Yale CANCER CENTER answers

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Nutrition and Cancer

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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 doctors Francine Foss and Lynn Wilson. I am Bruce Barber. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and he is an expert in the use of radiation to treat lung cancers and cutaneous 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 week, Francine and Lynn are joined by Dr. Barry Boyd. Dr. Boyd is Director of the Integrative Medicine Program at Greenwich Hospital and an Assistant Clinical Professor at Yale School of Medicine and he joins us this evening for a conversation about nutrition and cancer.

Foss Let's start off by having you tell us a little bit about your role and the whole topic of integrative medicine and what it actually is that you do with nutrition in cancer?

Boyd This has evolved over the last, at least, five years. I originally helped set up an Integrative Medicine Program at Greenwich Hospital, interestingly, in part because I was the only physician who really had training in nutrition and the dilemma is that for many people nutrition is alternative medicine. I was trying to fill in the gaps for people and I helped set up a program but not as somebody who works in the complementary medicine field, but by virtue of the fact that this is where nutrition has often fallen in terms of patient care, and that led me to spend more and more time working on nutrition, but ultimately my background for the last 25 years in practice I have been devoted to developing a program for patients looking at the role of nutrition in cancer prevention, and as a result helping them to understand the potential for nutrition and cancer care as the field has evolved. I have been much more interested in the science behind this and as a result, in the last three years I have taken over the directorship of the curriculum at Yale in nutrition, so I run the medical school curriculum at the Yale Medical School. I have given quite a few lectures to the first and second year medical students, and more recently, they have created a position for me as director of cancer nutrition for the Yale Health System in order to help bring more nutrition education to the patients.

Foss Was there anything before you started this program, was there any education on nutrition?

Boyd It's interesting, and I will tell you a little story. When I went to medical school I had an hour of nutrition. Preceding my medical school, I had four years of graduate school in nutrition, so I immediately saw the enormous disparity between what physicians learned. I always made the joke that I had an hour of nutrition in medical school and then I went through residency and fellowship in cancer and had no nutrition. The basic nutrition training was the phone number for the dietitian, and I often found that the dietitians while very good and trained in how to help with diet, they are really not trained in research nutrition and we are familiar with many of the controversies in this field, and so for 20 years, I essentially have been using my background on nutrition more and more to fill in the gaps for patients. I see myself in many ways as a nutrition educator and that is what led me to first working with some of the people in the School of Public Health, Susan Mayne, Melinda Irwin and others who have invited me up to give lectures on nutrition and cancer

3:37 into mp3 file **http://medicine.yale.edu/cancer/podcasts/2011_0710_YCC_Answers_-_Dr_Boyd.mp3**

survival related to my interest in the role of insulin, weight, and energy balance, which is really more of central growth which we can talk about, and from that recognizing that there was a need to create a nutrition curriculum at Yale and then being invited to do that, which is a full time job that I do part time, in addition to my full time oncology practice.

Wilson You obviously have a tremendous amount of experience and expertise and you have bridged that gap for Yale students, the community of Connecticut, but gaps still exist other places, in other parts of the state, for example.

Boyd I see on a daily basis two to three patients a day coming to me because they get misinformation or they do not know where to go for valid nutritional advice and it runs the gamut from, what do I do about supplements to, what about an alkaline diet? Do I have to stop dairy? And I have spent an enormous amount of time in each of these controversial areas and look at the signs and what it tells us and how valid are these "complementary nutrition approaches" in order to help people make reasonable and healthy choices and give them a little broader and more science based understanding. Most physicians' sort of say, that's not my expertise. I would not say they will dismiss it, but they do not have time for that and having developed this, I have discovered a gigantic unmet need out there, and it is very hard and very few people naturally do this, and the people that I have worked with and seen in this field very often themselves do not know the science well enough to provide valid information.

Foss Can you comment on the role of nutrition in a broad sense in cancer, are there certain cancers where nutritional contributions are more important or do you view that nutrition is important overall for all cancer patients and that there should be a nutritional program as part of the therapeutic approach for these patients?

Boyd The answer to all of that is yes. To make it a little more comprehensive what I would say is that we are learning more and more about how nutrition fits into a person's lifestyle, their individual biology and where nutrition as a component of lifestyle can influence not only tolerance to therapy, but survival. What is really fascinating is the evolution of our understanding about what nutrition is. It used to be that we spent an enormous amount of time on the role of micronutrients and so that led to millions of dollars in research and what is it about plants that is linked to their relationship in terms of better survival and reduced risk. Now what is most fascinating in this field is in just the last three to four years, we have had the maturation of large cohort studies that show that within the population of adults the relationship between high versus low fruits and vegetables plays a role in about 2% to 4% of cancer risk, far less than all of the early case control studies showed, suggesting that maybe we missed the timing and I would say to parents, make sure your kids eat fruits and vegetables. If you actually think about it, the anticarcinogenic effects of these nutrients may play a big role in the very early stages of cancer. One of the things I educate patients about is that nutrition is a lifelong part of your life and in fact the origins of cancer very often are decades before the onset of the cancer and many of the things we associate or assume are related to it as an adult, may play a bigger role when you are child. More importantly in adulthood

7:27 into mp3 file **http://medicine.yale.edu/cancer/podcasts/2011_0710_YCC_Answers_-_Dr_Boyd.mp3**

one of the biggest factors linked to outcomes with cancer are things that are promotional factors, like hormones. We know estrogen clearly is a risk factor for breast cancer and for uterine cancer, and the level of estrogen is not simply whether you take hormone replacement therapy, which raises the risk of long term, particularly combined hormones for breast, but your weight and weight gain over adulthood plays a role in the risks for many cancers, not just breast cancer. Increasingly we are seeing that the relationship between lifestyle and one's metabolism can actually change survival, where weight and energy balance and things like insulin and insulin resistance seem to play major roles in survival and how through lifestyle interventions, exercise, and weight control, we can actually target that. In many ways we talk about other cancers, where we use targeted therapies, and what is fascinating is the evolution of this as a paradigm to understand that lifestyle can actually be a targeted approach for many cancers.

Foss A lot of patients actually did not do the right thing when they were younger and maybe they are overweight and they didn't eat the right things, but they come into your office now that they already have cancer, and the question is, if I change everything right now is that going to make anything better for me? Is it going to make an impact what I do right now going forward?

Boyd There is data that is observational for the most part that suggests that in a few cancers, we can reduce recurrence. For instance, in breast cancer and in colorectal cancer, there is very interesting observational data that increasing levels of physical activity can actually lower recurrence rate in some cases, by 50%, but again that is observation, and so there are studies that are using that as part of lifestyle to see if we can truly impact on that. My interest is that while we look at breast and colon cancer as being very sensitive to growth factors like insulin, which I think is actually one of the most important growth factors, that is more ubiquitously expressed in tumors, and even in hematologic malignancies, we know that weight plays a role in outcome for lymphomas and leukemia and that has been recent. There is evidence that insulin and IGF receptors are present in acute leukemia cells, chronic leukemia cells, and there may be the potential to impact on the speed with which those cells will proliferate if we can make changes in ambient levels of insulin in populations, that is just a theory but it is more exciting and certainly biologically a more plausible one that can explain the relationship between, for instance, how exercise may reduce recurrence rates. We have this new horizon around us that is interesting and that these interventions can actually change survival. We can promise it. One of the most interesting things, I think, that is a part of this much of translational research is identifying biomarkers that are predictors of this response. There is work in basic science that insulin and IGF signaling will reduce and by reducing those levels it will reduce growth of tumor cell populations. David Sabatini and others at Harvard have shown this, and one of the things he has discovered is that if you actually have constitutive activation of PI3K/Akt in these downstream activators, it eliminates the ability of these signaling changes to work. So we may actually be able to identify within studies people who will actually respond to exercise and lifestyle.

Foss Can you talk about the whole insulin story, you have mentioned this a couple of times, but for the

audience, what is insulin? How is it important? And how do we modulate that in a more favorable direction?

Boyd What is interesting is insulin is a hormone that for most people they considered important for modulating and controlling blood sugar, and for many years, this was of course recognized as a factor involved in diabetes. There are two types of diabetes. There is diabetes type1, which is actually a condition often either autoimmune or viral mediated, and it frequently starts in childhood, in which there is a loss of the ability of the pancreas to make insulin. More frequently and unfortunately more common with weight gain is the population that is called type 2 or non-insulin-dependent diabetes, in which people as they put on weight, particularly in certain types of weight gain, what we call visceral obesity, it engenders the loss of the sensitivity to insulin. So, in order to control blood sugar levels the body has to continually generate more and more insulin. So people with this condition called non-insulin-dependent diabetes, or type 2 diabetes, have higher levels of insulin long term and for many people prior to the development of diabetes, there is a pre-diabetic state, which we now call the metabolic syndrome. This, unfortunately, is incredibly common and up to 40% of adults over 40 to 50 have this, and as we look back now retrospectively we are seeing a very broad effect of this condition. Gerald Reaven, who described this, called it syndrome X, and we knew that this was a potential precursor of diabetes and actually was linked to the incidence of cardiovascular disease, stroke, and other vascular events, and he actually showed in a study of adults in the St. Francis School where he is out of Stamford that people who had this condition had surprisingly much higher incidences of cancer as well. That has led to more and more research studies showing that people with this pre-diabetic state have risks of cancer that are far greater.

Wilson Tell us what the metabolic syndrome is?

Boyd The metabolic syndrome, as I mentioned, is a pre-diabetic state and there are five criteria for that. We do not actually measure the insulin as part of that but it is the people who have high lipids but particularly have high triglycerides, whose cholesterol may or may not be elevated but they have a disproportionately low HDL. They also have a disproportionately high glucose level above 110 fasting, and they also may have hypertension and they are heavier. We use body mass index but simply stated, we look at the waist size. So, for a woman it is a waist over 35, and interestingly most women do not know, you have to measure it. They know their dress size, but they have never known their waist size, and for men it is a waist over 40, and those are the five criteria for this. If you look at cancer mortality, it is clearly higher in people with a metabolic syndrome and the more of those five criteria you have, the greater your cancer mortality will be and the question has always been, is it sugar? We all know that sugar is necessary and is disproportionately used by tumors, but insulin itself, in addition to improving glucose uptake, directly stimulates cell proliferation, and of course, in adulthood the way to speed up the rapidity with which the tumor will develop and evolve, is to enhance cell proliferation. How do we shrink down the levels of these growth factors? We know through lifestyle studies in preventing breast cancer, exercise and even modest weight loss can lower insulin enough to potentially effect outcomes and there is one

study of breast cancer that has actually shown that, and it is an intriguing idea. We think about how tamoxifen reduces breast cancer by simply blocking estrogen. The idea is we might be able to do the same thing by suppressing insulin. It may have the same impact on reducing tumor cell growth but for more cancers and that is the most exciting part of this and this is where I think the future of cancer nutrition is looking, at the role of this metabolic syndrome, metabolic stress in affecting long term survival.

Wilson We are going take a short break for a medical minute. Please stay tuned to learn more information about nutrition in cancer with Dr. Barry Boyd.

Medical Minute

It is estimated that nearly 200,000 men in the US will be diagnosed with prostate cancer this year and over 2,000 new cases will be diagnosed in Connecticut alone. One in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for prostate cancer. The Da Vinci Robotic Surgical System is an option available for patients at Yale that uses three-dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co-host Dr. Francine Foss. Today we are joined by Dr. Barry Boyd, and we are discussing nutrition in cancer. Barry, tell us about some of the methods that you incorporate in your practice to help patients live a healthier lifestyle, or at least try to do that, and what are some of the challenges you face in trying to do so.

Boyd One thing I do is a central assessment as a medical oncologist and of course I do a detailed history, and then in addition to the standard history, I go into detail about dietary history and family history of things like diabetes. One of the things that I have discovered is that we tend to be a one system focus, so we think about the cancer, but I broadly look at cardiovascular risk and endocrine history, do they have a history of vascular disease or is there a family history, do they have gestational diabetes. Gestational diabetes is a predictor of developing diabetes later in life and the clue that they may have insulin resistance, and then I use basic laboratory evaluations including measures of insulin resistance, so I will do fasting lipids. Many oncologists won't do that, but I have recognized more and more that if you know a person's metabolic status, if they turn out be predictably endocrine hormone resistant or insulin resistant, there is a whole different focus and we tend to think of that as being weight related and a perfect example is a woman who came to me last

week who had HER2 positive breast cancer, metastatic. She has not been treated. She has been going through non-conventional therapy since she came to me recognizing she needs to be more aggressive because her disease was progressing and she needed to simply come back into the system. I spend a lot of time encouraging people to understand the value of conventional medicine rather than making them fearful, and I did a simple workup. She was a Phys-Ed teacher who had been physically active, healthy, and had normal lipids in the past. She had been sick for a year and I did a metabolic profile. Her triglycerides were over 200. Her glucose was elevated. Her HDL very low and unpredictably, with very low weight. Despite having weight loss, she had a metabolic syndrome now and so it is a clue that not only do people who are healthy have this lipid risk but once you have cancer you may develop it in the setting of an unhealthy life because you are less active, your diet has changed, you may have lost weight, but your weight is now more lipids, more water weight, and you lose mean body mass and so we all need to be aware that even within this thinner population there is a thing called metabolically obese normal weight, so with this woman I was able to tailor her dietary approach, work with our nutritionist and encouraged her to exercise. One more fascinating part of this story is this new information that metformin, if appropriate medically, seems to be able to target the high levels of insulin and is a medicine that I sometimes use if appropriate medically because there is an enormous amount of information growing that metformin has a potential secondary effect in terms of tumor progression. Clearly, patients with diabetes on metformin have lower cancer risk. There is a lot of information that metformin has a targeted effect on tumor stem cells, which is really fascinating, and a study not yet published that metformin, because it lowers insulin, may actually be able to reduce the need, the doses of chemo that have an effective anti-stem cell effect, so it is part of the insulin story but it is really what I see as a light into the role of pharmacologic approaches as well as lifestyle in targeting the metabolic syndrome and potentially substantially changing in the natural history of some diseases. It remains to be seen in research, but I think it is where we are going in terms of nutrition.

Foss Can you comment on other nutritional issues that you see in cancer patients? Are there specific dietary recommendations that you make in general to cancer patients?

Boyd Yes, I do. One of the things is that there is this fear about foods. One of the most interesting things is people come to me with dietary myths, for instance I hear, I must drink green tea and I must not have coffee. I do not know how many people know that but intriguingly I have done a lot of research into the epidemiology of coffee and it turns out in many studies that coffee is actually linked to substantial reduction in some cancers, reduction in cirrhosis, because of what coffee has in it. In the Norwegian population, which has a disproportionate amount of coffee in their diet, 65% of the total antioxidant constituents of their diet comes from coffee.

Foss Can you tell us the same thing is true for chocolate?

Boyd The dilemma between chocolate and coffee is yes, in modest amounts, and actually there is a reference that I use all the time from David Jacobs who is a public health specialist at the

University of Minnesota and works with people in Norway. He has catalogued based on laboratory studies the relative antioxidant power of different components of food, and if you look at the highest antioxidants within food, what I found is, for instance, what is in there is things like Cocoa Krispies, and because of the chocolate, in fact, there is more antioxidants per gram in Cocoa Krispies than there is in broccoli. This is an example of why mythology is important. A patient comes to me with breast cancer receiving radiation, the physician and the radiation therapy technologist at the hospital told her to stop the green tea, it will interfere with radiation. It turns out green tea is not a very potent antioxidant and it is very unlikely to have effects on radiation therapy but simultaneously, she admits to me that she is taking eight capsules of ground cloves per day. Now, what is interesting is in that list of antioxidants, ground cloves is two orders of magnitude more potent as an antioxidant than any other food and I said if there is anything you should not take during radiation it is ground clove, and she had no clue and nobody in the radiation field was aware of this. That is a pharmacologic dose like taking a thousand units of vitamin A and we all know now that we have to be concerned about antioxidants during radiation, particularly where the radiation impact is largely the oxidative radical formation that damages membranes and cells, so you do not want to be on antioxidants, but that is an example if you do not know about nutrition you may neglect something that potentially could interfere with therapy.

Foss Could you talk about all these supplements that people are taking? My patients come in with long list of things and ask whether they should or should not be taking them and I think they are also taking things that I do not even know about. Can you comment on the role of supplements in general and herbal therapies?

Boyd This is a gigantic field, as you know, and the problem with supplements is in large part they are unregulated. The patients are desperate. This is a field where as we know many people have diseases that we may not have a cure for and so they will seek out answers, and this is a field fraught with problems for patients. I have individuals in my practice that will spend two to three thousand a month, I have had patients who have mortgaged their house and they are afraid to stop these supplements. One patient, she was taking 135 capsules a day, 35 with breakfast. She was spending 3000 dollars a month and the only thing that might have a positive effect was she was overweight and losing weight because of this. It was a calorie restricted effect of all these supplements making her sick, but clearly the people recommending it are in the field and they had created a combination of nutrients, each of which you could find a research study suggesting this might affect a portion of the pathway and now you would be intrigued in clinical cancer research, other journals within the American Association of Cancer Research, that suggested some benefit and then you put together 100 nutrients or more and you have no clue of their pharmacology, how they interact, and a very simple thing I tell patients is that there is intriguing data that a component of tea, ECGC, has an antiproliferative effect on chronic lymphocytic leukemia cells. There is another study showing that turmeric, or curcumin, has the same effect and when given together in a sequential fashion there is interesting data that it can suppress the progression of those cells, but if you put the two together they actually antagonize one another and that is a simple example

25:29 into mp3 file **http://medicine.yale.edu/cancer/podcasts/2011_0710_YCC_Answers_-_Dr_Boyd.mp3**

where people do not realize that if you use many nutrients all the pharmacologic side effects are totally unpredictable.

Foss What do you tell people about Chinese herbal medicine if people are going to an herbalist?

Boyd With Chinese herbal medicine, number one, you need to know your Chinese herbalist. If you are on chemotherapy, I am anxious about that. I am particularly anxious about one setting where we use chemotherapy and that is in the adjuvant setting. Let us say I have a patient with breast cancer or a patient with Hodgkin's or non-Hodgkin's lymphoma and you have a curative setting. If you do not have, for instance, in breast cancer, anything to measure, you are now treating a patient to prevent recurrence and there are no measurable cancer cells, there is no marker. You have virtually no way of knowing if you are going to interfere with that disease. Ethically to do anything to affect the value of adjuvant therapy would be dangerous and many people come to me and I say on no circumstance ethically could I recommend using anything that could impact on that. I have people with end stage disease who want to take a nutrient, I say look I have a tumor that I can measure, I have markers I can measure. I will be watching over you if you choose to do it, I don't recommend it, but at least I can monitor you and then I will look at the nutrients and I say what are the potential adverse effects? What are the pharmacologic consequences? Does it alter Coumadin? Does it alter coagulation status? Does it have impacts on medications? Does it have any other potential adverse effects? An example of this is high folic acid. Folic acid is a proliferative stimulus in populations and so it turns out that there is interesting data that too much folic acid may actually enhance the speed with which tumors grow or increase the risk of developing malignancy in at risk populations and many people are not aware that. B12, the same thing, B12 and folate are very involved in what is called DNA precursor synthesis and there is intriguing work now that you can actually label B12 and use it as an imaging technique to look for tumors. And yet there are people who have no idea what they are taking and coming to me with bottles of supplements and I asked them do you know how much B12 is in this and they have no idea. I asked them how much medication they take and what is their dose? They all know their doses, so people have this gigantic experiment now. In phase one trials 80% of patients are taking supplements and my concern is many of our phase one trials may be confounded by unrecognized and unmeasured supplement use and it could impact on the effect of these medications. We really need as physicians to be very cautious and careful that they are asking what they are taking and my goal is to try to educate them about the potential risks for that.

Dr. Barry Boyd is director of the integrative medicine program at Greenwich Hospital and an assistant clinical professor at Yale School of Medicine. If you have questions he would like to share your comments, visit www.yalecancercenter.org where you can also get the podcast and find return transcripts of past programs. You are listening to the WNPR health forum on the Connecticut Public Broadcasting Network.