Welcome to Yale Cancer Center Answers with doctors Susan Higgins, Anees Chagpar, and Steven Gore. I am Bruce Barber. Yale Cancer Center Answers is our way of providing you with the most up-to-date information on cancer care every Sunday evening on WNPR. The doctors welcome some of the nation's leading oncologists and cancer specialists who are at the forefront of the battle to fight cancer. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu, and if you are interested in listening to past editions, all of the shows are posted on the Yale Cancer Center website at YaleCancerCenter.org. This week, Dr. Anees Chagpar will be speaking with Dr. Melinda Irwin. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Irwin is Professor of Epidemiology and Chronic Diseases, Associate Director of Population Sciences at Yale Cancer Center and Deputy Director of Public Health for the Yale Center for Clinical Investigation. Here is Dr. Anees Chagpar.Chagpar We talk a lot about cancer, especially on this show, and it is really a disease that no one wants to get. Talk a little bit about what we can do to prevent ourselves from getting cancer, aside from the usual things like, don't smoke?Irwin In fact, smoking and obesity are the two largest factors that are related to cancer mortality that are preventable or modifiable, which is the term we use. For many years, smoking has been the primary or the leading modifiable cause of cancer mortality, but now unfortunately, obesity has overtaken smoking. A lot of this is because of changes in our food environment as well as improvements in treatment. Maybe back in the day women getting treated for breast cancer, for example, may have lost weight because of some of the treatments, but now that our treatment are improving and we have medications to offset nausea and what not, women are not really losing weight related to treatment, but in turn might be gaining weight for a number of reasons, maybe going into menopause and then that changes their metabolism. But right now, the best way to really prevent cancer is related to some of our lifestyle factors, being aware of what we eat, our physical activity level, and with that, decreasing our sedentary activity level. These diet-related and exercise-related factors might explain up to 30% of our risk of developing over 13 cancers.Chagpar All of us have seen those maps of the United States that go back to the 1960s and they show the number of states that have normal weight, overweight and obese, and the map keeps getting worse and worse and worse. What percentage of the US population is overweight, and having said that, are we finding that cancer rates are increasing if obesity is related to cancer?Irwin Such a great question. Those obesity maps you are referring to were put out by the Centers for Disease Control and Prevention in the 1980s that showed that about 15% of Americans had a BMI of 30 or more, defined as obesity.Chagpar Wait a minute, what is BMI? Just so that everybody knows this and how do you calculate that?Irwin BMI is body mass index, and it is actually weight adjusted for height and so you can take your weight in kilograms and then divide it by your height in meters square. That is complicated, so 3:51 into mp3 file https://ysmwebsites.azureedge.net/cancer/2016-0101-YCA-Dr-

Irwin_288275_5.mp3you can just Google BMI calculator and pull it up and you can put in your weight in pounds and your height in inches and figure it out. If your BMI is 30 or greater, that is defined as obesity. What these obesity maps have shown is back about 20 years ago, maybe 15% of the population had a BMI of 30 or more, but currently today, one in three, or 33% to 35% have a BMI of 30 or greater, and it is projected that in the next 10-20 years, it will be 50% of the population has a BMI of 30 or greater. And a lot of this has to do with changes as I just mentioned in our food environment, changes in technology, that have created more sedentary lifestyle for many, and when experts have looked at this, it comes down to just about 200 calories a day that is causing this over many years, this increase in BMI, and that is very feasible to think about how our energy expenditure, for example, how much movement we do, physical activity, has decreased by about 200 calories a day because of sitting more because we can do a lot more via e-mail and online, a lot of people are on social media a lot more now, yet they say one of their biggest barriers to being physically active is that they do not have time, yet they are spending a lot of time on social media. So that, as well as our food environment, if you walk into a grocery store today, it is vastly different than it was 20 or 30 years ago. There are a lot more foods that are making it quicker and easier to cook, but with those foods, some of them might be processed or have a high sugar intake that is changing the amount of calories that we have taken or the quality of our diet. So, this has led to a change in BMI over time for the worse. There are many things we can do to reverse this trend or stop it. Because we know that obesity is not only related to cancer but also cardiovascular disease and diabetes. Cardiovascular disease is also a primary cause or one of the top leading causes of mortality after, for example, a breast cancer diagnosis. There is a lot we have to do. When a woman with breast cancer is diagnosed, she sees a surgeon and then the oncologist, she could also maybe see a registered dietician and a physical therapist and what not, so that right at the start, the whole patient is being treated in regard to taking care of not only her cancer but other comorbidities that go along with it. With cardiovascular disease, for example, we have had cardiac rehab programs that are either reimbursed via Medicare and other ways, but we do not have a cancer rehab program and that is hopefully where we are going.Chagpar It sounds like while that is a great idea and we are going to unpack that in just a minute, it sounds like a lot of the work that can be done in terms of preventing people from getting cancer in the first place would be reverse the obesity maps that we have seen over the last 20 or 30 years.Irwin Yes, and we can also learn a lot from the efforts in smoking cessation. There has been a lot of policy changes with tobacco control, regarding in restaurants or in public settings and smoking. So, what can we learn from what has been beneficial with tobacco control and apply that to preventing or treating obesity? What policy changes can be made? There is a lot going on regarding primary prevention of obesity. In 2013, the American Medical Association defined obesity as a disease and with that general practitioners or primary care physicians can treat obesity in their clinics, and that can be reimbursed. Unfortunately, where it falls short is it is

the primary care doctors who have to deliver this and they do not necessarily have the best training in nutrition and exercise and weight management. A goal here at Yale is that we develop an obesity medicine fellowship to train the next generation of clinicians on doing this as well as having a 8:15 into mp3 file https://ysmwebsites.azureedge.net/cancer/2016-0101-YCA-Dr-Irwin_288275_5.mp3comprehensive weight management program to treat obesity. We can take that from a primary care setting and hopefully not only will it improve or lower rates for cardiovascular disease and diabetes, but also prevent a number of cancers associated with obesity.Chagpar When you started mentioning primary care doctors treating obesity, I was hoping that we would be able to go to our primary care doctor and say "okay, where is the pill" and be treated that way. But as you were talking more, it sounds like this is much more about really changing your lifestyle; what you eat, how often you move, what you do, rather than simply a magic bullet because I think a lot of us are waiting for the magic bullet.Irwin If you think about a pill for a certain disease, it targets a particular pathway; usually, one pathway. But when you think about exercise and healthy eating and weight management, there are a number of different pathways that are targeted. So, it is difficult to think of how to develop a pill that would target multiple different signaling pathways. The benefits of exercise and healthy eating are not just through the insulin pathway, but there a number of different pathways, as well as effects on mental health -- depression, anxiety and stress, and then all the other comorbidities such as cardiovascular disease and diabetes. So, really, the best pill – exercising and eating healthy and trying to maintain or prevent weight gain over time is what we have to do, and while it is difficult to say change your lifestyle to try to increase activity or decrease your sedentary time or try to eat a better diet, there are approaches to doing this and working with a registered dietician or an exercise trainer can help you look at it step by step.Chagpar But it sounds really hard, right? We just went through the whole 20 or 30 years of grocery stores have changed and there is much more processed foods that make things faster and easier, we have become more sedentary, we are working at computers more, we do not need to walk down the hallway, we can e-mail somebody; there are a lot of things that have changed and so it seems that it would be difficult to turn that back and adopt these healthier lifestyles. And so if it has been so easy to gain obesity on that map, how easy is it to turn back, how easy is it prevent? We all get the fact that this is really a good thing, we can prevent cancers and so on, become healthier, prevent heart disease, but it seems to me that we have known that for a while and yet we continue to become more and more obese.Irwin Yes. It is going to take a collective effort. It involves the individual wanting to make the change, but also an effort in our work environments; for example, employers could support exercise for example by having facilities available and say reimbursing or supplementing costs associated to their health insurance plan or the 401K sort of rewarding them for exercising, having that involved, having numerous environments such as we mentioned the primary care doctors involved. It is going to take a large collective effort, but it also should not be an overwhelming message. You

do not have to train for a marathon. The current recommended amount of exercise is 2-1/2 hours per week of a moderate intensity activity, such as brisk walking but that does not require going to a gym say three times per week and paying a gym membership, it just really requires a good pair of walking shoes and a safe neighborhood to walk in. Here in New Haven, there has been a large 12:10 into mp3 file https://ysmwebsites.azureedge.net/cancer/2016-0101-YCA-Dr-Irwin_288275_5.mp3effort on creating bike lanes throughout the streets of New Haven which is wonderful. I know through the Hospital and the Yale Medical School, there are maps of 1-mile walking routes all inside, so you cannot have poor weather be an excuse to not exercise. So, it does take a collective effort and a personal effort to want to create this change, but it does not have to be much. It could be that 200-calorie deficit in our exercise or an increase in our eating that led to these changes. So, if you think about 200 calories a day, whether that be 100 from increasing exercise and 100 from changing your diet, it is not overwhelming when you think of it from that approach. And we have to take a long look at this lifestyle change rather than a quick fix or quick diet to lose 10-20 pounds in the next month or two. Oftentimes, when I give presentations on our research and I meet with study participants or patients, we talk about preventing weight gain because losing significant weight can be overwhelming to them, but preventing weight gain and then ideally a 3-5% weight loss has been shown to be clinically meaningful in regard to a number of metabolic and inflammatory biomarkers related to cancer and cardiovascular disease. So, preventing weight gain, decreasing sedentary time, then increasing exercise and ideally maybe a 3-5% weight loss, that sort of end gain has to occur over the long term with lifestyle changes rather than a diet, quick-fix, in the next month.Chagpar As you were talking about all of these changes and engaging the built in environment – bike lanes, healthier grocery stores, you start wondering about the impact that all of this has on disparities and the difference we see in African-American communities and Caucasian communities, poor communities and rich communities, and whether all of this could build into the outcomes that we see between these populations that it might be that part of this is related to obesity. We are going to get your opinion on that and learn a whole bunch more about your research in terms of how preventing weight gain and potentially losing weight can actually have a beneficial impact for cancer patients and cancer survivors. We will be right back after this medical minute.MedicalMinute There are over 13 million cancer survivors in the US and over 100,000 here in Connecticut. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life-changing experience. Following treatment, the return to normal activities and relationships may be difficult and cancer survivors may face other long-term side effects of cancer, including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as the one at Yale Cancer Center and at Smilow Cancer Hospital to keep cancer survivors well and focussed on healthy living. More information is available at yalecancercenter.org. You are listening

to WNPR, Connecticut's public media source for news and ideas.Chagpar Welcome back to Yale Cancer Answers. This is Dr. Anees Chagpar, and I am joined tonight by my guest, Dr. Melinda Irwin. We are talking about diet, exercise, cancer prevention and control, and how small differences can really make an impact, not only in the general population but also in cancer patients. Right before the break, Melinda, I was hypothesizing that the differences that we 16:10 into mp3 file https://ysmwebsites.azureedge.net/cancer/2016-0101-YCA-Dr-Irwin_288275_5.mp3see in terms of obesity rates may actually impact differences that we see in cancer incidence and mortality rates in different populations based on socioeconomic status, race or other things. Can you comment on that?Irwin Lifestyle behaviors are a very complex area to study. That is why I am fascinated with looking at these behaviors that are modifiable. They are upstream and downstream factors that cause these adverse behavior changes that then affect disease. So, when you think about the very upstream factors, it might all come down to education and other socioeconomic factors that then lead to personal factors with the way our lifestyle is and then more downstream to certain diseases. So, when you look at different educational and socioeconomic factors that cause changes or poor eating habits or exercise, we then have to think as I mentioned earlier about the collective entity stakeholders to make these changes that are really important especially in underserved communities and what needs to be done there to improve on these lifestyle behaviors.Chagpar Right, so safe neighborhoods, food, desserts and so on.Irwin Yes.Chagpar And that is really important for all of our public officials to think about because this really does have an impact for cancer patients. Tell us a little bit more about the work that you have been doing to study the impact of obesity in cancer patients and whether in fact we can make a difference in terms of longevity and survival.Irwin For about 20 years now, I have been studying the role of exercise and weight in regard to cancer prevention and control. I come about this from a population perspective. I am an epidemiologist, which looks on a larger scale on a population level how these behaviors affect cancer risk and prognosis. And my earlier research was targeting the role of physical activity in preventing and treating breast cancer in particular, and there has been some really exciting findings from observational studies showing that in women with breast cancer, those who exercised such as just brisk walking, had a lower rates of recurrence in mortality than women who did not, and we also showed that those who increased their exercise after the diagnosis, so maybe they were not exercising before their diagnosis but became active afterwards, had also a lower risk of recurrence in mortality than if they had stayed inactive. Those were observational studies. I then took those findings and wanted to see what were the mechanisms, how was it that exercise was lowering risk of recurrence and mortality? So, we did some randomized control trials where we took, in this case, women with breast cancer who were not exercising, they had finished their chemotherapy and radiation, and we randomized them to either a year-long exercise program or care group and we collected blood and some other measures to look at changes in markers. We measured in

the blood things that are related to breast cancer such as insulin and other inflammatory markers such as C-reactive protein. And we showed that these markers changed with exercise and that was really encouraging because we know that if insulin levels decrease, then your risk of recurrence or mortality improves for not only breast cancer, but for colorectal cancer and other cancers as well. 19:37 into mp3 file https://ysmwebsites.azureedge.net/cancer/2016-0101-YCA-Dr-Irwin_288275_5.mp3We then moved in the last 5-10 years, to looking at what about exercise plus healthy eating, which together lead to weight loss or prevention of weight gain. We did a study called the LEAN trial which showed diet-induced weight loss with exercise, also in breast cancer patients in the post-treatment setting, improved these biomarkers measured in the blood. And this is really exciting research. We have also measured some other downstream markers such as collecting breast tissue from biopsies to look at some of these downstream markers that also change with weight loss. We are doing those analyses now and looking at Ki-67 as a cell proliferation marker to see if weight loss or exercise slows cell proliferation, which could be a very good thing for cancer. We have also collected stool samples to look at the gut microbiome and there is a lot of research right now on the microbiome and how that can be related to cancer, and so we are going to look at that and how exercise and weight loss influences that. But what is really exciting now is a study that we are about to start, that is taking our exercise and healthy eating weight management program into the first year right after diagnosis. All the research to date that I have done as well as many others in the field have looked at the role of lifestyle after treatment, so about 2-3 years after diagnosis. And the patients at this time, when they are first learning about the benefits of preventing weight gain, weight loss and exercise, they are sort of stunned to hear the associations and they wish they had heard this information earlier. We are going to take the research we have done and implement it in the breast clinic in women newly diagnosed with breast cancer. So, with the help of you and other breast surgeons and the breast oncologists, after their surgery for lumpectomy or mastectomy, they will then be enrolled into our trial of preventing weight gain, increasing exercise and healthy eating, and this is what is really exciting about the trial. The primary endpoints of this trial will be to look at chemotherapy completion rates, adherence to endocrine therapy such as aromatase inhibitors and tamoxifen and then also the changes measured in the blood and in the gut microbiome as well as quality of life, which is so important to look at. And so what we are hopeful to find is that these lifestyle behaviors improve adherence to the critical treatments necessary for improving recurrence and mortality rates as well as improving their quality of life. That will be occurring over the next couple of years and we hope to share those results with you in a couple of years.Chagpar That sounds really exciting and I am sure that there are a lot of people out there who are thinking, "Wow! I would really love to be in that trial if ever I got breast cancer." Tell us who is eligible? Can people with precancers or DCIS, we talk about true invasive cancers, are you looking at the whole spectrum or people who have had chemotherapy; for example, if chemotherapy adherence is an endpoint? Who

exactly is eligible?Irwin Great question. This study is a collective effort of a number of colleagues. Dr. Tara Snaft, who is a breast medical oncologist at Smilow, is also co-leading this project with me. You are also involved being the head of the breast surgery program, and there are a number of other clinicians and scientists involved. What we decided to do for this first trial is to focus on women with breast cancer who will be receiving chemotherapy. Because the research to date really shows that women receiving chemotherapy are the ones that have the most adverse changes in their lifestyle behaviors. They have the most decreases in physical activity after their diagnosis as well as 23:29 into mp3 file https://ysmwebsites.azureedge.net/cancer/2016-0101-YCA-Dr-Irwin_288275_5.mp3adverse changes in diet because of chemotherapy and changes in their menopause, either going from pre or to postmenopause. This is still what we call an efficacy trial; even though we are implementing it in the breast clinic, it is an efficacy trial where we want to have a little bit more control over who is enrolled so that our findings are more valid from an internal perspective. It will be limited only to women who are receiving chemotherapy, not in the neoadjuvant setting because their treatment may occur over a longer period of time. It is the adjuvant chemotherapy – it can be pre and postmenopausal women and most importantly it can be women with any BMI, it is not limited to women with a BMI of 30 or more because we know that we want to prevent weight gain, and actually the women who gain the most weight after diagnosis are the women who have a healthy BMI – a BMI of less than 25. And so we do not want to ignore that group of women thinking that their BMI is fine, because they might have adverse changes in diet and exercise, which causes them to gain weight. So any BMI, but for this trial to be eligible, they cannot already be exercising at high levels or eating a really healthy diet, because we would not expect to see much improvement. It is limited to stage I through IIIc because those are the women who usually get chemotherapy, pre and postmenopausal and not currently practicing healthy lifestyle behaviors.Chagpar Which I anticipate will be a lot of people given what we said before the break about how this obesity map has really changed and how many of us, me included, are not necessarily the healthiest in terms of diet and exercise. Melinda, one question that I have and I think many of our listeners may have, is when we think about people going through chemotherapy, we think about it being hard, and we think about people losing their hair and they can get nauseous and they do not necessarily feel great all the time and then you are going to tell them to exercise and to eat spinach and collard greens? Do you really think that people are going to do this?Irwin We will find out and I have an amazing registered dietician, Maura Harrigan, who has many, many years of experience working with cancer survivors, and as I said, mostly in the posttreatment setting. So this will be really exciting for us to learn. We know from work that I have done and others, that exercise is feasible during chemotherapy. We did a trial called the IMPACT Study years ago, which was a telephone-based walking intervention. They received a weekly phone call from our exercise trainer to increase walking during chemotherapy. As you know, chemotherapy is now delivered usually every 2 or 3 weeks and

so there is usually definitely one day that they can exercise and maybe that lingers to the day or two after, but then there is another 12 days that they can increase their exercise level. As far as the eating, that is a great question of what they are going to want to eat. It is going to be personalized even though there are recommendations – dietary guidelines of what is healthy eating, primarily plant-based diet lower in sugars and saturated fats, limited alcohol intake. So, we will work with that framework but then personalize to the patient's preferences and side effects that they are having from chemotherapy. We are very hopeful that this is something that the patients will find beneficial to them not only in regards to treatment and side effects but their overall quality of life.Chagpar And the great thing is that this intervention is for how long now?27:23 into mp3 file https://ysmwebsites.azureedge.net/cancer/2016-0101-YCA-Dr-Irwin_288275_5.mp3Irwin It will be for their whole first year. Ideally they will be enrolled, they have to be enrolled before initiating chemotherapy, and then will be followed for a whole year. And then we will have an additional year after that to just follow them, so the intervention will be done, but we will continue to follow them to see if they have maintained those behaviors.Chagpar And that would be a really interesting and exciting part because certainly if they do maintain that, then I think a lot of us who may not even have a cancer diagnosis may want to know what the secret sauce is about how we can engage these healthy lifestyle behaviors and keep them going.Irwin And I think what is important too is hopefully our results will show a benefit on the treatment adherence and the quality of life and the biomarkers related to recurrence and mortality, so that in turn these programs are part of our cancer treatment plan so that not only at Smilow Cancer Hospital, but other hospitals around the country, when a patient comes in and sees the surgeon and the oncologist, they are also seeing the dietician and the physical therapist and it is all part of their treatment plan. And while this study is specifically focused on breast cancer, as I said there are many other cancers related to these lifestyle behaviors, so in the future the hope is that we will also extend this to other cancers.Chagpar Melinda, can you tell us a little bit about any research that has talked about whether diet and exercise impacts recurrence rate of cancer or survival because we give drugs for this, but can we give diet or exercise as a potential therapeutic?Irwin Great question. A new large study is being initiated right now called the Be-Well trial. It again is specific to women with breast cancer, but unlike the studies I just mentioned to you that we are doing, this one is a large trial of about 3000 women with breast cancer recruited from around the country with the primary endpoint being recurrence and mortality. And really it is a weight loss trial and the goal is 5% weight loss and if the 5% weight loss improves recurrence and mortality, hopefully there will be recruitment and reimbursement of these into our lifestyle behaviors in the clinic.Dr. Melinda Irwin is Professor of Epidemiology and Chronic Diseases, Associate Director of Population Sciences at Yale Cancer Center and Deputy Director of Public Health for the Yale Center for Clinical Investigation. If you have questions, go to yalecancercenter.org where you will also find past episodes in audio and written form. I am Bruce Barber

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