

CENTER FOR MIND-BODY MEDICINE
COMPREHENSIVE CANCER CARE 2001: INTEGRATING COMPLEMENTARY &
ALTERNATIVE THERAPIES

CONCURRENT: New Research on Women's Cancers: Herbal Therapies and Supplements

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CLASS: -- and we have Dr. Evans here, who's an oncologist, a surgical oncologist, and Mary Beth Augustine, who's a registered nutritionist. And Dr. Dobs is going to be accommodating. So the way this morning is going to work is, Dr. Evans is going to present first, and then Dr. Dobs will kind of synthesize everything that he said, and we're going to open up the field for questions. And then Mary Beth Augustine will then talk about the nutritional aspects of women's health, essential fatty acids, soy, botanicals for ovarian, endometrial, and cervical cancers. And, once again, Dr. Dobs will then comment, and we will open up the field for questions. So that will be kind of the flow of the morning. Dr. Dobs is the professor of medicine and oncology and vice chair of the Department of Medicine for Clinical Research and the director of the Johns Hopkins University School of Medicine Clinical Trials. She'd going to be your moderator, and she's going to introduce Dr. Evans.

DR. DOBS: Well, welcome again to this morning. We will have formal presentations, but we certainly would like this to be as interactive as possible in that this gives us a chance to learn from each other. Allow me to introduce our first speaker this morning. This is Dr. Richard Evans. Dr. Evans is a board-certified surgical oncologist and founder of the Texas Cancer Center, which is a nonprofit foundation and a medical facility located in Houston, Texas. He specializes in conservative treatment of cancer, and I'll mention this, since he's really not allowed to advertise, I guess, but I will advertise that he has recently published this book called *The Cancer Breakthrough*, and there are a couple of copies here for you to look at as well, and I think later in the day, he's having a signing ceremony. So shall we begin? Dr. Evans, your formal title is called, "New Research on Women's Cancers."

DR. EVANS: Very good. Thank you very much. I want to thank all of you all very much for being here. This is a great turnout for this breakout session. I see a few men in the audience, and men, if we have time, I'm going to say a little bit about some men's cancers as well, prostate cancer, because the principles that I would like to talk to you about are things that apply to most, if not all, solid tumors. I like to begin, when I'm talking about this subject, where I began, and I became interested in cancer treatment about 25 years ago when I was working in Houston St. Joseph Hospital with Dr. John Stalen (phonetic). And Dr. Stalen was a cancer surgeon who was a pioneer in the use of lumpectomy for breast cancer. And he was really the second surgeon in the United States following George Crio (phonetic) at the Cleveland Clinic to begin to advocate and to practice lumpectomy or conservative surgery for women with breast cancer. And I was just fascinated with his approach, his brave, pioneering approach to breast cancer, and I said to him,

"Dr. Stalen, what can I do? I'd like to do something. I'm just a lowly resident here, but can I help you in some way?" And he said, "Well, I'll you what, Dick," he said, "You know, I'm getting ready to write a paper about my experience." He said, "I've only treated about 80 women since 1970, but I would like my paper to be more than just my own experience. I'd like to summarize the experience of all the world's physicians in conservative surgery. So why don't you go to the library and just do some research?" And that's what I did. Off and on for over a year, I went down to the Texas Medical Center library, and I researched all the papers, tried to find everything I could find on conservative or limited surgery. And what that meant was any woman with breast cancer who went through treatment, curative treatment in which she ended up and she still had her breast left intact. And I discovered in 1976 that there had been over 60 articles in the world's medical literature that had come from North America and Europe. They involved hundreds and hundreds of patients. There were dozens of hospitals, there were decades of experience, going all the way back into the '40s, the '30s -- really in the '20s is when it had begun. There was an enormous amount of experience with conservative surgery, even in this country, even in the U.S. And every single paper, when viewed from the point of view of survival, of overall survival, every paper said the same thing, and that was, conservative surgery is safe and effective and it works. It works in our hands. And those institutions that had started it were still doing it; there weren't any that had abandoned it. And it was unbelievable, what I found, because in 1976, a woman with breast cancer in Houston or certainly any city in the United States, she could have had two opinions or she could have had two dozen opinions, and she was going to have a mastectomy, in spite of the overwhelming evidence to the contrary. There was this huge, huge gap between what was published in the libraries of the leading medical journals of the world and information that women were getting from their doctors. And I hate to say this, but I think we have closed some of that gap -- certainly for breast cancer we've closed that gap. But for many other malignancies, that gap still remains. It still remains. And I'm going to talk about some of that this morning. Another thing happened very important in 1976, and that was that the NSABP trial on lumpectomy -- the U.S. lumpectomy trial -- began. It entered its first patient in 1976. And by 1989, that trial had achieved numbers that were acceptable to most practicing surgeons. And it was determined that the result, which I'm sure you're all familiar with, which is that lumpectomy and radiation therapy is just as effective as mastectomy in the treatment of breast cancer. Now, there's one aspect of that trial, which you may not be quite as familiar with, and that has to do with over 300 women who were treated with a third kind of treatment. There was a third arm to this trial, and the third arm to the trial was that these women were treated with a lumpectomy alone. There was no radiation. And in that trial, the lumpectomy actually really was -- technically, it was just sort of a scoop-it-out type operation. They tried to get clear margins, they tried to do a total removal of the tumor, but it was not a wide excision. It's not the kind of surgery that we would do today if we're doing a lumpectomy. It was just a very narrow margin of excision. And in that group of women, the recurrence rate was very, very high. And it's a number that you may have heard before, because it's so widely quoted, and usually misquoted, by surgeons when they say that women treated by lumpectomy alone in this trial had a recurrent rate of about 40 percent, local recurrence -- a local recurrence rate of about 40 percent. And that is in contrast to the other two forms of therapy, either mastectomy or lumpectomy and radiation, in which local recurrence rate was 5 percent or less. So there was a huge gap, again, in this group between the lumpectomy alone and the other forms of treatment. So I'm going to ask all of y'all a question. Maybe there's somebody in the room who knows the answer. I hope there are some people that know the answer. What happened to the women who were treated with lumpectomy alone in that group? Forty percent

got a local recurrence. The recurrences, of course, were treated. They had additional surgery to remove the recurrence. But they were still followed. They were still kept a part of the trial, and what happened to that group of women in terms of their overall survival, as compared to the other two forms of treatment? Is there anybody who really knows the answer? I see some hands. I'm not going to ask you, because I think what I'd like to do is -- for those that don't know the answer, I'd like you to be thinking about this question while I continue my talk, and then we're going to answer the question in a few minutes. What I'm going to do now is, I'd like to go back and start and leave you a little quick history on how we got into this situation, and start about a hundred years ago, when surgery came into being in this country, or in the world, because of general anaesthesia. They understand the infection and accepted technique and that sort of thing. That all happened about a hundred years ago. And obviously, when we could start putting people to sleep, we could start doing big operations, and that's how William Halstead really was able to do the so-called radical mastectomy. And William Halstead, in his very first paper that was published in 1894 on his experience with radical mastectomy, the treatment of breast cancer, the first sentence of that very first paper said, "We've been doing a radical operation on 50 patients, and our local recurrence rate was 3 percent." The very first sentence, his most important sentence of his first paper, had to do with local recurrence. And if you're going to understand cancer, if you're going to understand the surgical treatment of cancer -- the use of surgery, the use of radiation, local therapy for a cancer -- then you really have to concentrate, again, on local recurrence. And that's this question we just finished with a few minutes ago, these ladies with a 40 percent local recurrence rate, and now we're talking about it again in the early history. I'm sure it's obvious to most of you that when you talk about a recurrence in cancer, there are really two main categories. One, of course, is distant recurrence, or metastasis or distant spread, and the other is local recurrence. Okay, so, in Halstead's hand, he was very pleased to have a local recurrence rate that was so low. And the reason for that is because surgeons at that time, and for many years even thereafter, observed a similar pattern in their treatment, and that was that they did a radical operation, and if the cancer came back again locally in the chest wall area, the patient very soon thereafter -- maybe a few months, maybe a year or so, but usually within 12 months -- that there would be evidence of distant spread, and the patients and the patients would eventually die of their disease. So for the surgeons of that time, local recurrence was a very important thing, because it was felt to be the cause of the distant metastasis. And in the surgical literature, even into the middle part of the last century, surgeons are saying to themselves and writing in their papers, you know, "We did an operation. The local recurrence rate was so-and-so, and the patients died and, you know, we're responsible." They considered themselves responsible for the death of the patient for having left behind two or three cancer cells. And so a whole strategy developed around surgery that treated cancer cells much the way we would treat infectious disease today. The idea of leaving behind one cell was just considered anathema to a surgeon. So we changed -- many of you have probably done this before -- you go into the operating room, you change gowns and gloves and instruments and everything, just to be sure that you don't leave one solitary cell behind. And that became part of the holy grail, almost a religious belief, a commitment to the idea that you have to take out every single cancer cell. And it progressed into the middle part of the last century where radical mastectomy became a super radical mastectomy, taking out the lymph nodes underneath the breastbone and under the ribs, et cetera, et cetera, and the surgery became more and more aggressive, usually without too much overall improvement in survival. So now let's go forward to the question that I asked you all a minute ago, because I guess I'm sort of leading you astray a little bit, aren't I, by telling you all these terrible things about local recurrence. So I'd better just go ahead and sort of get this

question answered. You raised your hand when I asked you the question, so I'll let you -- do you want to answer what happened to the group of women who had the lumpectomy alone and had the 40 percent recurrence rate? What happened to their overall --

QUESTION: No difference in survival.

DR. EVANS: There's no difference. There was absolutely no difference in survival. And that's the cancer breakthrough -- that's why I give the title, "The Cancer Breakthrough You've Never Heard Of," because there are so few people that have heard about it. In fact, really the book title applies -- I can sort of still say it's okay to call it that, because the book really applies to a whole slew of cancers, and all available evidence we have for every cancer seems to follow that very same pattern. And we're going to talk a little bit more about some of the others in a minute. So it's really a surprising result, isn't it? It's really surprising. This guy has got me confused, because on the one hand he's telling me that the local recurrence for so much of the 20th century was a harbinger of death, and now he's telling me we've got research studies that show that it's not such a bad thing, that it really doesn't compromise survival at all. This research was not just one study -- this is not just the NSAB study -- that since 1989, there have been four additional randomized prospective trials; there have been five additional non-randomized but still scientifically sound studies, all which come to the same conclusion. So the information that I'm giving you now that says that this local recurrence is not such a threat has been confirmed over and over and over again. But I'm not aware of any studies being done anywhere in the world today that are addressing this issue. The kinds of studies going on now in breast cancer, as you probably know, oftentimes have to do with ductal carcinoma in situ or the use of tamoxifen or raloxifene and these kinds of things. They're not studying this issue. It's been solved. It's over. It's done. It's finished. So explain this now. Okay, first of all, you have to understand that there are probably at least two different kinds of recurrences when we talk about local recurrence. Let me talk about the lumpectomy recurrence first, the one which is so innocent. I'm starting to call that -- I'm trying to get other doctors to call that -- local persistence. And other doctors use it in the literature some, but it hasn't become quite as unique as I think it needs to be. But I call it local persistence, because that is where you do an operation and you leave behind a few cancer cells, left in the breast. Those begin to multiply. And then you have a recurrence again, or persistence of that tumor. Local recurrence, on the other hand, is a word which has had such an ominous sound to it, at least among surgeons, that I like to use that phrase to talk about the kind of recurrence that we thought of during the last century. And what happens there is very probably this: That the surgeon does a mastectomy, he removes the breast. There's no evidence of any spread of disease on just scans or X-rays or that kind of thing. But probably in a lot of women, there already has been spread. There's already been spread to some distant site, but it's not present on any testing that can be done. So the first thing, now, that the surgeon sees is a recurrence in the chest wall, and what that represents is tumor cells that probably have migrated from the distant site back to the chest wall, and that's where the surgeon sees it. And then it's only maybe months later that it clinically appears in the distant site. I hope that's clear. Does everybody understand that? Because that's a very important distinction, that you see that you are really talking about two different phenomena. We're talking about a very ominous form of disease of local recurrence where the disease has probably already spread and then comes back and initially reappears at the site of surgery, but that kind of local recurrence is very distinct from the kind of recurrence that occurs if you just leave a few tumor cells behind. Now, why is it, based on this, that local persistence, or the reappearance of cancer in the breast after a

lumpectomy, is such an innocent event? Why is it? That really is perplexing, isn't it? So let me kind of try to give you my brief explanation for that. And that is -- also, this comes from research done back in the 1970s -- the old question, when did cancer cells start to circulate in the body? You know, this has never been discussed very much. It's very hard to see cancer cells in the body, as you might imagine. No one -- well, it's just very hard to do, you know, even if you do a blood -- if you have somebody in septicemia with bacteria in the bloodstream, you've got let it sit in a lab for 2 or 3 days for the bacteria to multiply enough for a pathologist to see them under a microscope. And so it's very difficult for somebody with a few cancer cells circulating among the millions of white blood cells and other cells in the blood to see cancer cells. So it's been a hard problem to do. But back in the mid-1970s, there was research done, in animals at least -- and there's been a little bit in humans -- but there's pretty good research in animals that shows that cancer cells begin to circulate very early in the course of a malignancy. Even from the time a cancer is the size of a mustard seed, the cancer cells are leaving that tumor, gaining access to the bloodstream via angiogenesis and the kinds of things you've heard so much about lately -- the new blood vessels growing at the tumor. So if you've got a cancer cell circulating from the time a tumor is very small, well, you say to yourself, well, that's bad. That's really terrible news to hear this. But maybe there's a flip side to that. Maybe there's some good news, because we know the cancer cell doesn't really metastasize, in the traditional sense of the word, until it's larger, at least for most people. So what has happened, what must be happening in most patients, is that as a tumor grows and pours those cancer cells into the bloodstream, at least for quite a while, those cells must be dying. And they're probably dying because they're attacked by the immune system. And again, some of this or some experimental evidence for it, but it hasn't all been wrapped up. But something is happening in the bloodstream that is killing these cancer cells. So what I have been saying -- I've been saying this, actually, for 20 years -- the handout that I have for you up here -- incidentally, it's up in the front of the table here -- is a paper that I wrote 20 years ago in which I said the patient who survives her first cancer, let's say that's 2 centimeters in diameter, and she survived her first cancer without developing spread of disease, since she gets a recurrence now, or a persistence in the treated breast, she can be expected to survive that recurrent cancer, because the same immune system that protected her from the spread of cancer cells from the first malignancy will be there to protect her from the spread of cancer to the second malignancy. And that's the answer to the question, is why is it that you've got 40 percent of women treated by lumpectomy alone and they do just as well? Well, in that treatment trial, we lost some of the patients. We lost some. We may have lost 10 percent or 15 percent in that group of women. But the women who developed a local recurrence only, who didn't develop -- they had only a local recurrence without spread -- their immune system worked the first time, they survived the first cancer, and they can successfully survive the second cancer. And that's the reason it works, and that's the reason why local persistence, at least, is not a threat to survival. And the way Bernie Fisher says it, and the way the NSAB says it, is basically, recurrent cancer, promptly treated local recurrence, or local persistence, I should say -- does not spread. It just does not spread. Obviously you've got to treat it in some sort of reasonable period of time. Now, this is supposed to be about women's cancer. I know it's been a lot about breast cancer, because it's -- I want to just say a few words here. I'm going to tell you a story about cervical cancer, and then I'm going to sort of wrap this up. But there was one other thing I wanted to throw in here, and that is that it's very important that a surgeon understand the difference between local persistence and local recurrence. It's very important that the surgeon have an idea in his mind, the way he views local recurrence and the threat of possible residual cancer cells. It is extraordinarily important that his whole philosophy of surgery -- it is because, as I've said many times before,

because every stroke of the surgeon's knife is affected by the way he views those microscopic cancer cells. Again, it's not the whole tumor. Every surgeon believes that the mass of the tumor needs to be removed. If you have a grape-size breast cancer, the whole thing has to come out. It's just that the probability of maybe two or three cancer cells or pre-malignant tissue that's in the surrounding area, that's the thing that the cause of the debate. I'm going to say a little bit here about cancer of the cervix. I think most of you are aware that early cancer of the cervix in this country can be treated with a local excision, just a conization or something like that. But for women that have it much more invasive, beyond about 5 to 8 millimeters' invasion into the cervix, in this country most every woman is going to have a hysterectomy recommended to her. And so I began looking around about -- in the early 1990s, I began to look around at other cancers to see what we knew about them and some of these principles about breast cancer might possibly apply. And so I called over to M.D. Anderson to a friend of mine about this, and of course, I couldn't get any help at all from the physicians there, except one nice lady said, well, I'll you, you might go look at a surgeon by the name of Dr. Dargent in France, because he's doing sort of a lumpectomy. So I wrote to him and he sent me back his paper. It had been published in '92. It was in French, so I had to translate it from French. And he had treated nine patients with cancer of the cervix doing a so-called lumpectomy. I included that in the first version of my book and about 2 or 3 years ago, I got a letter -- or not a letter, I got a phone call from a gal who called me to say, "Dr. Evans," she said, "I am 26 years old and I'm pregnant. I'm 2 months pregnant now. But I went to see my gynecologist and my gynecologist just told me that I have invasive cancer of the cervix, and I'm going to have to have a hysterectomy. And I've talked to two or three other gynecologists, and they all say the same thing. I've never had any kids. This is my only opportunity. And I heard about the research that you had published, and I wanted to know if you know anything else." And I said, "Well, I don't know anything else. Dr. Dargent has not published anything else that I know of." But I said, "We certainly can call him up." So we got on the phone and we called him up over in Leon, France. And luckily, his English is a lot better than my French, so we were able to communicate. And by that time, he had already treated 51 patients, and they were all doing very well. And he was still doing the operation. He was still doing it. And he had a colleague in Toronto, Canada -- Michel Roy is his name -- at Quebec Hospital in Quebec. And he had done 19 cases at that time. So the lady who called me went back to her doctors in Southern California and said, "Listen, I'm going to Canada. I want to keep my baby." So they said to her, "Well, okay, if you're that committed to doing this, then we'll carry out the surgery here." And so they did it, and they did the lumpectomy and she went on with her pregnancy. And she called me several months later, and she said, "I wanted to tell you that I had my baby. The baby was delivered, and he's healthy and he's fine, and I want to thank you so much for helping me through this." And anyway, it all worked out. And I said, "Do you have any cancer left?" No, and she didn't, and she was obviously very pleased with that result. But I just tell you this story as an indication of how we still, even now, even now in the year 2001, there's still this huge chasm between what we know about and what has been published in the world's medical literature and what doctors are practicing. There still is. And that's why -- I guess I can't advertise my book anymore, but I will tell you that you can get some free information on our website. We have a website called TexasCancerCenter.com. And at our website, most all of the information that I talked about here today is available on the website. And one thing we're doing is all the references -- we've got hundreds of references to support all this information, and most of the references were available. You can click on them, and there's a hyperlink directly to the National Library of Medicine. So you can see that this is not just stuff I'm pulling up and inventing. This is stuff that's in the National Library of Medicine. Dr. Dargent, for instance, in

April of last year, April 2000, published his results in English for the first time. And so now this doctor doing the lumpectomy for cancer of the cervix is readily available right on the Internet. So I think that's -- I'm running out of time here. I could keep talking forever, as you all can probably tell. I've enjoyed this very much. It's given me a chance to such an interested group of folks and I look forward to your questions. DR. DOBS: I think that was a fascinating talk, and what I'd like to do is to review a couple of the concepts that Dr. Evans mentioned in summary, and then leave us with some questions, and then open it up to the floor for further questions. Historically, as Dr. Evans was emphasizing that surgery for cancer had always been radical, meaning with large areas of tissue that was resected. And the philosophy behind that was that every cell had to be removed to minimize any kind of recurrence. He did mention some data that it was actually old, but has not been out to the public until recent years, and that is that a lumpectomy versus a mastectomy actually showed no difference in survival. Dr. Evans was trying to emphasize the difference in the mechanisms of cancer spread -- that is, there is a local persistence, and in this situation, there's a few cells that are still left over, and these may continue to grow, versus the concept of recurrence, in that there's already been distant spread prior to the surgery of the cancer cells that really are leaving the tumor very early on in the course of the disease. Now surgeons are finally sort of rethinking the problem and thinking that there might perhaps even some benefits of minimizing the surgery done, and perhaps this might assist in diminishing local recurrence. I'll use an example that's been discussed now in the pediatric world, and that is the issue of tonsillectomy. It's always been thought that, oh, someone's having recurrent tonsillitis, let's do a tonsillectomy, therefore taking away the tonsils, and you won't have a problem if there are no more tonsils. But we're now accumulating data to say that perhaps there's some benefit to leaving the tonsils in place, that there's some immune benefit that might be had for this child later on down the line that we really didn't understand several years ago. And Dr. Evans does mention briefly the issue of cervical cancer. We're learning that a lumpectomy, or just taking out the tumor itself in the uterus, may be just as good, if not better, than taking out the entire uterus. So these are some questions that I had at the end of this talk -- and again, I want to open it up to the forum after this -- the residual tissue that is left, does it do anything to fight recurrence? Is this in some way mediated through immune function? Should we be leaving tissue because somehow it helps to fight any local disease or distant spread? And, really, what is the correct amount of tissue to be resected? Is surgery necessary at all? Maybe it really doesn't do any good to have surgery done. And what are the differences in the quality of life with the different types of surgery? And I think that's certainly a very important question here for individuals that are going through surgery. So those are my sort of summations of some of the things that I got out of Dr. Evans's talk. How shall we work this? Do you want to answer some questions? Shall we open it up for questions from the floor? Dr. Evans, please.

DR. EVANS: Either way. Well, I will answer that directly. I do want to say one thing. One problem is, I oftentimes come across as sort of the big proponent of conservative surgery. And that's because I'm sort of out here in a vacuum, sort of preaching something that you don't hear very often. I really think the most important thing is for the patient to make his or her own decision about what is best for him or her with all the information that's available. For many people, more aggressive treatment is appropriate. So I'm not here criticizing and saying that mastectomy is always wrong or radical prostatectomy is always wrong, hysterectomy, et cetera, things like that. Let's look at the issue that she raised with how much tissue should be removed at the time of surgery. For breast cancer, I did some of my own little mathematics on several of the studies I told you about -- I think I mentioned about nine studies of women who had been treated

with lumpectomy alone. And in those studies, the margin of excision varied among the various investigators. And once you got out to about 2 centimeters away from the tumor, you really had done about all the good you were going to do in terms of reducing local recurrence. That's what you're trying to do. So I'm going to give you an example of an aunt of mine, who used to live here in Washington, D.C., and she had a breast cancer. She had had previous surgery, and she couldn't really have radiation to her upper chest wall, because it just wasn't appropriate. So she was then faced with, well, shall I have a lumpectomy only? Or should I have a mastectomy, maybe a reconstruction? So in her situation now, the mathematics works out this way, that if she has the tumor removed and she has a margin excision of about 2 centimeters in all directions, her local recurrence rate is going to be somewhere around 10 percent. That's just what the odds are. If she went and had the radiation, if she'd been able to have it, it could have reduced it down to less than 5 percent. So there is that advantage of the radiation, of being able to reduce local recurrence. But as I said, it doesn't really affect survival very much.

QUESTION: Are you going to speak to other research on women's cancers other than surgical, such as tamoxifen, such as soy?

DR. EVANS: No, I think in a minute, we're going to hear about some of the CAM research.

QUESTION: Oh, okay.

DR. EVANS: Yes, we're going to address both of them. I'm really on the front end, and then --

QUESTION: Got you.

QUESTION: I have a question regarding cervical cancer, that you're saying now that research has shown maybe like a lumpectomy of the tumor --

DR. EVANS: Right.

QUESTION: Of Stage II-B where you've got ----- involvement, and further up, or what -- because my mother just went through it, and they recommended no hysterectomy. Nothing surgical. Radiation.

DR. EVANS: Radiation?

QUESTION: Chemotherapy is the standard of care that's out there -- that's from Duke University. So I'm just curious. What is your comment to that?

DR. EVANS: Yes. Well, obviously -- I mean, I think that Dr. Dargent has done a couple of patients that maybe II-B -- that may be a little -- that may pushing it. I mean, I think the principles are pretty fundamental, that you really ought to be able to remove all of the obvious cancer with your excision, and depending on the age of the patient, if the patient wants to have future children, then you need to have a competent cervical os, so that she can have the child. But if she's not going to have future children, then maybe you can do a little bit more.

DR. DOBS: Thank you. We're going to take one more question, and then we're going to move on to the next speaker.

QUESTION: Could you comment on the no surgery -- in view of no surgeries, particularly concerning some of the evidence that certain cancers, particularly breast being one of them, reduce substantive endostatin and inhibit growth of metastatic ----- . Do we have any data on what happens when you don't have the surgery?

DR. EVANS: I think that every woman that has a cancer in the breast needs to have it removed. I've seen other approaches; I've seen it destroyed using radiation with rods and things like that, which to me are much more cosmetically unacceptable than just going ahead and making a little incision and taking the tumor out. But I don't know of any cases where I would tell a woman who came into my office with a breast cancer that I think you need to leave it alone, because of some sort of -- the endostatins or whatever it is that you're talking about. I'm somewhat familiar with the theoretical presence of these substances. But I don't think we're at a stage yet where we can distinguish between those women who can safely have the tumor left in and those that can't. So I would remove them. Every woman who has a breast cancer, I think, needs to have it removed.

DR. DOBS: Okay. Thank you very much, Dr. Evans, that was great. Our next speaker is Mary Beth Augustine. We actually have two speakers here. We have her and her little fetus here. Anyway, Mary Beth is a registered dietician. She's a certified nutritionist for New York State. She runs a private practice in New York and also works at the Beth Israel Center for Health and Healing. She's going to talk to us today about essential fatty acids, soy, botanicals, all those kinds of things that we want to know how they affect, if they affect, in which ways can we combine them with breast, ovarian, and cervical cancers. Thank you.

MS. AUGUSTINE: Since it's obligatory to start with a joke, you kind of stole it -- that's what I was going to say -- that contrary to popular appearances, this is not a lecture on pregnancy after cancer survivorship. But I am a cancer survivor. I'm a health care professional. So I'm honored to be here today. Should I go into labor, I also know I'm in the right room. We have lots of professionals. What I wanted to talk about is basically dietary supplement use in conjunction with conventional treatments, and just go over very briefly, before I get into the research, some of -- because I think, as much as it's a clinical issue and as much as it's a research issue, it's hugely a patient care education issue. So I want to just discuss a moment on informed shared decision making and assumption of risk, covering treatment choices, and I think that's really important, because I mean, even here today, I'm fielding questions about what patients are doing in the absence of evidence. So I think it behooves us, really, to help guide them to make a decision based on the strength of evidence or the lack thereof. The one thing that I think really is critical to make your patients understand is assumption of risk. And we know that with conventional medicine, that all treatment choices have risks. When I was diagnosed with Hodgkin's disease, I had a choice: Did I want to do MOPP or did I want to do ABVD. I had to choose one regimen that had more cardiotoxicity, one that was more ovotoxic. I chose the one that was more cardiotoxic for me, because I thought, well -- actually, I chose -- yes, that's what I said. Even though I was 22 years old, I said I'll go with the one that's more cardiotoxic because -- I'm getting confused -- I went with the one that was more ovotoxic, because I wanted to be around. I figured if I was dead from heart disease, what good were my ovaries? And I'm happy to

say I made the right decision. But assumption of risk is something that we balance every day, the realization that all treatments have choices, and this absolutely applies to using dietary supplements. So getting that across to patients is critical, that even if they're natural approaches, that there are risks, and that safety does not necessarily mean the absence of side effects. Safety is basically a low incidence of side effects. So this is something that, in patient education, I feel it's critical to tell your patient right away, about assumption of risk and safety, meaning really that there is a lower incidence of side effects, not that they are absent. What I do with patients is basically what I'm going to do with you today, a nutritional consultation where I walk them through the evidence that is out there on the use of melatonin, IP-6, green tea polyphenol abstracts, MSM-3, MGN-3, in the use of women's cancers. So it's not that I'm advocating the use of these, but I'm trying to get them to understand and make an evidence-based approach to informed shared decision making.

MS. AUGUSTINE: -- and some of terms that I use with patients are really to get them to think in terms of a decision making framework about the strength of the evidence. Is the strength of the evidence convincing? Is it probable? Is it possible? Is it insufficient? Or is there limited data available to support or reject a judgement? This is the process we go through every day when we evaluate something. Why not teach them that? I think there's definitely a role here in social work for patient advocacy and decision making in complementary therapies, because this takes a lot of time, to educate the patient, and if I've got an hour to meet with them about diet, nutrition, and managing their oral and gastrointestinal side effects -- oh, and, yes, let's talk about these agents -- it's very difficult. So I think there's really a strong role here for patient education and informed shared decision making. This is really basically how I explain to my patients the strength of the evidence, how it decreases. As health care professionals, we're all familiar with this. Safety. One of the things I encourage them to think about when we do talk about safety is, you have to use qualifying terms because there is not complete safety. Is it likely safe? Possibly safe? Possibly unsafe? Likely unsafe? Or unsafe? Or is there limited data available to support or reject a judgement? I go through the concept of a dose response relationship, different doses affecting safety, different uses or routes of administration affecting safety, a product may be effective but be unsafe, and that no product is safe for all people all the time. And I make it clear to patients that efficacy really differs depending upon use. What may be good for one cancer may not be specific to another cancer. And I go through the same qualifying terms with efficacy about likely and possibly. But what I'd like to do is go to some of the research in women's cancers and co-enzyme Q10. Most of the data that I found on women's health cancers, women's cancers, really, the bulk of it is with breast cancer. I included as much on ovarian and cervical cancer as possible. There are still, as we know, not enough human trials. A lot of animal studies, a lot of in vitro studies with different cancer cell lines -- breast, prostate, ovarian, cervical -- and where applicable, I did include some information from other cancers -- prostate, colorectal, hepatic -- just because it may have supported some of the literature. So for co-enzyme Q10, they did a study looking at malondialdehyde levels, antioxidant enzymes, and co-Q10 measured in tumor and surrounding tissues of 21 breast cancer patients. The results were that -- and I'll talk a little bit about cell culture slides before I discuss the human -- the co-enzyme Q10 significantly was decreased; MDA levels were much greater in tumor tissue; and antioxidant enzyme was significantly increased in the tumor tissue. With 200 women hospitalized for breast biopsy and/or tumor ablation, 80 who had carcinoma and 120 with nonmalignant lesions, the results were that co-Q10 deficiency was noted in both carcinomas and nonmalignant lesions, and correlation was observed between the deficiency of the co-Q10 and the disease prognosis. In some promising

animal studies of co-enzyme Q10 on cardiotoxicity, we have seen studies with doxorubicin-induced cardiotoxicity, adriamycin as well, and, you know, some good results with ejection fraction. Now, more and more people are looking at co-enzyme Q10 in reducing tumor burden and not just supportively reducing cardiotoxicity. But there's a lot more data on the cardiotoxicity. In an uncontrolled clinical study in Denmark that I think was reported on here last year at Comprehensive Cancer Care, they had 32 node-positive breast cancer patients treated with conventional therapy plus a number of nutrients: Co-enzyme Q10, antioxidants, and essential fatty acid. The dose used was 90 milligrams a day of the co-Q10. The outcome was that no patients died during the study. The expected number was 4. There were no further distant metastases. The quality of life improved. There was no weight loss, less pain meds. And six patients showed apparent partial remission. In a follow-up study, one new patient and one of the patients who had a reported remission were treated with high doses of co-enzyme Q10 for 3 to 4 months. Both the patients had breast cancer remaining after surgery. After a period of high-dose co-enzyme Q10 -- we're talking 390 milligrams per day -- both patients appeared to experience complete remission. There is a lot of criticism of these studies, in selection bias; they were also given multiple nutrients, so it was hard to weed out were the benefits attributable to just co-Q10. In a third study conducted by the same researchers, three breast cancer patients were given high-dose co-Q10 -- again, 300 to 400 milligrams a day -- and followed for 3 to 5 years. One patient had complete remission of cancer that had spread to the liver. Another had remission of cancer that spread to the chest wall. And the third had no evidence of breast cancer remaining after surgery. When I talk a little bit about antioxidants and essential fatty acids, I'll mention the doses that were used in the study. Green tea. The data looks much more promising here. In a perspective cohort study of 8,000 Japanese women, 10 Japanese-size cups of green tea per day -- and I like it that they emphasize the Japanese-size cups, because here in American where everything is super-sized, and you know, you get your 12 or 16-ounce cups of coffee, the Japanese-size cups of green tea are 4 ounces as opposed to our 8, 12, or 16 here. Well, there is no data to say how many ounces were drunk per day. You can guess, roughly, based on the average dietary intake of a 4-ounce cup, that would be about 40 ounces per day of the green tea. But what they said was that increased tumor latency period in 472 cases of stage I, II, and III breast cancer, increased consumption of green tea was associated, yet nonsignificantly, with the increased number of auxiliary lymph node mets for pre-menopausal breast cancer and increased expression of progesterone receptor and estrogen receptor for post-menopausal breast cancer. Recurrence rates on a 7-year follow-up were approximately 17 percent for greater than or equal to 5 cups a day, and 23-1/2 percent for less than or equal to 4 cups a day. The relative risk of recurrence was 0.564 after adjustment for the lifestyle factors. The hospital-based epidemiological research program at a cancer center whose name I can't pronounce, which they've conveniently put into an acronym, HRPAC, 1160 Japanese women with breast cancer with cases diagnosed between 1990 and '98, the hazard ratio assessed for recurrence with reference to green tea consumption -- what you saw was the decreased hazard ratio adjusted for stage observed with consumption of greater or equal to 3 cups a day. So that's kind of the close to the 4 to 5 cups in the other study, again, these being Japanese-size cups. And the hazard ratio was 0.69, which was significant in stage I and a similar tendency for stage II, but there was no correlation with stage III cancer. This was an interesting study. Fifty pre-menopausal Japanese women assessed for the effective caffeine-containing beverages on sex hormone binding globulin and estradiol levels. They looked at black tea consumption, green tree, Oolong tea, cola, and coffee. High intakes of coffee, green tea, and total caffeine were correlated with increased SHBG, and green tea, which I thought was of note, but not other beverages, was significantly inversely correlated with estradiol levels. So that's just

another benefit there. Curcumin. In epidemiological studies, dietary turmeric intake is associated with decreased incidence of breast, stomach, oral, and skin cancers. In animal studies, dietary curcumin inhibits chemically induced spore stomach duodenal and colon carcinogenesis. In animal studies of radiation-induced mammary tumor initiation, dietary curcumin significantly decreased tumor incidence, increased the latency period. Interestingly, a study with pregnant rats showed no change in litter size, body weight, teratogenicity, or toxicity. Now, how do you apply their dietary intake to our dietary intake of turmeric? But in India, the estimated intake per capita intake of turmeric per day is 6/10ths of a gram per day -- does that sound like a lot to people here? Sixth-tenths of a gram, 600 milligrams? Put it in context with an American diet that contains salt, a minimum of 4 to 6 grams per day, we're still getting 15 times more salt and no protective benefits from the turmeric, so. Curcumin inhibits nitric oxide production in rat mammary glands. Curcumin is one of a number of natural compounds with selective COX-2 inhibitor activity and may therefore have a role in chemo prevention of cancer of the colon, liver, breast, pancreas, prostate, lung, skin, and urinary bladder, according to an article in Drug Metabolism and Drug Interactions. Curcumin extract demonstrated cytotoxicity in in vitro studies of ovarian cancer cells as well. Not a lot on ovarian cancer with the curcumin. Curcumin showed inhibition in vitro in multi-drug resistant breast cancer cell lines in a time and dose-dependent effect. Curcumin also has demonstrated cytotoxic antioxidant anti-inflammatory activities against leukemia, colon, central nervous system, melanoma, renal, and breast cancer cell lines. And then in a study looking at the effect of pesticides and environmental pollutants, the pesticides DDT and 4-nonlphenyl and 4-ocetylphenyl were investigated for their effects on estrogen receptor-positive and -negative breast cancer cells, and a combination of curcumin and genisteine inhibited growth of estrogen receptor-positive cells by up to 90 percent, and to a lesser extent, in estrogen receptor-negative cells. I'm going to comment very briefly on genesteine and soy in a few minutes. Melatonin. A lot of data on melatonin. In animal studies, melatonin alone decreased tumor incidents and multiplicity and increased the tumor latency period. This was in, I think, DMBA, dimethylbenzo-anthracene-induced mammary tumors. Melatonin in drinking water significantly inhibited cervical and vaginal tumors. And in a study of 250 patients with metastatic cancer, 27 with head and neck cancer, 42 with GI tract cancer, 104 with lung, and 77 with breast, all with poor clinical status, given chemotherapy alone -- for breast they used doxorubicin, paclitaxel, and mitoxantrone -- so they were given either the chemotherapy alone or chemotherapy plus melatonin, 20 milligrams PO QD -- the one-year survival rate and tumor regression rate was significantly greater in patients given chemotherapy plus melatonin. Also observed were reduced frequency of thrombocytopenia, and there's another study to support that, another in vitro study; neurotoxicity, cardiac toxicity and stomatitis. In a phase II study, 14 females with metastatic breast cancer, treated with epirubicin weekly and weekly administration of 20 milligrams of melatonin, also daily, times 7 days before chemotherapy, before each chemotherapy cycle, they had normalized platelet counts during their chemotherapy administration, allowing the therapeutic administration of the chemotherapy without stoppage. So that's pretty significant. In a phase II study of tamoxifen plus melatonin in metastatic breast cancer, 14 patients with disease progression were treated with tamoxifen plus 20 milligrams of melatonin orally per day. A partial response was observed in 4 out of 14 patients, or 28-1/2 percent with median duration of 8 months. Insulin growth factor 1 levels also significantly decreased in melatonin responders and no toxicity was observed. And I think last year also at Comprehensive Cancer Care, Dr. Lisoni came and spoke about much of the work being done with melatonin in Italy. Melatonin and combination therapy in animals. Melatonin alone and melatonin plus retinoic acid decreased tumor frequency. I think this is mammary tumor

frequency. If I didn't put it, it was pretty much chemically induced mammary tumor in rats. Melatonin alone and indomethacin plus melatonin had a pronounced chemo-preventive effect. And melatonin plus 9-cis-retinoic acid decreased tumor incidence 5 percent compared to controls. That's a number wrong there -- oh, no. Yes, decreased the tumor incidence down to 5 percent compared to the controls with 55 percent. Melatonin and suboptimal tamoxifen study. Melatonin significantly suppressed second-generation tumors and increased the latency period. Suboptimal tamoxifen alone did not suppress the second-generation tumors, and tamoxifen and melatonin had no additive synergistic effect beyond that of melatonin alone. And tamoxifen and melatonin suppressed tumor incidence to 0 percent, which was comparable to tamoxifen alone, also in rat mammary tumors. It's good to be a rat and have breast cancer. Okay, melatonin combination therapy, vitamin D and vitamin D analogs.

QUESTION: -----

MS. AUGUSTINE: Yes, I did not focus at all on pharmacological, pharmacokinetics, or mechanism of action, because it's all proposed, it's all theoretical, and I'd be in a 20-minute discussion about, you know, circadian rhythms and -- so, no, there's not a lot. That's one of the things that I was basically closing with, is that these are the types of studies we need more of, you know, mechanistic studies, dose escalation studies, et cetera. And any study, obviously, can be disproven. Animal studies. Rats given vitamin D analogs had 53.3 percent tumor incidence and 1.22 tumors per rat, versus an 80 percent incidence and 1.6 tumors per rat in control animals. The vitamin D3 analog -- and most of the analog studies are done because of the limiting effects of using active vitamin D, their hypercalcemic effects. So it's just kind of a battle to find analogs that are less calcemic. Vitamin D3 analog and paclitaxel on breast cancer cell lines in vivo. D3 analog had greater effect than paclitaxel alone and exhibited an additive effect when combined with paclitaxel. And combination therapy with paclitaxel's ----- vitamin D analog inhibited breast tumor weights by 83 percent, again, all in animal studies. And in in vitro studies -- I'm not sure if this is a vitamin -- it must have been a vitamin D analog -- inhibited human breast, ovarian, prostate, and myeloid leukemia cancer cell line growth, and human studies, a phase I dose escalation trial with 36 patients where they were really looking at just the hypercalcemia, not disease progression, although they have some data on that, 36 patients with advanced breast and colorectal cancer -- 6 patients were treated for greater than 90 days, and they showed stabilization of disease. Adverse affects were dose-dependent, with all patients experiencing hypercalcemia at the highest dose. And there was a suggested dose, which I didn't include in here. I think it was like -- I don't want to guess at the number, but a suggested dose that was kind of halfway in the range that was the most tolerated. Omega-3 fatty acids from fish and flax seed select studies. Rats fed high omega-3 diet had a 31 percent lower tumor growth versus controls. Melatonin plus omega-3 fatty acids from flaxseed oil significantly decreased tumor multiplicity and volume with omega-6/omega-3 ratio, close to 1 to 1 in the diet, which is astonishing. Does anybody know what the omega-6/omega-3 ratio of the typical American diet is?

QUESTION: Six to one, six omega-6.

MS. AUGUSTINE: I've heard 20 to 30 to 1. I've heard optimal would be in the neighborhood of anywhere between 4 and 10, according to the literature, if you're looking at some of the atherosclerosis reports journals and lipid journals. But optimal is anywhere from 4 to 10, and now some practitioners are recommending closer to even this 1 to 1 ratio. But 20 to 30 times

more omega-6 than omega-3 in the standard American diet. Four percent DHA added to a 20 percent fat diet partially suppressed growth of human breast cancer cells in mice. The 20 percent fat diet is what's being advocated in the Wind study. Fifteen percent is what they're looking at, but preliminary data at the Women's Intervention Nutrition Study is suggesting a 20 percent fat diet for patients with breast cancer. Fish oil-enhanced CPT-11 efficacy against human breast cancer cells in mice and reduced intestinal side effects, which is pretty significant, given the copious diarrhea that these patients go through. So if you can have enhanced CPT-11 efficacy, perhaps using a lower dose, less intestinal side effects, that would be fabulous. Not any human studies on it, though. High dietary fish oil enhanced the efficacy of mitomycin-C treatment of human breast cancer cell line in mice versus the control, a corn oil diet, and significantly increased tumor antioxidant enzymes. In rats with human breast cancer cell xenografts, postsurgical treatment with EPA and DHA inhibited lung mets versus controls, and there are a few studies supporting that. But again, how long after surgery? In the rats, you do it for 7 days. In humans, you know, and the dose. Trying to extrapolate to humans is so difficult. And rats fed high omega-3 fatty acid diets had significantly decreased cyclo-oxygenase-1 activity by 28 percent and COX-2 activity by 36 percent versus controls. Okay, calcium D-glucarate inhibits chemically induced rat mammary tumors alone or in combination with suboptimal doses of 13-cis retinoic acid or 4 hydroxyphenylretinamide -- big area, the retinoids and calcium D-glucarate. It inhibits chemically induced hepatic carcinogenesis in rats and decreases rat colon aberrant foci formation and intestinal colon carcinogenesis. I can tell you, a lot of my patients are taking calcium D-glucarate without a lot of human literature to support it. And they're not happy just hearing that dietary glucarate is in oranges and broccoli and potatoes. They don't want to hear that. They want to take something that's going to alter their disease progression. Maitake D, which -- I don't know if it's a session this year, but I know that there have been sessions on this in past years here at Comprehensive Cancer Care. Animals in -- well, actually, I guess -- there are about six different compounds from mushrooms that have been pretty well studied. Lentinan from the shiitake mushroom and maitake D fraction from the maitake mushroom, schizophyllan, which I can't pronounce, actopexos (phonetic) correlated compound, which is a proprietary extract from several different species. Polysaccharide K, polysaccharide P. Polysaccharide K and polysaccharide P have been investigated more in Asia versus here. There's a lot more research being done with maitake D fraction. There was a recent article in *Alternative Medicine Review* discussing the use of polysaccharide P and polysaccharide K in clinical trials in China, and there was some data on significantly extended 5-year survival in esophageal cancer with polysaccharide P and with polysaccharide K in Japanese trials in extended 5-year survival in cancer of the stomach, colon, rectum, esophagus, nasopharynx, lung, and a subset of breast. Again, here in the United States, most of the research is being done with maitake D. There are two classes of polysaccharides that are getting a lot of investigation: The beta-glucon polysaccharides, which are made of glucons found in oats, barley, and mushrooms; and the oligosaccharides. And other than cancer care, they're also being investigated for their benefits in hypertension, hyperlipidemia, hepatitis, and HIV. Animal studies of maitake D demonstrated anti-tumor activity in induced breast, lung, liver, prostate, and brain cancers. In vitro studies of maitake D have demonstrated increased natural killer cell activity and increased interleukin-1 production. In vitro prostate cancer cell lines -- maitake D demonstrated 95 percent cytotoxicity. And low-dose maitake D plus vitamin C demonstrated 90 percent cytotoxicity, and I mean very low-dose, and low doses of vitamin C. I was surprised that there was such efficacy. MGN-3. MGN-3, a lot more patients are inquiring about nowadays. It's basically an extract from rice brand that has been modified by enzymes from different mushrooms, mainly maitake. In vitro

studies show that MGN-3 is a potent tumor necrosis factor alpha inducer, and also in a dose-dependent effect, and increases production of interferon gamma. That was just published last year. In vitro studies with MCS-7 breast cancer cell lines showed arrested cell growth and increased production of interleukin-10 and interleukin-12. In vitro studies suggest that MGN-3 used in combination with low levels of recombinant interleukin-2 may significantly potentize the effect of recombinant interleukin-2. Results showed that MGN-3 and recombinant interleukin-2 increased natural killer cell activity by 140 and 180 percent respectively. Interestingly, a synergistic effect on natural killer cell activity was noticed post-cultural peripheral blood lymphocytes with MGN-3 and recombinant interleukin-2 to 332.7 percent of control, a staggering number. The conclusion was that, given immunotherapy with recombinant interleukin-2 appears to depend upon the administration of high doses frequently associated with excess of toxicity, the immunomodulatory function by a low concentration of recombinant interleukin-2 on anti-tumor activity by natural ----- cells could be greatly augmented by the concomitant use of MGN-3. And this author -- I think he's also presented here last year his work -- I don't recall where he is if he's in the United States -- MGN-3 examined in 27 cancer patients, 7 with breast, 7 with prostate, 8 with multiple myeloma, 3 with leukemia, 2 with cervical cancer, undergoing conventional therapy, given 3 grams of MGN-3, which seems to be the typical dose -- and that's something I'm very clear with my patients also when we talk about -- it's not what is the recommended dose; it is what is the typical dose, the dose typically used in studies, because if they hear "recommended," that's what they hear -- "You recommended this." But given 3 grams of MGN-3 orally daily, natural killer cell activity assessed at baseline 2 weeks, 3 months, and 6 months, the results -- the low baseline natural killer cell activity, which was in the range of 10.8 to 40 percent, increased in all patients at 2 weeks, with breasts having as much as 154 to 332 percent increase, and cervical, 100 to 275 percent increase in natural killer cell activity, and continued to rise, yet less slowly, at 3 and 6 months. And that was presented at the American Association of Cancer Research at their 87th annual meeting, the proceedings from 1996. IP-6. Inositol hexaphosphate-6, which is also a brand derivative, in animal models of chemically induced mammary tumors and human breast cancer cell lines in vitro demonstrated reproducible and striking anti-cancer action of IP-6. In DMBA-induced rat mammary tumor genesis, IP-6 alone and IP-6 plus inositol in the drinking water resulted in a significant reduction in tumor incidence and multiplicity. And they actually looked at if they were to give gavage brand in very high dosage to get the similar amount of IP-6, was it as effective. And I think there was such significant gastrointestinal side effects from that high, high-dose brand, the conclusion was that using the IP-6 extract was preferred. Very limited data on MSM, methylsulfonylmethane. In animal studies -- yes, a lot of patients are taking it. It's a precursor source of sulfur, for cysteine, and methionine. In animal studies in DMBA-induced mammary tumors and DMH-induced colon cancer, MSM significantly decreased the latency period and resulted in fewer poorly differentiated tumors. No weight loss or toxicity was observed -- I'm sorry, I don't have a citation for that -- but there's very limited data on MSM. What else did I want to tell you? Propolis. Two recent studies in animal studies, extracts of propolis, decreased chemically induced mammary tumor incidence and multiplicity in a dose-dependent manner. And I am seeing more and more patients taking propolis. I think they're reading the literature as much as we are. And in vitro, it inhibits growth of MCS-7 human breast cancer cells, induces apoptosis, and decreases estrogen receptor protein expression. Antioxidants. This is how I feel about this. The big question. When I spoke with someone beforehand, I really -- antioxidants and soy, there are two sessions being dedicated to this topic today. There are international symposiums held on the soy issue. This is the most vexing -- I know you all are familiar -- this is the most vexing issue in patient care

today, but that's dermaceptor-positive breast cancer. And I'm familiar with the pro literature; I'm familiar with the con literature. There's going to be a great presentation on it today. And I really just didn't want to even -- it would take 20 minutes just to give a very brief overview for each soy and antioxidant, so I kind of just went with the big questions. Black cohosh -- does it have estrogenic action? Many patients with a surgically induced menopause are taking lots of natural alternatives to hormone replacement therapy, and there are a lot of contradictory results as far as black cohosh, does it have estrogenic action? In vitro estrogen receptor in progesterone receptor binding acid is a red clover chaseberry, hops, Dong Quai, and licorice were done and reported in a journal in May 2001. Red clover, chaseberry, and hops all demonstrated significant estrogen receptor binding and increased presenilin-2, which is an estrogen-inducible gene in breast cancer cells. Dong Quai and licorice showed only weak estrogen receptor binding. Chaseberry also demonstrated progesterone receptor binding. Black cohosh showed no estrogenic activity. In vivo in ovary-optimized rats, black cohosh exhibited significant dose-dependent inhibition of radial labeled estradiol binding to estrogen receptor. I think this is an area that is still inconclusive. Limited data available to support or reject a judgement, basically, I tell patients. And I think that was pretty much it. There are tons of supplements. I mean, you could get into shark cartilage and every other supplement under the sun. What does the data show in women's health cancer?

DR. DOBS: Well, that was a little overwhelming. I learned so much. I never heard of some of these things. And I think that goes to show how difficult it is for us as health professionals or as individuals who are requiring health assistance to have to face with this overwhelming amount of information. And I think that Ms. Augustine has really brought up some very important issues of what is the balance of the risk versus the benefits of treatment, and a lot of that information really is not available yet, and it's a very difficult decision. We try to think in terms of evidence-based medicine, and it was brought up that there's a wide range of that. We've gone from anecdotes to randomized clinical trials. And unfortunately, we don't have much in the way of evidence here. Most of the stuff is from small sample size. Our goal is to help women with cancer, obviously, and to try to provide them with as much information as we can. Everything has side effects. Walking into a hospital, walking into a room with vents may have its side effects. And I think we have to be sensitive to this when thinking in terms of how to counsel women, and thinking in terms of safety, we're always -- there is no just broad statements about safety, but rather, what is the dose, what is the disease, what is the host, who is the person, and how are they responding to a particular issue when it comes to safety? Ms. Augustine went through several specifics of diseases. Again, many of them I'm not very familiar with at all: Co-Q10, green tea. I think this issue of emphasizing amounts is very important. Ten Japanese cups is equal to, what are we saying, 5 U.S. average cups, is that what you would say?

MS. AUGUSTINE: Uh-huh.

DR. DOBS: I mean, I think that's a lot of green tea for most people, a lot of tea.

MS. AUGUSTINE: And then if you start to question it, I mean, there's data out there on oxygen - ----- absorptive capacity, should they do it with X-rays or -----.

DR. DOBS: I think there are a lot of issues. The whole issue of hormones is one that I am, as an endocrinologist, particularly interested in, what it really does to the same hormone levels. These

are some other specifics that were mentioned. A few things I felt were interesting is that curcumin may be a natural COX-2 inhibitor, and there is some suggestion that that may have some anti-cancer effects. On melatonin, I thought it was interesting mentioning that it may reduce the incidence of thrombocytopenia, which is low platelets, which is a common side effect of chemotherapy. So it suggests that some of these dietary supplements may have important use in combination with chemotherapy, because it might prevent some of the side effects. These are some other things that were mentioned: Vitamin D, calcium glucarate, maitake D, MGN, and then IP-6 and black cohosh. Some of the statements -- I would say in summary that there really is an overwhelming choice of options now for women. Part of our job is to try to give some guidance on what's evidence-based or what is just in the form of anecdotes. Most of the studies suffer from sample size problems. There are some interesting questions about combination treatment of classical conventional chemotherapy in combination with CAM therapy. We have very little data on mechanism. I'm very concerned about safety issues with dietary supplements, and I'll give an example of phytoestrogens. A lot of women come to me and say, oh, this is great. I want to take phytoestrogens instead of estrogen itself. And one of my comments to this is that we don't even know much about estrogens themselves, and at least you know exactly what dose is to be given. I'm concerned about recommending phytoestrogens to any woman, because I have no idea what they're taking. I'm very familiar with a colleague of mine who is working on broccoli, and he has some beautiful data showing that the components, the nutrients, the micro-nutrients that exist in broccoli from stalk to stalk are vastly different. It really depends on how the plant is grown, what are the conditions that the plant is grown in. So we have a very big problem with standardization across dietary supplements. So that's what I have for a summary here.

MS. AUGUSTINE: That's great. Any questions?

DR. DOBS: Are there questions? We're going to take a couple of questions, and I know it was an overwhelming amount of information.

QUESTION: The information you gave about red clover, chaseberry, and hops, what was the implication for what you said about the genetic change? I didn't understand.

MS. AUGUSTINE: Basically that there is estrogenic activity is the bottom line, from them, but not the black cohosh.

QUESTION: Gene changing -----?

MS. AUGUSTINE: All estrogen receptor mediated gene expression from estrogen, basically.

DR. DOBS: And on the black cohosh they're doing studies now to see its effect on the endometrial lining, and they've done studies to see its effect on --

MS. AUGUSTINE: And there have been some studies that looked at FSH levels, LH levels, you know, vaginal mucosal cell atrophy. And it's just so inconclusive. One study says there is some action; one study says there isn't. And the studies that were done with women looking at hot flashes are also inconclusive, what is a significant reduction in hot flashes according -- so there are just a lot of contradictory findings.

QUESTION: I wonder if you would comment on prevention, any of the substances ----- about prevention.

MS. AUGUSTINE: I'm a nutritionist. The bottom line is, when it comes to prevention, I mean, of any chronic degenerative disease, 6 out of 10 of the top 10 leading causes of death have a dietary component. The basic thing I advocate is a plant-based diet with Mediterranean and Asian influences. If we're going to look at other cultures and their protective dietary intake, like looking at the Mediterranean diet, the high intake of garlic and high intake of olive oil and tomatoes and fruits and vegetables and grains, the low fat -- the high fish-eating society, same for Asia. Low-fat intake, fish-eating society, everybody seems to just think of soy and green tea, but they also eat sea vegetables, and fish. So, really, a plant-based diet, two-thirds plants to one-third animals, which is 2 out of 3 meatless meals or filling your plate with two-thirds plants -- it's as simple as that -- and emphasizing Mediterranean and Asian influences.

QUESTION: ----- clearly indicated -----?

MS. AUGUSTINE: From prevention? No. I mean, do I encourage my patients to use turmeric? Yes. Do I encourage them to use a lot of the spices that -- I mean, that the Nutraceutical Institute in Rutgers in New Jersey, Dr. Paula Chance is doing some excellent work there with rosemary, abstracts of rosemary, carnosol and ursolic acid as novel chemotherapy agents in animal studies. Do I encourage them to use rosemary? Yes. Or the extracts in lavender and cherries and different things. But when it comes to diet, going to a plant-based diet preventively, exercise, lifestyle -- everything we've been saying for years.

QUESTION: -----.

MS. AUGUSTINE: Yes, uh-huh, yes. A very controversial area. Yes, it's -- I mean, the idea of echinacea stimulating the immune system and -- you know, it's very unclear. I'm seeing a lot of patients at the Center for Health and Healing that are coming in with autoimmune disorders who are doing high-dose antioxidant regimens. But it's very limited data, very limited data. I think, yes, there's a potential for more harm than good there.

QUESTION: What's your position on dairy?

MS. AUGUSTINE: Dairy in the diet?

QUESTION: ----- going towards a ----- based diet.

MS. AUGUSTINE: I think there are pros and cons to dairy. I think there are some great nutrients in it that are being investigated, conjugated linolic acid ----- body fat composition, its immune-stimulating activity of whey -- I think there are a number of compounds in dairy that are great, beneficial. Not all populations can tolerate it. There's the issue of hormones. I saw a staggering number on the millions of pounds of antibiotics used. It was all in relation to the anthrax, of course. Twenty-six million pounds of antibiotics are used in our animals to prevent infection, whereas they estimate only 2 million pounds per year are needed to treat infections in our animals. And I think the comparison to what -- I think the whole U.S. population only takes 3 million pounds of antibiotics per year. So I feel very strongly about high-quality dairy and

poultry and fish and meat in general with hormone-free, antibiotic-free -- although the American Cancer Society would say that the data is limited. Less than 1 percent of all cancers, according to them at this time, could be attributable to pesticide, additives, dyes, and hormones, et cetera. But I think there's a lot of information on endocrine disrupters from pesticides, and I think in the next 10 to 15 years, we're going to find out a lot more how harmful it is.

DR. DOBS: One more question.

QUESTION: -----.

MS. AUGUSTINE: Yes, I think Dr. Dobs lit up a great point. I speak to health care professionals about the issues of quality control of supplements. I mean, I could do an hour lecture on quality control of supplements and what you look for is, you know, the supplement manufacturer -- how are they certified? Are they for good manufacturing practices? Are they certified for drugs, over the counter, or foods? So are they triple-certified? So you're looking at quality control issues. Did they get materials of analysis for their raw materials? Do they do HPLC analysis on the finished product, et cetera? So I think that some of the combination products out there have demonstrated anti-tumor activity, like if you were to look at the SEFT, yes, some of the herbs individually have demonstrated anti-tumor activity in in vitro studies. But in combination, when they've been tested by MSKCC or NCI, they haven't. So it's really hard. It's the type of thing I try to educate my patient on, with the goal being, you know, the benefits outweighing the risks. And if they're just wasting their money and there's no harm, or no harm that we know of at this time, that may be something I'd tell them, too, making sure that it goes in the medical record, whatever they're doing, so you can look for beneficial or adverse side effects. So not a real answer on formulated products versus individual nutrients.

DR. DOBS: Thank you very much. Just make sure all of you fill out your evaluations on the way out. Thanks.

(Whereupon, the PROCEEDINGS were adjourned.)

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