to a certain threshold.

Chris Apfel 11:33
But, that's fitness, not aging?

Lee Jones 11:36
Fitness is a marker of aging.

Chris Apfel 11:40
Yes, but if you want to “have aging independent of your fitness…”

Lee Jones 11:45
Aging independent of your fitness–what do you mean by that?

Chris Apfel 11:51
People can have different fitness levels based on how much they exercise, right? For example, if you are 40, 50, or 60 years of age and you exercise, your exercise ability varies. You mentioned that, generally, there’s a 1% decline per year in terms of fitness. But people exercise in different amounts and have different starting points, so to speak. “Biological aging” should be measured independently of fitness. Fitness is a kind of epiphenomenon (or secondary effect that has no influence) of biological aging.

Lee Jones 12:35
But fitness is not just a marker of how much you exercise. It's a marker of a lot of different things. This is why we love fitness: it is an integrative measurement. We do have, not from our group, but thousands of studies that have looked at fitness levels in individuals without cancer, and so we know what the age predictive fitness rate should be based on your age and your exercise levels, for males and females. We've had this normative data. What we were able to do then is take fitness measurements in individuals at various stages of cancer, and then compare it to the normative data. In a study we published in 2012, what we wanted to know, from a physiologic perspective, is “Are cancer treatments causing this accelerated aging?” What we found is that if you look at the fitness level of, for example, a woman with breast cancer who's age 50, they should have a fitness level of 25 on average. But what we found in our breast cancer survivors is that their fitness level would typically be around about 17. From an aging perspective, our breast cancer survivors were at a physiologic age which was 10 to 15 years older than it should have been, especially compared to women who had not been through breast cancer and breast cancer therapy.

Chris Apfel 14:32
Were the participants comparable in terms of exercise, activity and all of the other variables?

Lee Jones 14:36
Correct. In these studies that we had, we only recruited individuals who were non-exercisers. We tried to control for that, and then we compared them against the norms of data, which is also from non-exercising individuals. That was our comparison.

Chris Apfel 14:53
Thank you. I was just curious–I mean, how do you objectively measure aging?

Lee Jones 15:05
I would be happy to send you the paper! There's been a number of studies that have looked at various measures of aging, but we quantified physiologic aging through fitness.

Brad Power 15:23
There’s a question from Elaine: have you looked at exercising with EWOT (Exercise with Oxygen Therapy), or exercising with hypoxic intervals in cancer patients?

Lee Jones 15:39
We have not.

Brad Power 15:42
Elaine, we had a session about EWOT with an individual in Arizona. I should remember his name. He was Dr. Tom; that was his moniker. I'll share that with you afterwards, because he was doing that kind of exercise.

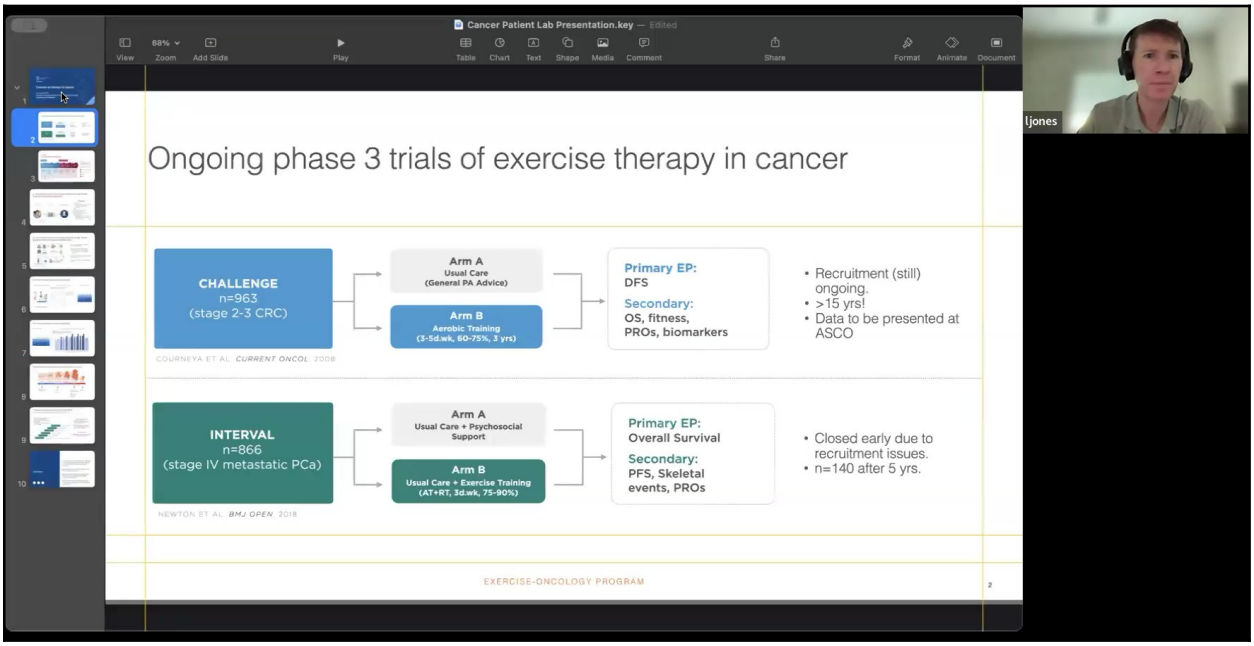
Lee Jones 15:58
Was he exercising individuals who were taking supplemental oxygen at the same time? There was a study I was involved in with individuals with COPD that did that, but then used helium, not oxygen, because helium actually has a better improvement in fitness, and that's what we found. But that study was performed in individuals with restrictive lung disease. We haven't done that in individuals with cancer.

Brad Power 16:27
Cindy has a question, and Roger wants to see your slides.

Cindy Ness 16:32
I work in the area of lifestyle and trying to improve cancer outcomes with all sorts of lifestyles. Let me just say that I feel like I want to kidnap you for four hours and then I would release you to be able to ask all my questions. Let me just start: did you look at cytokines or natural killer cells? In other words, in terms of exercise, did you look at the levels of various biomarkers? Fitness can be impacted by so many things. Let’s say that, if there were people who hadn’t exercised when they started in your study, they could still have different levels of fitness that are related to many other things, other than how much they're exercising. I just wonder about that. Heart rate variability, inflammatory markers, and things of that sort… I think there is enough evidence to at

least consider that those markers may have something important to say about cancer progression. I wonder if you used any biomarkers like that at all at this point.

Lee Jones 17:57
We're doing that now in our current study. We didn't do it in all of our studies. Let me get to our slides so I can give you a “flavor” of what we are doing.



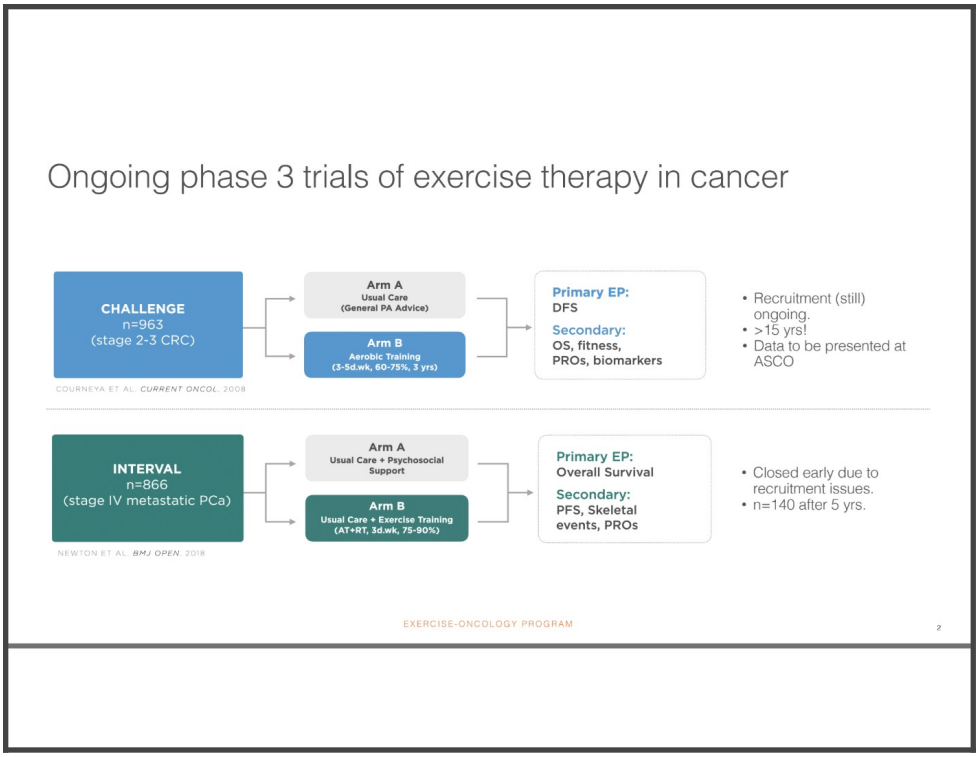
Lee Jones 18:33
I just wanted to frame the conversation: we're talking about exercise and cancer outcomes here. We're not talking about quality of life, we're not talking about fatigue. We're not actually talking about fitness, which is hard for me to say, because that's where I was born and raised thinking about fitness. I wanted to start the conversation about what we think we know and what we actually do know. With exercise, we often think that we have all this incredible data that supports exercise as being this incredible therapeutic, both in and outside of cancer. But my point was that, if you look at the gold standard data, evidence for any intervention is phase three trials. You might think that there are an abundance of phase three trials outside of oncology that prove the efficacy of exercise in the number of different disease conditions. Anybody has a guess of how many phase three trials we have of exercise, in any population, like heart disease or diabetes?

Brad, you're saying zero?

Well, it's actually three. It's only three. There's one in heart failure, one in heart disease, and one in aged individuals. But all three of those trials have been negative. All of them for their primary endpoint were all negative studies. Now, I'm an exercise advocate. I exercise every day. I love it, but I'm also a scientist, right? For me, it always comes back to the evidence. To figure out the reason why all of the trials today have failed, we have to contemplate whether exercise does not

work for individuals with heart disease or heart failure, or whether it’s because of the limited way that the trials have been developed and conducted.

There's a problem here with many different aspects of how exercise trials are conducted, in terms of the selection of the individuals that come into the trials, compliance with the actual prescriptions in the first place, and also the actual exercise prescriptions. All these problems typically resonate in many behavioral interventions, be it exercise or diet. We haven't had a positive vitamin trial in the U.S. for the past 25 years. We've had continuous studies with increased fruit vegetable consumption that haven't worked. Vitamin D has also just recently failed. Omega three also recently failed. Metformin also failed. We've had all these negative trials.



I wanted to start here by saying that there are ongoing phase three trials of exercise on cancer endpoints. The first one is called the “challenge trial,” which is actually being run by my former advisor, Kerry Courneya. This is a trial that was out of Canada, but this is an international, phase three, and randomized control trial in almost a thousand individuals with colorectal cancer. The trial examines individuals who completed therapy to their usual care, which is no exercise, or individuals who performed exercise training three to five days a week. The goal of the individuals who exercised is to get to something called 18-met hours of exercise per week, which is approximately about 300 minutes of exercise per week, and they're looking to do this for three years. The primary endpoint of this trial is recurrence or disease-free survival. Secondary endpoints are overall survival, fitness, patient reported endpoints, and various biomarkers.

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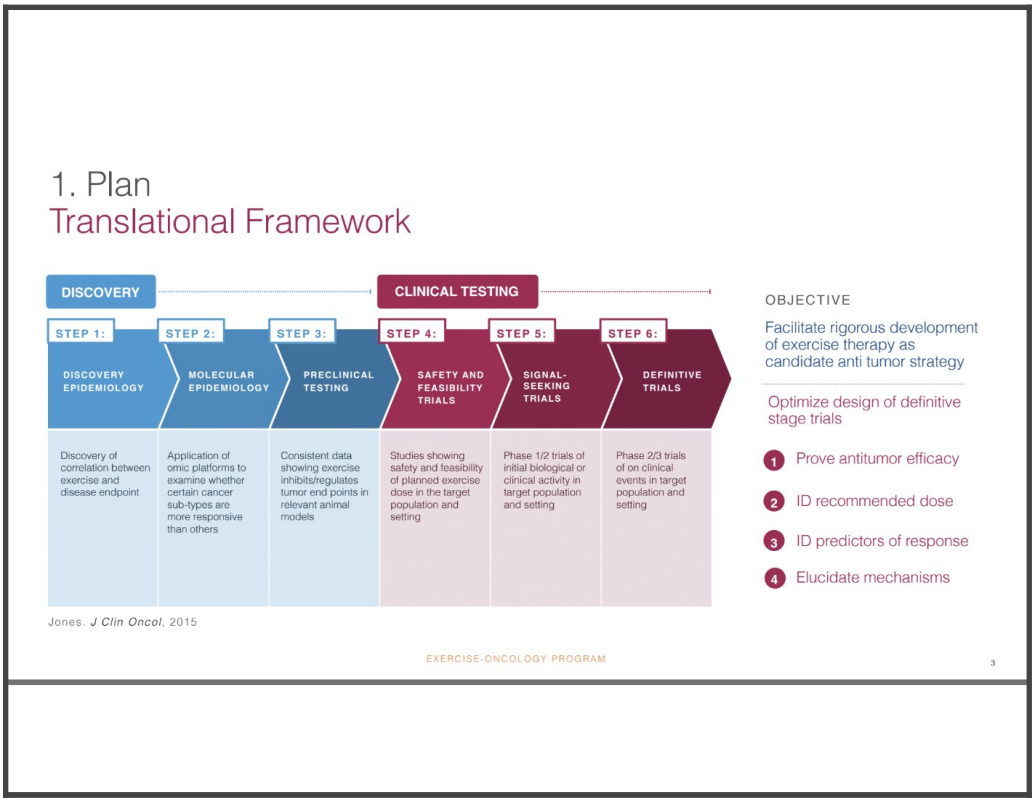
This trial was started in 2008. I actually just spoke to Kerry yesterday, and apparently this trial now the trial results are going to be reported at ASCO this year and published after being underway for almost 20 years. This trial was designed without knowing what the right dose of exercise was and who the right patients were. We don't know if three years of exercise training is too long or long enough. I think these trials were designed without understanding all the fundamental prerequisites that are required to design a phase three trial.

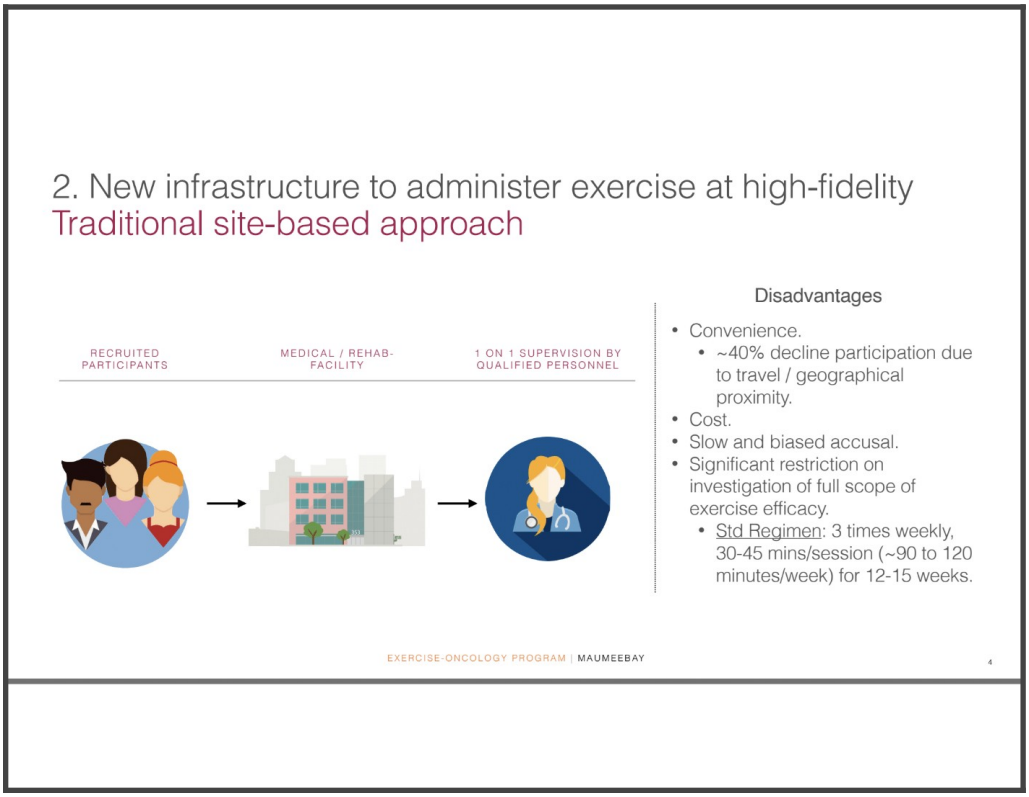
The second trial was called this interval trial, which was out of Australia, funded by Movember. This, again, was an international phase three trial in men with stage four metastatic prostate cancer with randomization to neutral care or exercise training. This was a combination of aerobic and resistance training, three days a week. This was high intensity exercise. It's 75-90% of someone's measured strength or fitness level. The primary endpoint was overall survival. But this trial just closed. This trial closed prematurely because of recruitment issues, and I think that raises another important issue. You can design these trials, but if you can't get individuals to enroll in these trials for various reasons, that is a problem.



I wanted to start with that, just to lay the groundwork of how we're trying to approach this problem differently. Our plan is to approach exercise like a drug. That might sound crazy, but when I did my training for my PhD, I was surrounded by medical oncologists, and it struck me that the way that we have been developing exercise and other lifestyle interventions has possibly been suboptimal. So I designed this framework that I wanted to apply to exercise–to develop exercise as an anti-cancer strategy, to use that word. Step one is discovering epidemiology. Let’s say you do a study in a thousand individuals and you found a relationship

between exercise and the risk of cancer progression. People might say, “That's very interesting. It's associated with a 40% reduction in the risk of cancer progression.” But that doesn't prove causality. Therefore, we now need to do a phase three randomized control trial to prove that is true. In essence, you make this large jump from step one to step six, and I think we miss a lot of steps in between. If this was a drug, you wouldn't be able to go from just an observation to then performing a phase three trial. You'd have to develop it along a series of steps.

This is not the only approach, and I'm not saying it's the right approach, but what we've tried to do is develop exercise across a number of steps that goes from discovering epidemiology into molecular epidemiology into preclinical testing. If those steps work, then we get into some of these early studies to make sure the exercise dose that we want to test is safe and feasible. We can then get into these other studies that are looking initially for a biological signal that exercise is effective in the cancer type of interest. Do you indeed see there's evidence for biological activity? If so, then you can move to definitive trials, but if you don't see these signals, then you wouldn't move forward. The idea here is to facilitate the rigorous development of exercise. If this works the way that we think it should, then we will prove the efficacy of exercise from a biological signal and identify what the right dose of exercise is and potentially what individuals respond the best to exercise. Of course, along the way, to answer the earlier question, we can elucidate how exercise works. For many diseases and especially cancer, we have no idea how exercise might affect their endpoints. We have a few signals that have come out lately, but really we don't know how exercise might mechanistically prevent or have an impact on cancer in people.



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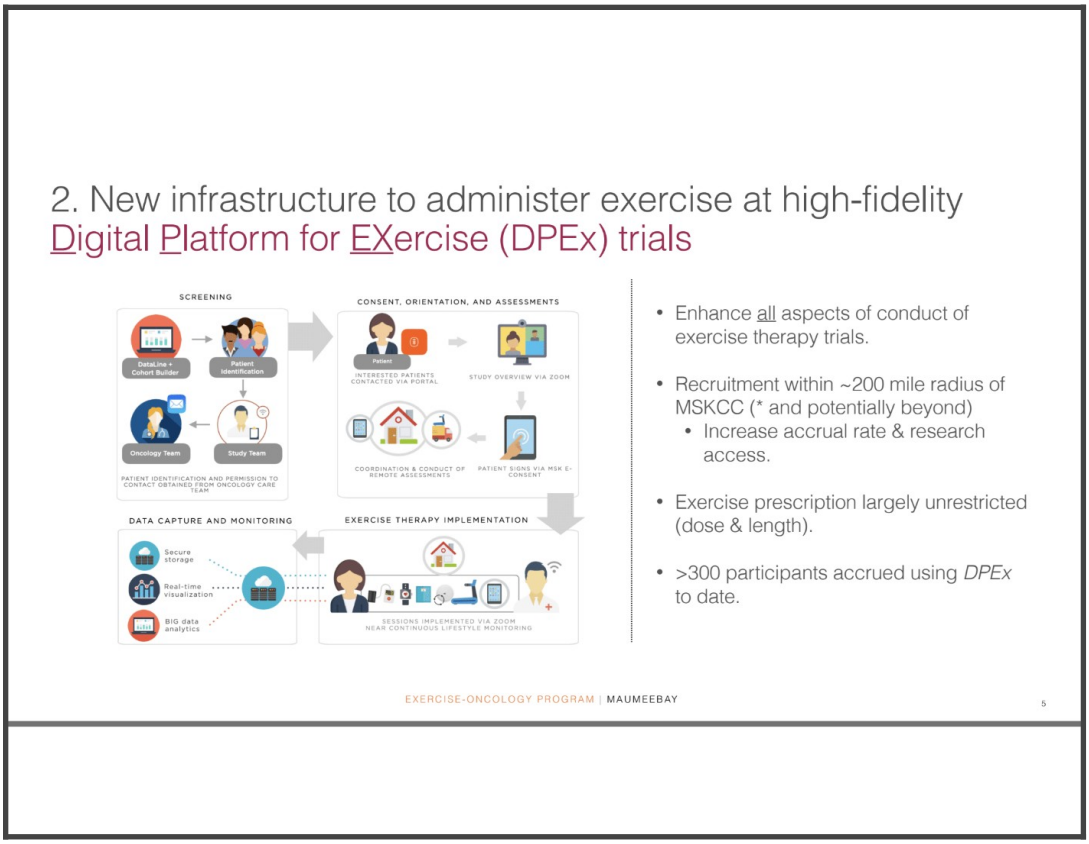
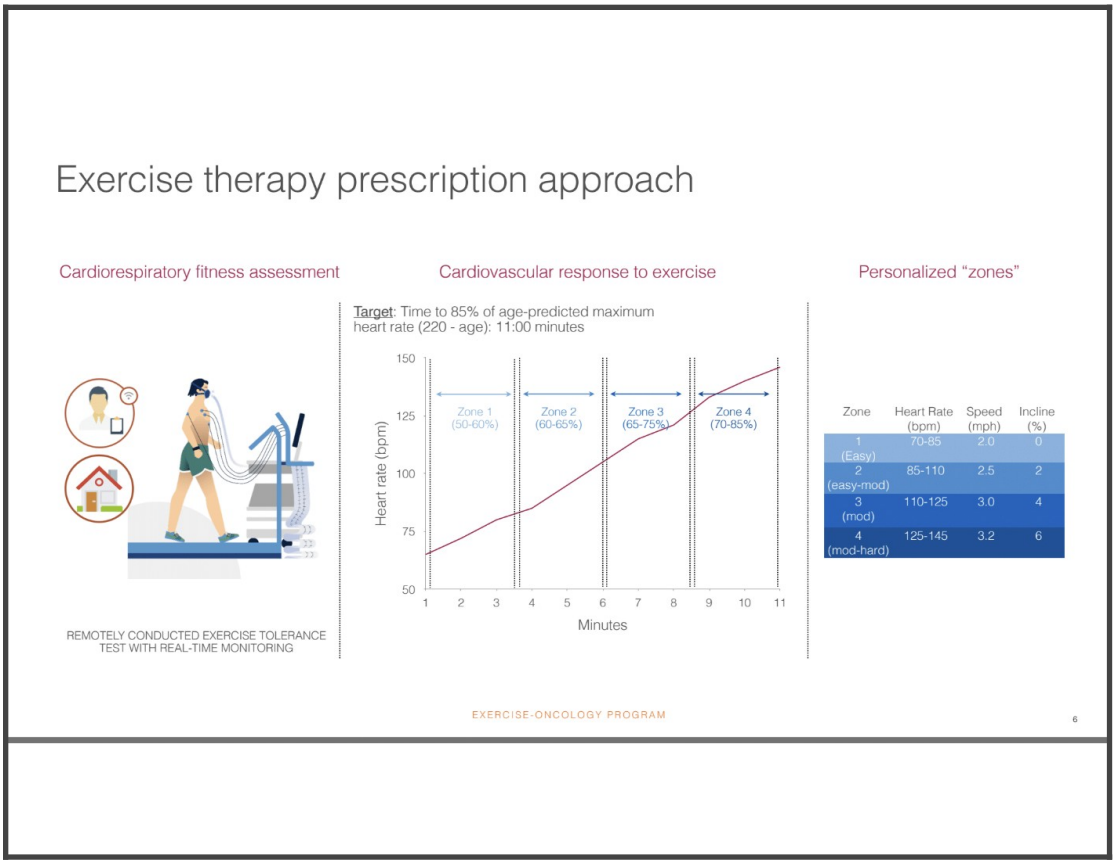
Lee Jones 27:15
If you come up with this development framework to test exercise, then we need to be able to develop and deliver exercise at high fidelity. Most studies in exercise bring people into a center and watch them exercise three days a week for, say, 15 weeks. This has been the model that we've used for 50 years, but it has a number of problems. Typically, you can't get people to enroll into these studies because of inconvenience or cost. This leads to slow accrual, which has had a huge impact on the types of studies that we can conduct. Why are most exercise studies 12 to 15 weeks, three days a week? Is it because that schedule is the optimal prescription for exercise? No, it's because that's what we believe individuals are going to be willing to commit to–anything longer than that and people might not want to enroll. If you try to do exercise more times a week, it’s going to be more costly. It's going to be hard for individuals to come in. Overall, the approach hasn't been empirically derived. It's been driven by what we think people are willing to do.



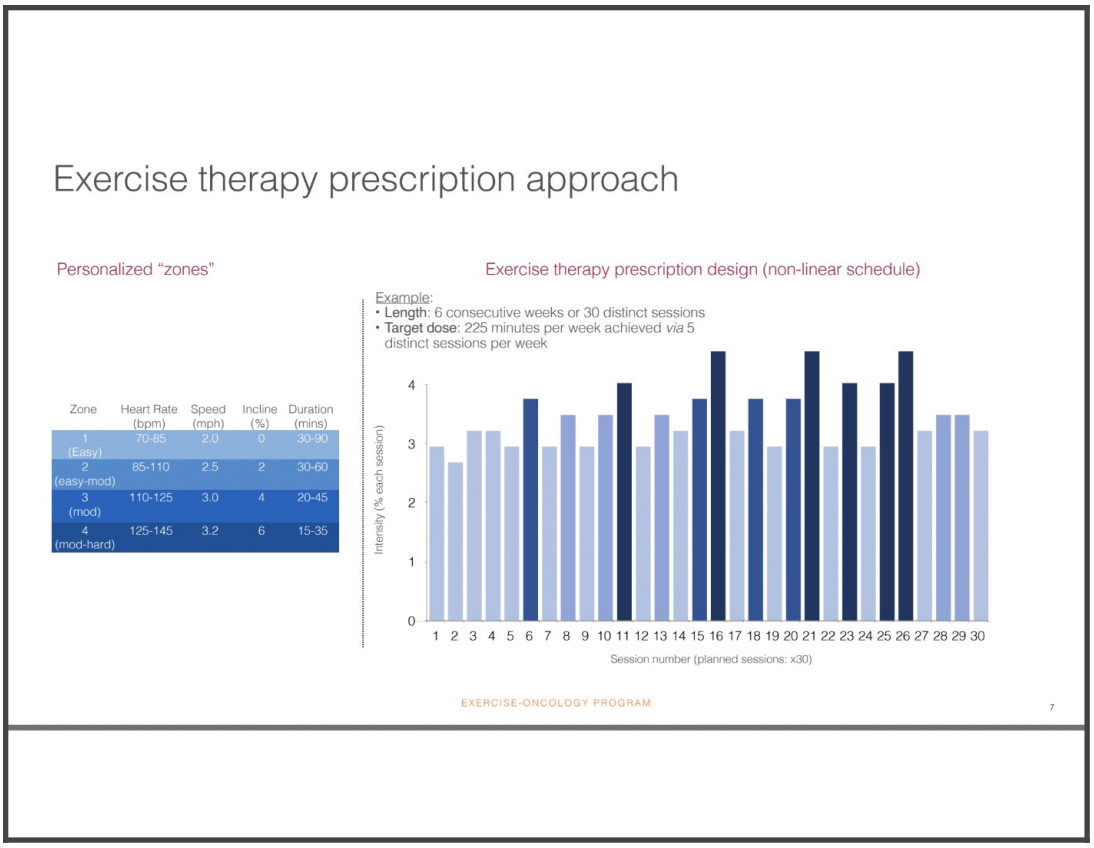
Prior to the pandemic, we developed this decentralized approach to exercise. Essentially what we tried to do is make this a patient-centric approach. Rather than trying to have the individuals come to us, can we go to the individuals? There are many pieces to this model that we came up with, but we primarily used technology to make our trials as efficient as possible. For example, we own a fleet of one hundred treadmills, and we send a treadmill to the patient's home or wherever they live in the tri-state area. We are now working on a national strategy. These treadmills come with an iPad and many wearable devices. With the iPad, the patient logs on where they receive a link and gets on a zoom call with an exercise physiologist waiting for them, who would then tell them what the exercise session is for that particular day. This is not a

negotiation. We have a prescription for every single individual. We know what they should do for every single session. We have the exercise physiologist deliver that session, and then we can monitor compliance to the nth degree. All this data then floods into our cloud passively. Now we can collect data and perform exercise trials in a way that previously wasn't possible. This, I think, enhances all aspects of the clinical trial, allows recruitment of individuals living up to 200 miles away from MSK, and now equips us to test exercise prescriptions, not only at higher doses, but also for a greater period of time far beyond the 15 weeks.



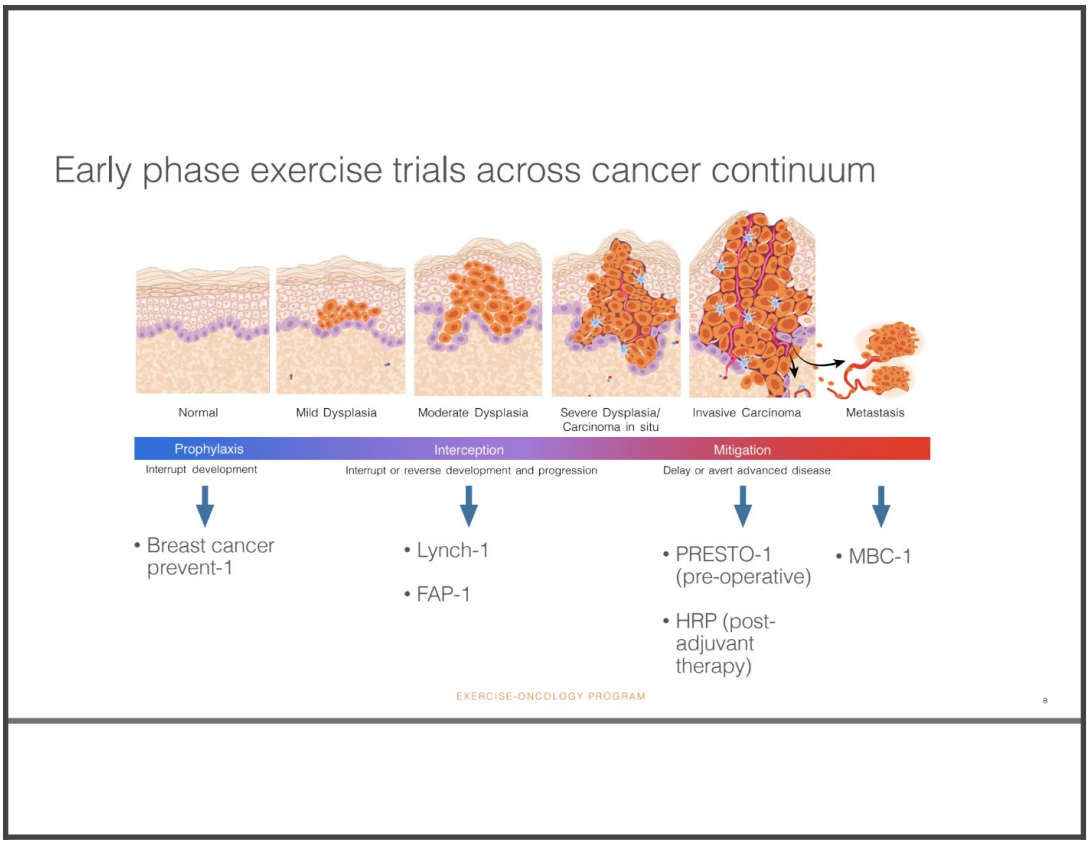
Essentially, for every single individual who comes through our trials, we send them a treadmill and perform an initial cardiorespiratory fitness test, because we need to know what that individual's level of fitness is to begin with. We then look at their response to exercise. We then stratify the response into different zones, going from zone one to zone four. You can see zone one is about 50% of their baseline exercise capacity. Zone 4 is 70–85%. Because we know this information, we then implement it into a prescription for each individual patient. We know, for example, what the heart rate zone should be for a zone one session. We know how fast they're walking on the treadmill and what the incline was. When we put this information into prescription for an individual, we know precisely how to set up the treadmill to elicit the physiological response that we want.

“Exercise and Cancer Development and Progression" (Lee Jones, PhD) [#143]



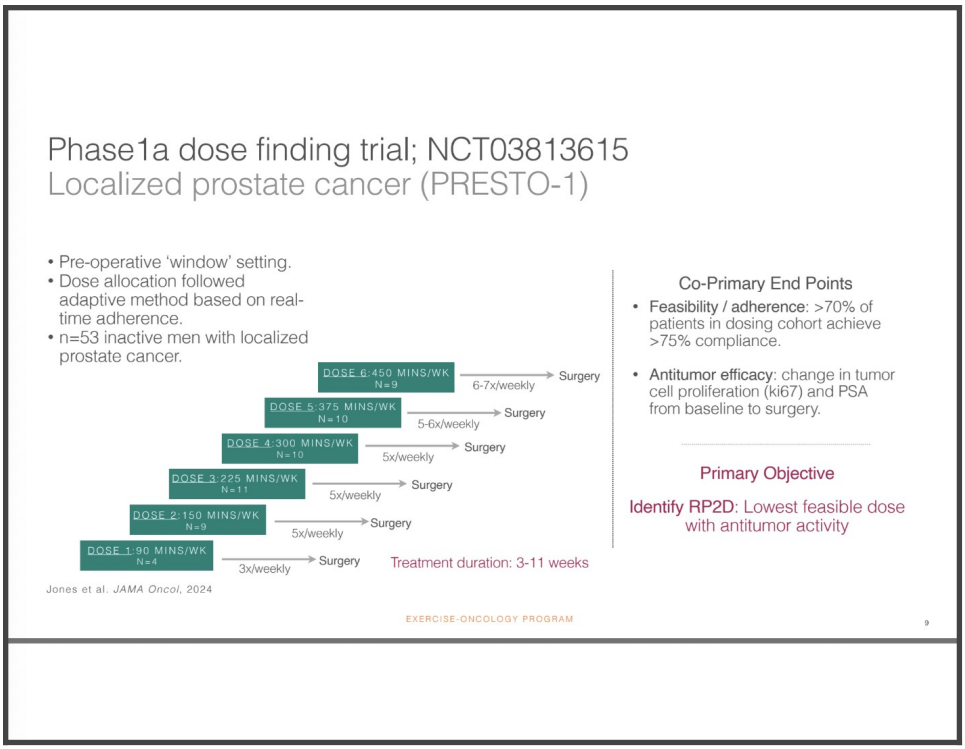
When we set up the exercise prescription, it looks something like this. This is called a non linear prescription, which means that every exercise session is either at a different intensity or duration, which elicits a different physiological response or stimulus on the body. Most exercise prescriptions are linear. Every time you exercise, you do the same number of times per week, same intensity, and same duration. That's a linear prescription. If you know anything about exercise physiology, that's not the way you should exercise. You should exercise using this non-linear approach. Anybody who's done a marathon will tell you this. You just don't do long, slow runs. You do interval training. You do some hill and speed workouts. That's the way that we design our prescriptions and all of our clinical trials.

“Exercise and Cancer Development and Progression" (Lee Jones, PhD) [#143]



Using this decentralized approach, we've now got a number of these early phase studies across the entire cancer continuum in individuals who are at high risk for cancers. We’re looking at women with BRCA1/BRCA2 mutations. We're looking at exercise to prevent cancer. We're doing work in what I consider the interception space, such as individuals with Lynch syndrome that are high risk colorectal cancer. Then in individuals with cancer, we've got studies in breast cancer and colorectal cancer. PRESTO-1 was a study in localized prostate cancer. We've also got studies in the metastatic setting among women with advanced breast cancer.

“Exercise and Cancer Development and Progression" (Lee Jones, PhD) [#143]



This is a study that we recently published. We have observational data showing a link between exercise levels and the risk of prostate cancer progression. There's about a 30% decrease in the risk of prostate cancer progression in men reporting exercise versus those who do not. But this, again, is observational data. What I wanted to know is, what is the optimal or most appropriate dose in individuals with localized prostate cancer. “Most appropriate dose” is defined by the level of exercise that men can do and the level of exercise that has initial biological activity in the prostate cancer itself. To address this question, I felt that we needed a phase one study of exercise. To my knowledge, this is the first phase one study of exercise ever done in any setting.

Lee Jones 33:51
We took advantage of the preoperative setting in men with prostate cancer. These were men all scheduled for prostate cancer surgery, and so we had a very short window of time from the point of diagnosis to the point of their surgery. The reason we use this window is because we wanted to look at the effect of exercise on the tumor itself without any other form of cancer therapy like chemotherapy or radiation being present. We wanted to just look at the unadulterated, pure effects of exercise. We recruited 53 men, all of whom were non-exercisers. These men were assigned to one of six different escalated exercise doses, ranging from 90 to even 450 minutes of exercise a week. All these sessions were one-on-one, monitored by a team of exercise physiologists. You might think 450 minutes is ridiculous, and I agree! When we designed the trial, we went up to 375 minutes, but because the compliance was so good, we increased the dose.

We wanted the tolerability of these exercise levels to be rigorously defined. For example, over 70% of individuals within a particular dosing group had to have a compliance rate above 75%

for us to deem that exercise dose feasible. We also looked at anti-tumor activity, cancer cell proliferation, and changes in PSA. The primary endpoint to this study was to identify the recommended phase two dose of exercise, or the lowest dose of exercise that is feasible and has anti tumor activity.

We found that all the doses were feasible from a compliance perspective. All were able to hit that compliance level, which is unbelievable. Admittedly, this is over a short space of time, but even so, still outstanding. When it came to antitumor activity, we found that 90 and 150 minutes of exercise–150 minutes, being the current guidelines, by the way–had no biological effect whatsoever. It wasn't until we got to 225 minutes did you start to see reductions in key 67 and PSA. When you went to 300 and 375 minutes, there was biological activity. But it was no better than 225, as higher doses of exercise were not associated with improvements or declines in these biological markers. When we got to 450 minutes, it had no biological effect; it was just like 90 and 150 minutes. Thus, we concluded, on the basis of feasibility and efficacy, that 225 minutes was our recommended phase two dose. Now we're doing a phase two, randomized control trial, where we're using that dose as identified in our phase one trial and now looking at biological activity over a much longer period.

This is the approach that we're using in many different settings, including metastatic in the adjuvant setting, to dial in on what the right dose is on the basis of whether individuals can do it at an adequate compliance and if, indeed, there is biological activity. That's the way we're developing these phase two trials where we're looking at the initial clinical efficacy of exercise, and if those work, then we'll go to the definitive phase 3 trials.

Alexander Lalov 38:07
I have metastatic, castrate sensitive prostate cancer. Currently, I'm under ADT with Lupron. My testosterone is below 10; undetectable. Despite five months of intensive weight training, there are no significant results. I'm also taking a protein supplement. Without testosterone, there is apparently not a lot that protein supplement can do. Are there any alternative therapeutic strategies that are available out there for me?

Lee Jones 39:00
The recommendation would be resistance training, but if your resistance training is having no effect, then I'd be happy to have you email me. I'd be happy to look at your exercise prescription. Maybe we can tweak that in a way that we can start to have an effect. I'd be more than happy to take a look at what you're currently doing, and I think we can make some tweaks. No guarantees, but let's give it a shot.

Brad Power 39:47
A related question from Jim Ward: how do you break down the 225 minutes of exercise per week from an ideal standpoint? It could be so many times per week, times so many minutes per day, at certain intensity levels.

Lee Jones 40:02

That prescription was five days a week for 45 minutes, in general. But as you saw from the prescription that I put up, that actual 45 minutes could range from 20 to 60 minutes. The average was 45 minutes. 20 minutes would be those so-called zone three, zone four workouts, which are a higher intensity, but for a shorter period of time. You also need to complement those higher intensity sessions with longer duration, low intensity sessions, or zone one, zone two sessions. That's where they have the recovery sessions. We have this nonlinear prescription. I know people are typically thinking, “Well, it's five days a week, 45 minutes. That's what you should do.” The five days a week is certainly true, but the duration or intensity of those sessions should be slightly different.

You can email me directly. I’m happy to provide some more guidance there on the basis of what the individual's current level of exercise is. Then we can put together these different zones to train it. That's the way all of us should be exercising. When you go out, some days, you should be going longer, but lower intensity. Other days, you should be going shorter but higher intensity. But it's not either one of those. It's both of those as part of a prescription that's important.

Brad Power 41:28
Lee, you're showing yourself to be very generous and open. Thank you for interacting directly.

Se asks: I would like to see the rest of the data. Do you have a website where you have a lot of your published research?

Lee Jones 41:47
I don't tend to do that, but I'm happy to send you the PDFs of lots of different papers that we write all the time. The general oncology paper, which was the PRESTO-1 study, should be publicly available. It’s on the general oncology website and was an NIH-funded trial. I'm also happy to send you the PDF.

Richard Anders 42:28
I'm really curious about whether you have p-values and what the level of improvement is in those cohorts. It seems like you have a good dose response and that it flattens out at 225, but I'm curious to know how significant it is. I don't mean “significant” in the clinical trial sense, but rather how significant the improvement is, and what are the p-values on that?

Lee Jones 42:58
This is a phase one trial–it wasn't designed to look at statistically significant differences in PSA or Q67, because, quite honestly, we didn't know what the effect size of exercise might be. This is typically what you see in a phase one trial: they're not powered from that perspective. But I think the differences we saw in the reductions in PSA were arguably clinically significant. At least our urologist thought that they were; they got pretty excited about it. Again, I'm happy to send you the paper. What was interesting with PSA is that we had about 15 to 20 historical controls (individuals who weren’t in the trial, but were recorded in other trials) who didn't go through our exercise regimen, and we saw in all those men that PSA increased over just a four

to six week period. Even exercise having a null effect, suppressing the increase, was beneficial, but we certainly decreased it as well. The delta was actually quite meaningful from that perspective.

Richard Anders 44:16
It's a fantastically complicated trial to think about. For starters, you can't blind this trial. The selection criteria, especially in a non-blinded trial, there's a significant bias of people who could take this trial, because a lot of patients are going to say, “I can't possibly do the exercise.” As a result, you're looking at a cohort of people who can only do the exercise and are willing to cut back or increase the exercise to some extent–then you don't have a blinding. It's a complicated trial, so I don't know if the right cohort is historical controls from a general population or historical controls from something akin to your trial. It's just really interesting and complicated.

Lee Jones 45:06
These trials are hard to do. Our enrollment rate of eligible patients was around about 40%. Compare that to typical enrollment rates in clinical trials, which is around about 7%.

Richard Anders 45:27
What were your enrollment criteria? These are patients who presumably could exercise up to 450 minutes?

Lee Jones 45:36
In theory, yes. Some non-exercisers had to be scheduled for surgery, but individuals could have had other comorbidities. We didn't exclude individuals on the basis of that. So our actual eligibility criteria was quite open. If the surgeons thought that they were eligible for surgery, then they're eligible for our study, essentially.

Richard Anders 46:03
I'm fascinated by this study because I think it's so interesting and would be wonderful to get meaningful information about it. It sounds like your drop rate for people at the higher levels is not fantastically high. I mean, I could have imagined, when you say to someone you need to do 450 minutes of exercise, you'd have a huge dropout rate in that cohort relative to, say, the 100 minute cohort. It sounds like that didn't quite happen.

Lee Jones 46:34
We had no dropouts in this for the entire 53 participants. Nobody dropped out before the end of the study. All completed it. The adherence rate, even at 450 minutes, was 81%, which is unbelievable,but it was lower than the others. I think this highlights the importance of doing this phase one trial, because we were able to find that using a lower dose was just as if not even more efficacious than 450 minutes. If we hadn’t done this trial, we wouldn’t have known that. If we can get the same efficacy, but at a lower dose, then that's what we should do as it’s more feasible. There's no way I would have picked 225 without knowing this. The participants were looking to do 300+ minutes, on the basis of observational data. But now we're finding that the

doses may not need to be that high, which is a very good thing. The lower the dose, the more people who are going to be able to do it.

Richard Anders 47:43
It's awesome. That would be a fabulous result, and it would be really meaningful to patients. It's great work. Thank you.

Lee Jones 47:55
I mentioned that we did just finish this. We just published the data for BRCA1/BRCA2: it came out two weeks ago in Clinical Cancer Research. In that study, we did three different doses: 75, 150, and 300 minutes of exercise for six months. We took biopsies of the normal breast before and after exercise. We looked at changes in key 67 and all these different biological markers. We did proteomics of the tissue as well. You might be interested in that. There, we found that 150 minutes was the sweet spot. 75 minutes did nothing. 300 minutes was inferior to 150 minutes. This is another example of where “more is not better.” It was a co-clinical trial. We did the mirror image mouse study: we prescribed three different doses of exercise in a mouse model of breast cancer, and we saw the same effect. 150 minutes was the only dose that actually extended time to breast cancer appearance.

Richard Anders 49:06
It's a little hormetic, but it would be really interesting to do an MSI study. I guess you've done BRCA. It's really interesting.

Lee Jones 49:21
Did you say hormetic, meaning hormesis? I completely agree. Hormesis is a sudden sublethal injury for physiologic adaptation. If you go beyond that, then you don't get the same adaptation. It might be plateaued. That's hormesis: a fundamental concept of physiology. Amazing. Thank you. Great comments.

Cindy Ness 49:48
Thanks for clarifying that the prescription, in terms of 150 and 225 minutes, was zone two. Is that correct?

Lee Jones 50:18
Well, all the doses, whether it was 90, 225, or 450 minutes, all had different intensities: one to four zones. All of them had the different zones as part of the prescription.

Cindy Ness 50:30
I see. Given that it wasn't necessarily zone two, could that mean that someone who exercised for 225 minutes could have been walking in a relatively relaxed fashion?

Lee Jones 50:45
In some of those sessions, yes. In the sessions for the men who were doing 450 minutes, some of those were zone one and zone two sessions.

Cindy Ness 50:54
You didn't try to break down how much of zone two or how much of zone one? It was just sessions that were over a period of a certain number of minutes?

Lee Jones 51:06
The prescription approach in every different dose level was the same. They had the same number of zone ones, same number of zone twos, and so on. It was just that the duration was slightly different to achieve the different dose goals, if you will.

Cindy Ness 51:25
You said that you saw biological results at the 225 increment. I'd love to know what some of those results were, and how it perhaps impacted tumor burden. In the study that we're doing, we're doing 150 minutes per week. We got that number from zone two training and from the American College of Sports Medicine, and other national bodies seem to suggest 150 minutes might be a sweet spot. My question is, do you think 150 minutes is actually too low? I think you were saying that it might be.

I think you were referring to RCTs before when you said there were only three trials. But, of course, there's so many observational studies that have shown a lot of efficacy. I am wondering where you value those observational studies, and why you think there might be such differences between what the observational studies are showing. Do you think that might just be “bad science,” or do you understand it?

Lee Jones 52:49
So is 150 enough? Well, it depends on the trial and the endpoint. We could talk about that.

Observational studies are incredibly valuable, but they are also the weakest form of evidence that we have. In these studies, it's retrospective as an association. There could be lots of reasons why exercise associates with an endpoint, such as cancer progression. Maybe individuals are eating or sleeping better. There are a lot of factors we can't control for in these observational studies. I think observational studies provide an initial signal that there might be something going on, but we need to go through different steps to confirm and validate that signal.

It's not as though I have an issue. I don't think we can take observational data and say, “Based on that data, there's proof that exercise does x”, because I don't think you could say “on the basis of observational data.” We've done lots of observational studies, but for us, that's just the starting point. It's not the end point. It gives us the initial signal to then start doing preclinical studies. We've got an interesting signal in some of our EPI studies suggesting that the relationship between exercise and recurrence in women with early stage breast cancer differs as a function of their clinical subtype, with women with ER positive tumors potentially being more responsive to exercise. I think there's some interesting biology. But again, just on the basis of that, we've got to go into our preclinical models and confirm that that is the case. Maybe

that will lead to a trial of exercise in women with triple negative breast cancer, as opposed to just any type of breast cancer. I'm just giving that as one example, but I think there's a lot we can learn from these observational studies. Again, observational studies are the starting point that needs to be validated through these other scientific studies.

Cindy Ness 54:50
Thank you.

Brad Power 54:56
There are three questions that are, again, in the vein of practical questions. Roger Royce, you want to give voice to your question here?

Roger Royse 55:13
I noticed in your studies that you showed us had to do with people with active disease. Is there any data on the role of exercising and preventing cancer or in preventing recurrence, and is it different?

Lee Jones 55:31
Good question. In the prevention setting, there's hundreds of observational studies that have looked at the relationship between exercise and risk of various forms of cancer. We just published a study on this last year by using a large data set. There's good observational data, and what I mean by that is that there's many studies that have looked at the relationships. Exercise appears to lower the risk of 13 different types of cancer, but also increases the risk of two cancers. One is prostate cancer and the second is melanoma. People don't talk about that very much, but that's important just in the scope of transparency. There is that data, the study I just talked about in BRCA is one of the first that's looked at the biological impact of exercise in individuals that are high risk in the actual tissue itself. There's no randomized data suggesting that exercise lowers the risk of any form of cancer. We don't have that data yet. Hopefully we're building up to that. We've got work in Lynch syndrome individuals, where we've done pilot studies–we just written and submitted the R1 where we're looking to exercise to lower the risk of colorectal cancer in individuals with Lynch syndrome. Those studies are being written and hopefully we'll get some funding to do them.

On the recurrence side, again, there's this observational data suggesting that exercise lowers the risk of recurrence in breast cancer and potentially in colorectal cancer. But that's it. We don't have any other data for any other tumor types. All the observational data has been exercised on cancer mortality, not recurrence. We just published a study on recurrence and breast cancer. We've got a large study underway right now at MSK with 35,000 individuals with pancreatic cancer. We have exercise data on them all. We've pulled all the recurrence events, and we're doing the analysis now. It's actually kind of cool. We're trying to do a target emulation trial using that data. Just to give you context, observational studies typically take exercise data that's reported at one time point, and then looks at that time point of exercise when it was reported. They might ask individuals, “how much exercise have you done over the last 30 days?”, and then follow individuals for a long period of time to look at events. The way that we measure

exercise data is cross-sectional, which, of course, has its limitations. But in our particular data set, we have repeated measures of exercise, so we have exercise behavior from these individuals reported every year. That allows us to emulate a clinical trial. Using observational data to emulate a clinical trial might sound crazy, but we're going to take the first report of their exercise behavior, and we're going to take all those individuals who report being nonexercisers–that would be our entry criteria for a clinical trial. Then a year later, we have their second report of exercises. We have individuals who remain nonexercisers–that's our control group. Then we have the individuals who now report they're exercising–that's our intervention group.

In essence we have this virtual randomization. It's not a proper randomization, but that's what we're doing. Now we're looking at the risk of recurrence between those two groups. Nobody's tried that before. People could say it's crazy and it could blow up, but we're going to give it a go, because we do think it's an improvement on just using one measure of exercise since we’re actually using repeated measures. Anyway, we're working on the analysis now; hopefully that data will be out in the next few months.

Roger Royse 59:43
People talk a lot about this issue of exercise and cancer itself, and they ignore the other aspect of this, which is recovering from the treatment. I went through seven months of chemo, and I came out of it being, like you said, much older than when I went in. The doctors told me all of this was irreversible, but that turned out to be complete bull****. I reversed these effects by exercising. My bone density went up, my blood glucose went down, my calcium score decreased, and my neuropathy went away. All of the stuff they said I'd have to live with the rest of my life wasn't true. I think exercise was the biggest thing that put me back to where I was before I started.

Lee Jones 1:00:33
Yeah, I couldn't agree more. I'm glad you had that kind of effect. We have thought about exercise from a recovery type standpoint. I don't want to diminish those effects either, because that's where I spent the first 15 years of my career: working on those kinds of studies. So if we can have that kind of impact, and possibly have a disease impact as well, that would be quite a thing.

Rick Davis 1:01:30
I always think about inflammation and how that interferes with analyzing your results, because whilst you're exercising more and it's doing you good, you're also liable to more information. How do you balance the damage from inflammation against the benefit from the exercise at high levels?

Lee Jones 1:02:08
An acute bout of exercise is pro-inflammatory. There's no doubt about it. If we all went for a run right now, it would cause chaos in our bodies. But that's the point. We talked about hormesis earlier. Part of exercise is through this hormesis effect where you need sublethal injury from things like inflammation that invoke the immune system to kick in and have a beneficial effect.

Now with exercise, acute is pro-inflammatory, but chronically, it's anti-inflammatory, right? Because what you get is the adaptation. In response to acute exercise, you get the pro-inflammatory response. It shoots up, but within half an hour, it's gone. If you look at levels of pro-inflammatory factors in exercise, those of exercise individuals are lower. But every time you exercise, you get that spike. That spike is incredibly beneficial from a cancer perspective, because that spike is now engaging the immune system to search for all those cells. We're writing a review on this right now that goes out to find all those damaged, mutated cells to either control or eradicate them.

Now what you're touching upon is at what point is the inflammation too much? The point where it's not recovered? I honestly don't know. It depends on a lot of different factors. Of course, it's complex, but maybe we're starting to see some of that in some of our initial data. We're not seeing an inverted U yet, but we're starting to see a plateau. We see that lower dosages don’t work–we get to that sweet spot, and then it starts to creep up on the other side, where these higher doses don't have the same benefit as the therapeutic index of exercise.

This is reflected in sports performance. You hear about this all the time. It's called over training. I think the risk of overtraining in individuals with cancer, particularly those going through treatment, is high, because the system is under a lot of stress. Unless you exercise properly in that context, there is a risk of pushing it in the wrong direction. This is why I think exercise prescriptions are so critical. We can't just say, “Well, do this and you'll be fine.” You really have to understand an individual's physiology and then prescribe an individualized prescription to that individual. That's the approach we're trying to take. Is there a risk in that? I think there is. I think we need to be careful.

Jim Ward 1:05:23
I'm assuming that most of this exercise centers on aerobic exercise. Do I have that right?

Lee Jones 1:05:37
Yes, you're correct.

Jim Ward 1:05:39
My question flowing from that is: are you planning at any point to examine, if not trial, the potential benefits of strength training when it comes to either prevention or slowing down cancer progression?

Lee Jones 1:05:59
Thanks for your question. The short answer to that is “no.” We have done resistance training trials, as well as the combination of aerobic and resistance training when we've been looking at outcomes such as fitness, strength, and quality of life in our studies. In particular, one of the very first randomized trials we did was strength training in men on ADT for prostate cancer because of the strength issues that were brought up earlier. To me then, it made absolute sense. We knew what the problem was–loss of muscle mass–which then tells us what the

intervention should be: resistance training. I know we often think that the combination of aerobic and resistance training is the optimal exercise prescription. I always push back on that and say, “Optimal prescription for what? What is that?” I'll give you another example: we did a study in lung cancer survivors, where we know muscle mass is a problem. We've done a trial of aerobic training where we found a little improvement in fitness, but not what we expected. What we found out is that some of these individuals were too weak to be able to exercise hard enough to get the physiologic benefit. We then did a four-arm, randomized control trial: aerobic only, resistance only, combination, versus control, under the physiological hypothesis that the combination would be more beneficial than either two. We didn't find that. We found that tolerability of resistance training in that population was problematic, and that aerobic training alone was actually better than resistance training. In fact, resistance training had no impact on fitness, and aerobic plus resistance training was equivalent to aerobic training only.

I think the efficacy of resistance training depends on the question. In terms of cancer and tumorigenesis, I think, mechanistically, resistance training does a lot, but I think many of those effects are all localized to the muscle themselves, causing muscle hypertrophy. Resistance training is great, but I think when we're looking at inflammation and the immune system, I think the data is pretty clear that aerobic training will have a superior impact on those pathways that we're trying to manipulate for anti-cancer benefit. Would resistance training also manipulate those pathways? I think it does, but to a lesser extent. Well, would the combination be better? I don't think so, but I might be wrong. Show me the data that the combination is better. So far, and even if you look at the observational data, all the observations are suggesting that it's aerobic that has the anti tumor benefit. Of the studies that have looked at resistance training, although it's hard to carve that out individually, there hasn't been the same association with cancer outcomes. I think there’s evidence that suggests that the combination is not the way to go. But I always start with, “what is the end point you are manipulating?” and then “what is the prescription?”

I think in exercise, when we start a prescription, we often say, “Okay, it's a hammer. Now, where's the nail?” I think we need to think about it in the opposite direction.

Brad Power 1:09:34
Lee, do you have any final words of wisdom or summary comments?

Lee Jones 1:09:42
I really appreciate the opportunity to have these kinds of dialogs. They are extremely important. There's so much work that I could have talked about that I think you would have found interesting. Maybe I can come back and talk about some of that, but please feel free to reach out to me individually at Lee.Jonesphd@gmail.com. You can also find me online, and I'm happy to get on another call, and send you any papers that we've published.

“Exercise and Cancer Development and Progression" (Lee Jones, PhD) [#143]

CHAT CONVERSATION

00:28:36 Robb Owen: How does diet/nutrition/gut microbiome function correlate to physical activity aging data?
00:29:46 Alane Watkins: Question: Have you looked at Exercising with O2 (EWOT) or exercising with hypoxic intervals in cancer patients?
00:30:42 Alane Watkins: Ty
00:31:06 Roger Royse: do you have slides?
00:32:48 Se: can we get to the slides? could some of these questions already be answered in the presentation?
00:32:59 Roger Royse: Reacted to "can we get to the sl..." with 👍
00:36:28 Alexander Lalov, Indiana, USA: I have metastatic CSPC, currently receiving continuous ADT with Lupron,
resulting in testosterone <10 ng/dL.
Despite five months of intensive weight training and protein supplementation, there has been no significant improvement.

Given the limited efficacy of protein supplementation in the absence of testosterone, what alternative therapeutic strategies are available?
00:36:49 David Plunkett: Reacted to "I have metastatic CS..." with 👍
00:39:19 Cindy Ness: Just a note - I believe you’re talking about only 3 RCT trials not observational intervention studies which there are many that have suggested improved outcomes. Do you think this latter success mitigates the RCT failures?
00:49:37 Rick Davis: Very cool trial!!!!
00:50:00 jamesward: Reacted to "Very cool trial!!!!" with 👍
00:53:35 jamesward: How did the 225 mins of exercise per week break down from an ideal standpoint — i.e., X times per week for Y mins at Z intensity level?
00:53:44 Se: I would like to see the rest of the data
00:59:22 Roger Royse: do you have data on exercise and cancer prevention or recurrence (as opposed to exercise when someone has active disease)?
01:00:07 Rick Davis: Doeinflammation issues at higher exercise levels complicate results?
01:00:51 Rick Davis: Do inflammation issues at higher exercise levels complicate results?
01:01:50 jamesward: Do you plan to evaluate or trial the impact of strength training on Ca, if you haven’t already examined that (and assuming that Presto-1 centered on aerobic/cardio exercise?
01:04:33 Dr. Chris Apfel: Lee, given that fitness as a surrogate for aging is confounded by exercise, you might consider adding established methylation-based tests that would give you a more objective measure of aging AND cancer recurrence or progression.
01:20:16 Richard Anders: Rather than a rule of minutes it might be better to have an exercise biomarker-based rule
01:22:26 Roger Royse: Replying to "Rather than a rule o..."

METS

“Exercise and Cancer Development and Progression" (Lee Jones, PhD) [#143]

01:23:07 Richard Anders: Replying to "Rather than a rule o..."

What’s METS
01:23:59 Roger Royse: Replying to "Rather than a rule o..."

a measure of exercise that is better than just time - https://www.healthline.com/health/what-are-mets#:~:text=METs%20are%20%EE%80%80metabolic%20equivalents%EE%80%81%20that%20show
01:24:06 Richard Anders: Replying to "Rather than a rule o..."

Thank you.
01:24:34 Dr. Chris Apfel: Lee, will have to log off now, but you might want to consider measuring age-related methylation for future analyses. https://www.cancertherapyadvisor.com/features/head-neck-cancer-epigenetic-clock-biological-aging-treatment-risk/
01:24:47 Richard Anders: Replying to "Rather than a rule o..."

Might actually not just be METS but also more tailored for given patients