

Dr. Melinda Irwin, The Impact of Exercise on Cancer Survivorship August 1, 2010 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Francine is joined by Dr. Melinda Irwin an Associate Professor of Epidemiology and Public Health at Yale School of Medicine for a conversation about exercise and cancer.

Foss Let's start out by talking about this relationship between exercise and cancer, can you explain it? Irwin For a number of years now, probably about 15 years, we have known that exercise is related to reducing the risk of getting cancer, primarily breast and colon cancer, but some other cancers as well. More recently, in the past five years or so, research has been published looking at how exercise can improve prognosis or survival. The mechanisms of how exercise decreases risk or improves prognosis is either indirectly through weight maintenance or weight control, because the more active you are if you exercise, you can maintain your body weight, but also directly, so even if there is no weight loss, just by maintaining your weight, there are hormonal changes that occur with exercise such as sex hormones or estrogens where exercising at a moderate to vigorous intensity will decrease the amount of serum estrogens. Other hormones are insulin, and insulin-like growth factors where exercise can decrease these levels. And these hormones, the insulin and insulin-like growth factors and estrogens or sex hormones, are known to increase cell proliferation or cell growth, so if exercise can decrease these hormones, then it may decrease cell growth or delay initiation of a cancer.

Foss A really important question here at the beginning of the show is, what is exercise? It sounds obvious, but I think it has different meanings for different people.

Irwin It is a good question because some people may think of exercise as having to train for a marathon and something that has to be very vigorous intensity. That's not the case, in fact, most of my studies that I conduct are brisk walking, so it is a sustained activity for at least 10 minutes where you get your heart rate up to a level that's of a moderate intensity and your breathing is a little bit irregular. It is something that we consider that you do for sustained amounts of time, ideally a 30 minute bout at a moderate intensity, and generally this is a more recreational activity such as walking or bicycling, or tennis or swimming. Some women and men might consider gardening or household activities exercise, but to me that is really physical activity, so just by being more active you are going to maintain your weight, but you may not see many hormonal changes, so in order to have the more direct mechanism associated with cancer, it should be something that's 30 minutes more aerobic type of activity such as the brisk walking, jogging, or going to a gym and doing activities there such as stair climb or stationary bicycle. And other sports as well like volleyball, golf, if you walk rather than riding in a cart, skiing, and perhaps some types of dancing.

3:33 into mp3 file <http://yalecancercenter.org/podcast/aug0110-cancer-answers-irwin.mp3> Foss So it's basically 30 minutes at a time, and how

many days a week? Irwin Generally 30 minutes probably five times a week, so about 150 minutes per week is the current recommendation of physical activity that's necessary for decreasing your risk of certain cancer and perhaps improving survival or decreasing recurrence. About 150 minutes per week of something such as brisk walking or stationary bicycling or another type of activity. Also it is recommended that adults do two times a week of resistance training program, some sort of strengthening program because as we age we tend to lose bone mass and lean body mass or muscle and that is what keeps our resting metabolic rate high and so as we age and we lose bone and muscle, our resting metabolic rate decreases. Even if we eat the same amount of foods, we might start to gain weight because our metabolic rate is lower. So adding in a resistance training program is recommended as well. It is a little bit more difficult to add in because you have to do it at the gym. Foss Melinda, it sounds like this is not the kind of program that the average person has right now in their repertoire, so it sounds like people actually have to dedicate time to do this. Irwin Yeah. Actually, the current recommendation that just came out last year from the Department of Health and Human Services, is to decrease sedentary time, so everyone can do that. If you are at home, you are sitting and watching TV or you are on the computer too long, every hour get up and walk around, so decreasing sedentary time, and then an aerobic activity such as the walking. Everyone can walk out the door and go for a walk or drive to a lovely beach or something like that. So it is the resistance training that's more difficult to add into a routine. Foss Great. I think what you are telling people now is really important, which is that you can show a direct link between exercise and these hormones that we know are important not only for cancer, but for other things as well. Irwin Exactly, so some of these hormones are not only related to certain cancers, but cardiovascular disease and diabetes. That's what the great thing about exercise is, it is multifactorial and it actually improves many chronic diseases and with little or no side effects associated with it. Foss How long have we understood this interaction between exercise and cancer? Irwin About 15 years ago in 1994 was the first publication by Leslie Bernstein published in the Journal of the National Cancer Institute looking at how physical activity decrease the risk of developing breast cancer. It was an observational study, which is how a lot of these studies are done. I do epidemiologic research, and we look at thousands of patients or healthy people. In this case, this study interviewed about a thousand women with breast cancer and compared them to healthy women without breast cancer who are matched on certain factors such as age and other6:24 into mp3 file <http://yalecancercenter.org/podcast/aug0110-cancer-answers-irwin.mp3> demographic characteristics and they asked them about their physical activity levels in their 20s, 30s, 40s, 50s, throughout their lifetime and they showed that the women who developed breast cancer, unfortunately, had lower physical activity levels at different points in their lifetime, and the women who did not develop breast cancer had higher levels of activity. When we would statistically adjust for certain factors like disease, stage, and treatment received, this association still held up. Since then, in the last 15 years, there have been 100 plus papers looking at this observational association of higher physical activity

levels and lower risk of breast cancer and colon cancer. It has only been five years since we looked at the association between physical activity and prognosis or decreasing recurrence risk or increasing survival. The first publication came out in 2005, out of the Nurses' Health Study at Harvard and this publication followed women who had been recording their physical activity levels every two years via a questionnaire and these women had breast cancer. In about two years after breast cancer, they looked at their physical activity levels and then followed these women forward and many developed a recurrence or unfortunately died from breast cancer, and those who were once again more active, were less likely to have a recurrence or die from breast cancer. A hundred plus studies were done looking at risk and looking at prognosis, but they are all observational. There really has never been any kind of direct trial or definitive trial looking at increasing exercise on improving survival or decreasing risk. And part of the reason is because those studies require a lot of participants in the study and we have to follow them for many years. In place of that, there have been trials looking at surrogate markers or how randomizing individuals to exercise or to control would change markers that are strongly related to risk of cancer or recurrence of cancer such as these hormones and that is the basis of my research, how exercise can improve these surrogate markers or these biological markers related to cancer.

Foss When we look at these big studies like the Nurses' Study and the Framingham Heart Study those are basically long term longitudinal studies looking at a number of different factors and trying to integrate those to an outcome. So with respect to exercise, say in that kind of a study, how good is that data given that a lot of it is retrospective over time.

Irwin The nice thing is that if you find an association, and usually we find about a 30% to 40% reduced risk of say developing cancer or decreased risk of recurrence among those who are active about doing this two and a half hours per week, versus those not doing activity, if you had a methodologically stronger study, you would probably find an even stronger association. So observing these associations, given the fact that it is women and men just completing questionnaires about their lifestyle, there can be some misclassification or bias on how they report their activity. We know there is a social desirability bias and people may over report how much exercise they are actually doing. In turn, if we are recommending 150 minutes per week or two and a half hours per week of exercise and we know people tend to over report, it may be that we need to do two hours or only an hour and a half per week of exercise to improve our risk or decrease our risk of recurrence.

Foss That leads me to a good question which is, how did you come up with that number?

Irwin The number of two and a half hours a week of physical activity was first based on cardiovascular disease and then last year there was a panel convened to look specifically at cancer. So it's really looking at the data in detail by cancer type and by type of exercise, and the strength of the study. If it was a study that did not have a large enough sample size, it was not included in the analysis and then looking at the questionnaire used to measure physical activity. So the strength of the studies that were included in this kind

of consensus statement show that it was about 150 minutes per week and it showed that those who did more than that amount of physical activity did not have a stronger benefit than those who did not. In fact, the risks improve with any amount of physical activity and then it kind of leveled off around that 150 minutes per week. Something really is better than nothing if you only have time for say 30 minutes a week that is better than doing nothing.

Foss Great, that's an important message. Can you talk about other cancers? We have talked a lot about breast cancer because that's primarily what the major studies were in, but what about prostate and lung, and some of those other common cancers out there?

Irwin The reason the majority of research has been done in breast and colon cancer is because those are common cancers, and so it's easier to recruit men and women into those studies and have them complete information. But there is emerging data, every month there are more publications looking at the role of physical activity with prostate cancer, with ovarian cancer, endometrial cancer, non-Hodgkin's lymphoma, and leukemia so there are a growing number of studies. They are not all consistent, they may show only 20% improvement and another may show 40% improvement or another study may show it trending in the right direction but it is a non-statistically significant finding. Basically we need more studies done in this field to really be able to come to more conclusive findings. But it is pointing in the right direction and the mechanisms are similar as with the other cancers. Prostate cancer is similar to breast cancer in that testosterone for men is similar to estrogen with women and how it could increase risk of prostate cancer.

Foss Do we know yet how important the age is that you start exercising, say if you started it in your 50s is that just as good as if you started it in your 30s?

Irwin I will tell you about a paper that I have under review from the Women's Health Initiative, which is a large study of 100,000 plus women around the country and the nice thing about this study is it recruited post menopausal women, healthy women, and they completed questionnaires every two years.

12:55 into mp3 file <http://yalecancercenter.org/podcast/aug0110-cancer-answers-irwin.mp3> years, it was an observational study, and there were some clinical trials looking at dietary components. We had questionnaires from all these women and then about 5000 women developed breast cancer and they continued to complete the questionnaire. We were able to look at the physical activity levels before diagnosis and after diagnosis. Looking at before diagnosis, we observed a decrease risk for breast cancer, but then also when we looked at recurrence and death, we showed their physical activity before and after diagnosis improved their prognosis. So those who may have been inactive before diagnosis, but initiated an exercise program after diagnosis, had a reduced risk for recurrence. Even if you are postmenopausal when you are diagnosed and you haven't participated in exercise, if you initiate after your diagnosis, you can have an improved prognosis.

Foss That is a really important message to get across to women. I would like to talk a little bit more about that when we come back. Stay tuned to learn more about exercise and cancer with our guest, Melinda Irwin.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and my guest Melinda Irwin joins me today to discuss the issue of exercise and cancer. Melinda, in the first part

of the show we talked a lot about observational studies linking exercise with decreased risk of cancer and I am wondering, could you talk a little bit about some of the work that you are doing because I understand that you are actually looking at this issue in more detail. Irwin While the observational research is really encouraging in showing the benefit of exercise, unfortunately it may not be enough to convince some clinicians out there or oncologists of the benefit, and it probably is not enough to convince the insurance companies to reimburse exercise into mp3 file <http://yalecancercenter.org/podcast/aug0110-cancer-answers-irwin.mp3> programs for cancer survivors or those who are at risk of developing cancer. My research is really focused on doing randomized control trials to look at how increasing exercise may actually improve prognosis, decrease recurrence, and improve survival among women with cancer. Specifically, my research is looking at breast cancer and ovarian cancer. I'll quickly talk about that trial in breast cancer, which was initiated last year and it was a result from some of my studies done previously looking at if exercise is feasible among women with breast cancer during treatment and post treatment, and it is associated with improvements in some of these biological markers. I was interested in looking at how exercise can improve some of the side effects of treatment. Women with estrogen receptor positive breast cancer, their tumors that are estrogen receptor positive, they are given hormone therapy, aromatase inhibitors, to block their estrogen activity and this is the standard of care for most women with breast cancer. Unfortunately, some of these women are discontinuing their treatment because of the side effects of the hormone therapy such as joint pain, bone loss, hot flashes, and we know that exercise improves rheumatoid arthritis or osteoarthritis and so given the joint pain or the arthralgias, one of the most common side effects and it is associated with discontinuation of treatment, we are looking to see if exercise can improve arthralgias, and if it can improve bone mass, as well as looking at the mechanisms such as inflammation. So CRP, or C-reactive protein, is a marker of chronic inflammation, and if exercise can improve CRP, improve joint pain, and arthralgias, it may in turn improve adherence to taking the aromatase inhibitor and then indirectly improve survival. That is one trial we have ongoing and we are recruiting for two years for that and if we show that it improves adherence to the treatment as well as decreasing side effects, maybe insurance companies will think about offering reimbursement for certain exercise programs that are either offered through the hospital or the community. The second study that I have is looking at women with ovarian cancer and this is a really exciting study that was initiated last year and it is exciting because most of the research in women with ovarian cancer is looking at treatment, so how to improve different chemotherapy regimens or if chemotherapy should be done before surgery or post surgery, but very little research is focused on how lifestyle may influence their quality of life and prognosis. We know that women with ovarian cancer unfortunately have a worse quality of life than other women diagnosed with other cancers, partly related to the high recurrence rate and unfortunately low survival rate. We are enrolling women about six months after their diagnosis of ovarian cancer to a home based physical activity program where our certified trainer and counselor

calls them weekly at a convenient time and motivates them to increase their walking to the recommend amount of 30 minutes five days a week, and then we look at how this improves fatigue, peripheral neuropathy, cognitive function, lower limb lymphedema, which has been unrecognized in ovarian cancer patients but we are also taking a sample of blood at baseline and six months after the intervention to look at if it can improve certain hormone markers such as CA 125 or lactin, or IGF-2 or insulin. Some of these markers we know are related to ovarian cancer risk and prognosis. If we show a benefit of exercise then it could also be recommended by a clinician and covered by insurance companies. 19:37 into mp3 file <http://yalecancercenter.org/podcast/aug0110-cancer-answers-irwin.mp3> That's the research that is going on and for two years we will be recruiting for that, then there are some larger initiatives that I am involved with that are not just here at Yale but that are multi-site around the country. For example, the National Cancer Institute funded a large initiative called TREC, Transdisciplinary Research on Energetics and Cancer where we look at interactions between physical activity, diet, obesity and certain genetic or molecular markers and environmental factors and how it can improve your risk and prognosis. Foss This sounds really exciting that we are now looking at symptomatic issues as well in cancer patients in addition to just preventing the cancer. What you are talking about with these specific cancers can that be applied to other patients with cancer as well, say prostate patients, colon cancer patients, would they expect perhaps to do better with their treatment if they exercise? Irwin Definitely. Since we know cancer related fatigue is quite common with most cancers, whether it be because of chemotherapy or because of radiation therapy, exercise is not only going to affect say breast cancer patients, it will have a similar affect with colon, prostate, endometrial, all these other cancers. There have been studies looking at exercise done during treatment, during chemotherapy, during radiation therapy, and then also post treatment and most of the findings have shown there is no reason to delay initiation of an exercise program and that, in fact, if you begin it during treatment than it could decrease your levels of fatigue. There is also some research showing that it increases your chemotherapy completion rate, so that by being active or involved in a moderate intensity exercise program during treatment, you may be able to better handle the chemotherapy. There have been some studies done looking at doing just a month long exercise program before surgery, and if that can improve your surgery with less time in the hospital perhaps and less side effects from the cancer related surgery. Whether it is exercise before surgery, after surgery, during treatment or post treatment, to me, I think, the patient has to look at their lifestyle and their work history and their family demands and stuff and when they can fit it in, but at any one of those time points, or all of those time points, there is definitely benefit of physical activity in improving side effects of surgery and treatment and then eventually improving survival. Foss As you mentioned at the beginning of the show, it just requires going out the front door of your house and walking, it does not require a health club or a trainer or anything like that. Irwin It of course requires you to look at your schedule and figure out, how do I prioritize, how do I fit it in? It's

difficult with, say radiation, if you are going five days a week for therapy, and that's why if these hospitals or community centers where treatment is delivered had some sort of exercise program, trainers, or physical therapists to initiate a program, that would really help. The one good thing is that we have the Connecticut Challenge Survivorship Program here at Yale Cancer Center where patients can be referred to this program to receive information on how to increase22:51 into mp3 file <http://yalecancercenter.org/podcast/aug0110-cancer-answers-irwin.mp3> exercise and there are other programs too on nutrition and smoking cessation and other benefits, so that's the benefit here having that program to get instruction on how to begin a program.Foss If a woman wanted to participate in one of your trials, ovarian or breast cancer trial, how would they go about doing that?Irwin They can contact our study phone number which is (203) 764-8426, or they can email me at Melinda.Irwin@yale.edu , or they can call Yale or go to the Yale website and either type in exercise and cancer and it might pull up a link to my web page.Foss Great. Is it your hope as a result of your research that a lot of this is going to be covered and provided by insurance companies as part of comprehensive care for patients?Irwin Definitely, that has been an ultimate goal of mine. Similar to cardiac rehab programs, it used to be 20, 30, 40 years ago that if someone had a heart attack they were told to go home and rest and they then realized that was the worst thing to do after a heart attack or surgery for heart disease. You had to get up and initiate some sort of program because what's putting you at risk for heart attack is carrying groceries or mowing the lawn or raking so you have to train your body to be able to withstand these physical activities. Similar to a cancer diagnosis, there should be cancer rehab programs even if it is just a 12 week long program, similar to cardiac rehab, that's a first step. We have made some advances, for example, just last year I was involved in a panel from the American Cancer Society, American College of Sports Medicine, where we developed a certification for personal trainers or physical therapists to take and get certified to train patients with cancer and how to adopt or modify an exercise program if they have lymphedema for example, and so by working or training with one of those certified trainers, insurance companies may recognize that as a first step and cover those sessions.Foss That's a huge advance for cancer patients. Can you tell us a little bit about the Cancer Prevention and Control Research Program at Yale?Irwin I co-lead the Cancer Prevention and Control Program here with Yong Zhu who is also the other co-leader and we are one of seven programs at the Cancer Center and we have two main themes in our program. The first is to look at what causes cancer, and a lot of that is sort of the epidemiologic research. We look at how genetic factors, environmental factors, or lifestyle factors may cause cancer, and so those are the observational studies, the case control studies, or the cohort studies, and we look at interactions between, for example, gene and environmental factors and how it may cause cancer. The second theme is these behavioral trials that I focus my research on. So, how a25:42 into mp3 file <http://yalecancercenter.org/podcast/aug0110-cancer-answers-irwin.mp3> weight loss program, an exercise program, or smoking cessation and alcohol, how these programs for risk of cancers or in prognosis,

can improve their cancer outcomes. Foss You mentioned the issue of a randomized controlled trials and I wonder if just for the sake of our audience, you could talk about the difference between the observational trials and these prospective randomized control trials and what the control group is in these trials? Irwin That's a very good question. In my studies that are with breast and ovarian cancer patients, our control is usually standard of care, so what the clinician is recommending that their patient do either during treatment or post treatment, but we actually enhance it a little bit. In my trials, we have what's called a health education, so both groups get health education and then the exercise group gets exercise on top of the health education. What we offer them for the ovarian study, which is 6 months long, is a weekly health education topic that we find important to women with ovarian cancer, peripheral neuropathy, lower limb lymphedema, or fatigue related to chemotherapy or how to find information on the web, so both groups get that. Actually the control group is getting a little bit more than what the standard of care actually is. But unfortunately, some of the participants they want all want the exercise program, so at the end of the trial we do offer them three, one-on-one sessions with our trainer and we develop a personalized exercise program for them. But it's really important to do randomized control trials compared to observational studies to show that you are controlling for all these other extraneous factors that could really be explaining the association. We want to zero in on the fact that it's physical activity or exercise that's improving risk or improving prognosis, and as I mentioned, physical activity can improve say chemotherapy completion rates. Is it those who are active that are actually receiving more chemotherapy and that's why their survival or prognosis has improved, or is it the exercise? So you need to do these randomized trials to isolate what the factors are improving the outcome. Foss Normally when we do say drug trials in cancer, we enroll say 30 to 100 patients, and for these epidemiologic studies you need far more patients. Irwin Yes, we need more patients because of the completing of questionnaires or collecting blood samples. There can be some variability in the serum hormone levels from day to day, and in the questionnaire, as I mentioned, social desirability bias. So the more participants you have on a trial, you can actually look at the association a little bit stronger. In drug trials, or in studies with animals, you can really get at the exact measure, so you can have smaller sample sizes. In my studies, in the randomized trials, it's about 200 to 300 participants and in the large observational studies it might be 1000 participants. It's anywhere from about 200 to 1000 participants, which is a lot more than say 50 or less that may be needed for some other types of trials in animal studies or something. 28:53 into mp3 file <http://yalecancercenter.org/podcast/aug0110-cancer-answers-irwin.mp3> Foss Melinda, in the last minute or two can you tell us about any other exciting research that is going on? Irwin As I mentioned there are a lot of trials here at Yale going on and we have a lot under review, some looking at women with high risk, who might have BRCA1/2 mutation and we are going to actually look at cell proliferation in the breast tissue and collect some of the breast tissue and look at the cells and the rate of proliferation. We are trying to get as exact of a mechanism as we can and then throughout

the country there are lots of studies being done in other cancers as well to really strengthen the association. Foss This has been a really exciting discussion Melinda, and we will have to have you back to hear the results of those ongoing studies. Irwin Great, thank you. Foss The message for everybody is continue to exercise. Until next week, this is Dr. Francine Foss wishing you a safe and healthy week. If you have questions or would like to share your comments, visit yalecancecenter.org where you can also subscribe to our pod cast and find written transcription of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.