

# Yale CANCER CENTER *answers*

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## **Exercise Interventions for Women with Cancer**

### **Guest Expert:**

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**Yale Cancer Center Answers** is  
a weekly broadcast on **WNPR**  
Connecticut Public Radio  
Sunday evenings at 6:00 PM.

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*Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to [canceranswers@yale.edu](mailto:canceranswers@yale.edu) or you can leave a voicemail message at 888-234-4YCC. This week you will hear about cancer epidemiology and exercise interventions for women with cancer with Dr. Melinda Irwin. Dr. Irwin is Associate Professor of Epidemiology and Chronic Diseases at Yale School of Medicine. Here is Dr. Steven Gore.*

- Gore Before we get into the meat of the matter which I am really fascinated to hear about, can you tell our listeners what epidemiology is?
- Irwin Epidemiology, a shortened term would be epidemics or diseases.
- Gore Like Ebola?
- Irwin Sort of, that would be infectious diseases. I study chronic diseases, in particular, cancer epidemiology. So epidemiology is looking at the determinants of a disease or the risk factors of disease. What causes disease. In this case, what causes cancer and distribution, how does it spread? And this is over populations over time, and looking at how cancer instances may have increased over time or how it might vary in this country versus another country.
- Gore It does not have to be an infectious or contagious kind of thing to be included in epidemiology then?
- Irwin No, not at all. It can be chronic diseases or diseases like heart disease or cancer or diabetes and looking at what the causes are of these and epidemiology is a public health focus looking at populations of people rather than more basic science or molecular science looking at the cellular level. We do do some animal epidemiology research, but mostly it is in humans and in populations we look at.
- Gore How do you study stuff like that?
- Irwin Epidemiology can be large prospective cohort studies, observational studies where you enroll hundreds and thousands of men and women at a certain age, maybe in their 20s or 30s and you follow them for forty or so years until many develop a certain cancer or another chronic disease, and every 2 years they might complete questionnaires or have blood tests done or other exams or x-rays and what not, and you can then, in measuring these variables before a diagnosis, look back, say someone develops breast cancer, and see what factors were associated with lowering the risk of developing the cancer versus other factors that might increase it. So that's one way of doing epidemiology.

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Gore If you started that study when you were 30, you are 70 before it is done right?

Irwin Exactly.

Gore That sounds like you have to be into delayed gratification as a scientist.

Irwin Yeah, and some studies, for example with my research, I will do randomized controlled trials, so we will do studies in say women with breast cancer, and we will randomize them to complete an intervention versus control or placebo and you look at various endpoints that you measure at baseline and at the end of the intervention, and you can see how the intervention affected that outcome or that endpoint that you measured. So usually epidemiology has observational prospective studies or clinical trials.

Gore Hmm.

Irwin And in some of the observational studies, you might study a higher risk group such as those who have developed cancer or heart disease and you can follow them for just five years until you want to look at an end point such as recurrence and what causes that.

Gore Can you talk to me about some of your interventional trials, what kinds of things have you been interested in?

Irwin My area of research focuses on lifestyle behaviors, so what individuals can do after completing treatment, let's say, or even some of my studies are during treatment, that may lower the risk of recurrence or mortality. Specifically, I look at exercise and weight loss and how it impacts prognosis as well as quality of life. I have done studies in women with breast cancer as well as ovarian cancer and also some recent studies looking at other cancers, such as colon and prostate. For example, a study that we have just completed is for women breast cancer survivors who are taking aromatase inhibitors that we know improve their prognosis, but these medications have side effects such as joint pain or arthralgia and these side effects are common, in about 50% of women and make them want to stop taking the medication, so their adherence to the medication is not that good. So we look at how exercise or other lifestyle behaviors in conjunction with taking the medication may improve not only the side effects of the medication but also their compliance to taking the medication which in turn improves recurrence risk. Another study that we have currently enrolling for women with breast cancer, is a weight loss trial and how weight loss may improve biomarkers for breast cancer prognosis such as insulin levels or inflammatory markers such as CRP, so if we show that weight loss lowers these biomarkers, that helps us to better understand how weight loss improves prognosis and what the mechanisms are of how it influences improving their outcomes.

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Gore Could you walk me through that a little bit more. You are going to take women and they are going to lose weight hopefully; tell me about these biomarkers of that CRP, isn't that an inflammatory marker?

Irwin It is, and one study that we have now is called the LEAN study, lifestyle, exercise and nutrition study.

Gore Good name.

Irwin Yeah and we have completed the first phase on 100 women, so these are overweight breast cancer survivors who completed their treatment, so they are roughly about two to three years post-diagnosis but they could be anywhere from six months post-diagnosis, and at baseline, they are all overweight and they are interested in a weight loss program. So at baseline, we collect a blood draw, we actually also do a biopsy of their healthy breast to collect some breast tissue, it is mostly fatty tissue, and then they are randomized to either a six-month weight loss program with 11 counseling sessions with our registered dietitian, Maura Harrigan, and then at the end of the six months, they have another blood draw as well as a biopsy and also a DEXA bone scan to look at body fat, bone mass and complete some questionnaires and then the control group is actually a wait list group, so at the end of the six months, then they are offered the full intervention. So we are then able to look at the weight loss between the two groups, and those enrolled in the intervention lose about 10% body weight with this intervention over six months and the control group actually maintains or even might slightly lose some body weight just because of being involved in the study and learning a little bit.

Gore They are allowed to diet if they want to?

Irwin If they want to, but we know that on their own people have difficulty maintaining a behavior change program and that is where the counseling is important. What we have been able to show is that looking at blood markers, such as CRP, which we know is related to breast cancer as well as some other cancers, we observed a 30% decrease in serum CRP levels with about 5% body weight loss, so this has implications not only for breast cancer but some other chronic diseases where inflammation is an adverse risk factor. We also found insulin levels to be decreased significantly with 5% body weight, and we know insulin is a strong risk factor for breast cancer so much so now that it is being tested as a target lowering it with metformin which is a medication originally developed for diabetes but now being examined for breast cancer by lowering insulin levels and therefore improving prognosis. So another way of lowering insulin is perhaps with weight loss and exercise.

Gore Hmm.

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Irwin So some of these studies have finished and we have results published on that and others we are still recruiting and enrolling participants for.

Gore That is really interesting, so you watch their CRP go down. They are done with their 11 sessions, you send them off on their way, and you hope they are going to continue to maintain their weight?

Irwin Very good question. In all of behavioral medicine, not just specific to cancer, but in healthy individuals and diabetics, heart disease, you name it, the maintenance of any behavior change is a very difficult factor, so what is really important is that we have access to programs in the community or even in the clinics with a hospital, so that when they are done with research studies, they can go to those, or even if they are not eligible or they do not want to do a research study, these programs are available, so at Yale, we have the Survivorship Clinic which is a great program offered where any survivor, one day post diagnosis or 10 plus years can come and they can meet with the dietitian; they can meet with the physical therapist or social worker and talk about some of the behaviors that they would like to change as well as some other factors related to work or family or what not and also another great program in the community that exists is the Livestrong Foundation that has partnered with the YMCA across the country to offer free three-month long exercise programs to any men or women diagnosed with cancer, also any time post diagnosis. So, these programs exist at certain Ys across the country and they are free to the individual and it is a really great start giving them those three months with a supervised trainer, it is a small group setting, giving them the skills and knowledge of how to exercise at the appropriate intensity, and then at the end of the three months, they even continue these sessions; they are kind of graduate programs and a lot of them also have reduced memberships after the free three month program.

Gore That's great.

Irwin So finding and creating more opportunities in the community will create access and hopefully increase changes in these behaviors and maintenance of them, but as we know, even if you have access to these services, it is still very difficult to change behaviors, so lot of our research is still examining what is the minimal amount of exercise that needs to be done, what is the minimal amount of weight that needs to be lost to see favorable changes. There is a whole body of research right now looking at sedentary behavior, how to decrease sedentary time, and if that can influence various outcomes; because we know people are becoming a lot more sedentary now compared to years prior because of technology. We are spending a lot more time on computers, on handheld devices, so we are not walking as much at work or even outside of work. Our foods are a lot more processed now so that we can cook them quicker and then sit down and go on Facebook or Twitter or something. So on a population level, our behavior, and our physical activity levels have decreased significantly which has led to some weight gain overtime. Looking at how just changing sedentary time may improve outcomes is an area of research. In fact, in the Yale School Public Health, a lot of the faculty members are now changing their desks to standing desks and also treadmill desks.

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Gore I was going to ask you about that, but before we get that far, I am still fascinated about this weight loss thing. How are you going to connect the loop that they lost the weight, they got their markers down, they were really successful in maintenance, God bless them, how are you going to know whether or not you really impacted their likelihood of having a cancer recurrence?

Irwin Great question, and in fact, the first question I had on my agenda here when I started at Yale over 12 years ago, and I actually submitted a grant to the National Cancer Institute to look at exercise on recurrence and mortality of breast cancer, but it is just a very expensive trial to get funded. It is millions of dollars because you have to enroll large sample sizes of women with stage II-III breast cancer. They have to be willing to be in the intervention or in the study for five years and so it is very expensive, but not any more expensive than drug trials that are currently in progress.

Gore Sure.

Irwin That was actually scored in the fundable range but there was not the budget available to fund it, so we went back to the drawing board and we submitted a weight loss trial on recurrence, mortality endpoints, that was also not funded, but now it is being revisited because it is a very major interest of the National Cancer Institute to look at some of these lifestyle factors on the direct endpoints of recurrence and mortality, so there is some movement now to fund it through the cooperative trials to look at a large scale weight loss trial on recurrence and mortality that I will be involved with as well, so hopefully that will get started next year and so we will have those definitive results of how much weight loss is necessary to lower risk of recurrence and mortality that will convince clinicians and third party payers to hopefully fund more programs related to lifestyle behaviors.

Gore That is great work and I want to pick up on that after the break. Right now we are going to take a break for a medical minute. Please stay tuned to learn more information about exercise and weight loss interventions for women, and I suppose for men with cancer as well, with Dr. Melinda Irwin.

*Medical  
Minute*

*The American Cancer Society estimates that more than 60,000 Americans will be diagnosed with head and neck cancer in 2014. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancer and their treatment. Clinical trials are currently underway at federally designated comprehensive cancer centers, such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments and in many cases, less radical surgeries are able to preserve nerves, arteries and muscles in the neck enabling patient's to move, speak, breath and eat normally after surgery. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at [yalecancercenter.org](http://yalecancercenter.org). You are listening to the WNPR, Connecticut's public media source for news and ideas.*

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Gore Welcome back to Yale Cancer Center Snswers. This is Dr. Steven Gore and I am joined today by my guest, Melinda Irwin, and we have been discussing exercise and weight loss interventions for women with cancer. Melinda, before the break you were telling me about some of your really fascinating but a little bit frustrating to get funded plans for what sounds like to me very important studies of trying to directly measure the connection between weight loss or exercise and/or exercise and cancer recurrence, but it sounds like you have had some frustrations in getting the funding for that?

Irwin It is interesting because whenever I give talks around the country or the world on this topic, clinicians and survivors will say, well how does it impact recurrence and mortality?

Gore That is what people want to know, right.

Irwin That is what they want to know.

Gore Not about their CRP in their blood.

Irwin Right, well that helps a little bit, but it is really the burning question.

Gore No offense.

Irwin With drug trials, you need to show its affect on progression free survival, how much it lowers risk of recurrence and mortality to get that drug approved.

Gore Sure.

Irwin And we are not there yet with exercise or weight loss because these trials have not been funded because they are very expensive, but probably not nearly as expensive as some of the drug trials. Most of the drug trials are usually funded by pharmaceutical companies who have an interest in that medication, and so they are willing to fund those expensive trials, but because exercise and weight loss does not really involve a medication per se, they are not as interested in funding such trials, so it is really left to the government or organizations.

Gore Foundations.

Irwin But the budget usually does not fit in the model of foundations. Foundations are great to fund ancillary studies and studies that look at surrogate biomarkers or intermediate markers which is a lot of what my research has looked at, so in the absence of the data, the results on recurrence and mortality endpoints, we look at how weight loss and exercise influence these intermediate markers or these surrogate markers of recurrence. For example, we have known for many years that estrogen is strongly related to breast cancer, so if you can lower estrogen levels, you are likely lowering your risk of developing or dying of breast cancer, so much so that we now have three

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FDA approved aromatase inhibitor medications for postmenopausal women with breast cancer and this has become standard of care for women with breast cancer, when they finish chemotherapy and radiation, if they have an estrogen receptor positive tumor, they are recommended to take one of these aromatase inhibitors or tamoxifen if they are premenopausal, and so another question is what else can we do to lower estrogen levels? Some research I have done in healthy postmenopausal women looked at how exercise could lower estrogen levels and these were women not taking a hormone replacement therapy. I mean, obviously, they were not taking an aromatase inhibitor or tamoxifen, and we showed that a year-long exercise program in women who were inactive before enrolled in the trial, decreased estrogen levels from 8-15% depending on if they lost body weight or not, so if they had no significant change in body weight, they had about an 8% decrease in estrone levels which are common estrogens in women with breast cancer, and if they had a 2% or more body weight or body fat loss, they had even greater decreases in estrogen, so not as much of a decrease as an aromatase inhibitor might have on estrogens but a decrease nonetheless and something that gives women and clinicians more information about the role of lifestyle factors in influencing development of a cancer or recurrence of that cancer.

Gore Do you think that 8-15% reduction could be clinically meaningful in terms of reducing risk?

Irwin I do think so. If we look at switching to metformin which has been prescribed for insulin and diabetes and is being looked at right now in breast cancer,

Gore This is a diabetes drug?

Irwin It is a diabetic drug that is being examined right now in a large phase 2 trial of women with breast cancer. Pam Goodwin out in Toronto is actually doing this study with results coming out in about a year or two, and if they find that metformin is favorable in lowering recurrence and mortality in breast cancer, it might become a standard of care in non-diabetic women with breast cancer.

Gore So these are people who have had breast cancer and have been treated with surgery or radiation or chemo?

Irwin Correct.

Gore And then they go on this diabetes drug?

Irwin Yes, because metformin was developed for diabetes, but the way it works is by lowering insulin levels, and we know insulin is a strong risk factor for developing or dying of breast cancer, so women at the time of diagnosis, if they have high insulin levels, say in the top quartile versus the bottom quartile.

Gore You sound like an epidemiologist.

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- Irwin They have a two to three fold higher risk of recurrence or mortality compared to women with lower insulin levels. So how to target insulin, or to lower insulin levels, has been an area of interest by epidemiologists and clinicians, but interestingly, metformin might lower insulin levels by about 20-25% and that may influence recurrence and mortality. We know from our studies of exercise and weight loss that the lowering of insulin by about 20-25% occurs with about a 5% weight loss or by doing two to three hours per week of aerobic exercise. So once again you see that some medications lower these surrogate markers, these biomarkers to a similar extent of some of these lifestyle behaviors, so it is just giving survivors, patients and clinicians more information because some might not want to take metformin after finishing chemotherapy or radiation, or some, unfortunately, may not even want to take an aromatase inhibitor even though the evidence is quite strong as to its benefit. So giving them another option with weight loss or exercise that not only influences recurrence and mortality but also benefits cardiovascular disease risk and other outcomes and quality of life, is important to consider.
- Gore Well it is also cheaper than taking medicine, you have to remember to take your medicine and you feel better when you are exercising, I think most of us really recognize that.
- Irwin So the problem is that over 60% of the population, these are healthy individuals as well as those with cancer, do not exercise and are overweight or obese and so how do we really affect change on a population level. We live in an environment that does not make it very easy to eat healthy and exercise, so I think we have to look at this on a large scale level, how to make the environment a little bit easier to practice these behaviors and then create more access, have insurance reimburse these programs more, just so that it is easy to actually do. You go to Amsterdam and everyone is biking. It is the way people travel there. I just got back from Vancouver, Canada and they have bike paths all over the city. It is so easy to get on a bicycle and bike all over the city. That is not as possible here in some of our cities or suburbs in the US.
- Gore Yeah, in terms of this metformin issue that you brought up, if you are lowering insulin, is there any risk you are going to induce diabetes in patients who have normal insulin levels or does it not work like that?
- Irwin It does not work like that, but it is a good question, that is why you do randomized trials. Interestingly, also the impetus for this interest of metformin, is 10 years ago a landmark study published in the New England Journal of Medicine was the diabetes prevention program. It was a three-arm trial of men and women who were healthy, they were impaired glucose tolerant. They had high glucose levels but they were not diabetic, and they were randomized to either taking metformin or a lifestyle intervention of exercise and weight loss or a control group and the study was stopped early after three years because the lifestyle intervention was so much more effective in preventing diabetes than the medication metformin.

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- Gore How interesting.
- Irwin And it lowered the risk of diabetes by about 57% versus the drug lowering it by about 30%. So in the last 10 years, this has been a huge area of interest, but yes randomized trials are important to look at toxicity, side effects, adverse events for both groups, the lifestyle intervention group as well as the medication group on a number of endpoints.
- Gore I will just share a little personal experience. I had the opportunity when I was living in Maryland to participate in what became a very seminal study of weight loss which randomized between just do it on your own, they were going to give you some information, and two different kind of monitored things, one was kind of a Weight Watchers like program and one was something that was mostly online with a coach online, and I was super excited about it. My internist had gotten me all revved up about it, but I was randomized to the control group and I was so angry that I said, I am going to show them, I am going to mess up their study, I am going to be the best weight loss guy and I was hugely successful in losing weight, way more than they were targeting, like 5% or 10%.
- Irwin But that shows the benefit of participating in randomized trials, even if you are randomized to the control group, you get benefit.
- Gore I still got benefit but here is the sad story, because I did not get the maintenance part, I gained it back.
- Irwin Usually what we do, in our interventions, we do a wait list group, so if the intervention is six months long or a yearlong and they get the control group, they get the full on intervention when the study ends, so all they have to do is be willing to wait, but that is.
- Gore Fantastic, I wish I had gotten that one.
- Irwin But I think there is a lot to be said of participating in trials because there is a benefit for all those even if randomized to control.
- Gore I was so excited just to be part of this thing and I think it was eventually published in the New England Journal of Medicine, so I am proud that I was a part of that but I also felt very engaged and I was coming in every six months for measurements and things like that. So I definitely encourage people to consider being in this kind of clinical trial. I found it really kind of fun.
- Irwin We recently just received a new grant from the Connecticut Breast Health Initiative to actually disseminate our LEAN study, this weight loss study on breast cancer survivors, and so what we are going to do is we developed this book that has these weekly chapters that guide the counseling sessions and this was a very effective trial, but we want to have this book be available to breast cancer survivors to be available in cancer hospitals and clinics and what not, but we want

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to test the effectiveness of the book alone without the counseling sessions. And so we are actually doing that now. We are going to enroll 100 women with breast cancer and give them the book and see how much weight they can lose on their own with the book without the counseling sessions versus a delayed group who does not get the book until the end of the study, and we hypothesize, we will see less weight loss without the counseling sessions, but it might be enough weight loss for prevention of weight gain because that is what actually is common after diagnosis, there is some weight gain, and as we age, we gain weight, so if we can prevent that weight gain or even lead to a little bit of weight loss that is something that we can give patients at their diagnosis or when they have completed treatment. So hopefully this book will add to the literature and be evidence based and something that the control groups can get from now on.

Gore That sounds great. And with the accountability thing and groups, which I think is one of the reasons that Weight Watchers is often so successful for people, being part of a team, all those things I see as positives, but obviously, not everybody likes to run that way and not everybody has access, or time.

Irwin I agree and that is the interesting thing about studying behaviors, is it the group dynamic, is it the one-on-one dynamic? How do you create an intervention that works for every patient that you are enrolling, when you have to have the efficacy and the tight control over the intervention that you are delivering, so to me it is a fascinating field, cancer epidemiology and behavior research, because at the end of the day, it is about the quality of life and these behaviors really can affect that and hopefully we can also show that they affect recurrence and mortality as well.

Gore And maybe it is not one side, so it is all based on people's work patterns and personality patterns, and you cannot really control for that in one trial. You have to kind of just stick to one intervention.

Irwin And that is why in epidemiology, you enroll thousands of people so that you can then either statistically control for that or stratify by different things like dose response effects to an intervention or by age, gender or race, ethnicity and look at how effective the intervention was in certain subgroups.

Gore Interesting. Before the break you had mentioned that many of your colleagues have taken to some of these standing desks and treadmill desks, in the last minute or so, do you think these are good ideas?

Irwin I do, at rest, when we are sitting right now we are probably burning about a calorie a minute, and if you stand up, you are burning about two calories a minute, so if you stand for an hour, you will burn about 120 calories versus 60 calories if you sit for an hour, so that is 60 calories which does

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not seem like much, but if you do that for maybe two or three hours of your work day, every day of the week, that is about 3500 calories, a pound of body fat, and you can see how creating this small behavior change over time might prevent weight gain or might even lead to some slight weight loss.

*Dr. Melinda Irwin is Associate Professor of Epidemiology and Chronic Diseases at Yale School of Medicine. We invite you to share your questions and comments, you can send them to [canceranswers@yale.edu](mailto:canceranswers@yale.edu) or you can leave a voicemail message at 888-234-4YCC. As an additional resource, archived programs are available in both audio and written format at [yalecancercenter.org](http://yalecancercenter.org). I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.*