

CENTER FOR MIND BODY MEDICINE
COMPREHENSIVE CANCER CARE 2001

CONCURRENT: The Soy Controversy in Breast Cancer Treatment

SPEAKERS: Mindy Kurzer, PhD; Bill Helferich, PhD
COMMENTATOR: William Fair, MD
MODERATOR: Monique Class, MS, RN

Arlington, Virginia
October 17 through 21, 2001

P R O C E E D I N G S

MS. CLASS: Soy controversy and, as most of you are aware, epidemiological studies have shown that soy can have a preventive effect on breast cancer. Today we have some distinguished speakers that are going to over some of the data and answer some of the questions that I get asked on a regular basis, how many milligrams of isoflavones, is it better from foods? What types of foods; soy; tempeh? Should premenopausal women have different milligrams than postmenopausal women? So we're going to get a lot of these questions answered today, and they're going to review their data.

The way the flow is going to go is we're going to have Dr. Kurzer speak first, and then we're going to field a couple of questions, like 10 minutes of questions.

Then we'll have our second speaker, help me pronounce it again, Helferich. He was helping me on how to say it properly. Then he's going to speak and we'll take 10 minutes of questions.

Then Dr. Fair will kind of wrap it all up and summarize and make his comments. Then whatever time we have left, we'll take comments and questions from the audience.

Dr. Kurzer is a Ph.D. She teaches and performs research in human nutrition in the Department of Food, Science, and Nutrition at the University of Minnesota. She received her Ph.D. in nutrition from the University of California in Berkeley in 1984.

She was awarded a NATO postdoctoral fellowship in 1985 for which she performed research at the National Nutrition Institute. She was a postdoctorate fellow in reproductive endocrinology at the University of California, San Francisco, from 1986 to 1989; a visiting scientist at the University of Helsinki, Finland, in 1992; and a visiting scientist at the International Agency for Cancer Research, in Lyon, France, in 2000 and 2001.

Dr. Kurzer received the International Life Science Institute Nutrition Foundation Future Leader Award in 1993; a University of Minnesota College of Agriculture Distinguished Teaching Award in 1994; and the Ruth Pike lectureship, Pennsylvania State University Award, in 1995. So with great pleasure I introduce Dr. Kurzer.

DR. KURZER: Thank you very much for that introduction, and I think the organizers for inviting me to come here to speak about soy and breast cancer risk.

I am going to present my views of soy and the risk of breast cancer and we'll begin by talking a little bit about phytoestrogens which are hypothesized to be active components of soy that may be involved in breast cancer risk. Phytoestrogens are small compounds that bind the estrogen receptor and exert hormonal and antihormonal effects.

The particular phytoestrogens that we're going to talk about today are isoflavones which are concentrated in soy foods. There's another group of phytoestrogens called lignans which are found more widespread in plant foods, particularly whole grains, and flax seed is very high in lignans, but isoflavones are the particular phytoestrogens that we find in soy foods.

Here we have a little picture of the structures of estradiol and DES which you know is a very potent synthetic estrogen, in comparison to the structures of genistein and daidzein which are the two main isoflavones found in soy. You can see that there are tremendous structural similarities which account for the estrogenic and antiestrogenic effects of these compounds.

So first let's talk about what are people actually consuming. We know that Asian cultures consume soy naturally as a part of their diet and there are a number of estimates that have been made of the amount of soy that's typically consumed in Asia and the probable amount of isoflavones. The range is very, very wide.

You can see that in terms of grams per day, in Asian cultures it seems to be somewhere between about 20 and possibly 140. Isoflavones in milligrams per day in Asia, probably somewhere between 20 and 40. Recently there have been some studies that have estimated it a little bit lower than that. So I would say probably between 15 and 40 milligrams per day typically consumed in Asian diets.

In Western diets, the amounts are much, much lower, and you can see that in terms of grams a day of soy, Western diets consume very, very little, less than 5 grams per day, and the milligrams of isoflavones are 1 or 2 milligrams per day. So there is a huge difference between the isoflavone content of a typical Asian diet in which soy is incorporated as part of the diet, and a Western diet in which there is very little soy consumed.

We actually in Western diets to consume soy, which we don't realize because it's snuck into foods as soy protein, vegetable protein. If you look at labels and you see textured vegetable protein or something like that, that's a little soy protein that's used as a filler with meats, for example. If you eat at a cafeteria and you have a hamburger, there very well could be some soy protein in that.

In fact, my suspicion is that there has been so much interest in soy, now that soy protein has been approved for a health claim of improving heart disease risk, soy protein is probably going to be added to more and more foods. So without realizing it, we may actually be consuming more soy than we would think naturally on the basis of soy foods. That's something we could talk about later on.

What do we know about the epidemiology of soy and breast cancer, and this is really where the story began. It was epidemiologists who noticed differences in breast cancer risk between women in Asia, particularly Japan, with Western women. Much, much lower; potentially, a third lower risk in Asia. When women to this country, within two generations or three generations their risk is up to that of the Western women who live in the United States. So of course scientists look at environmental kinds of issues as being responsible, and soy foods because of the phytoestrogen content became a prime candidate for potential protection against breast cancer, mainly the thought being that possibly the phytoestrogens may act as antiestrogens and block the effect of endogenous naturally occurring estrogen and might actually prevent breast cancer risk.

So what do we know about soy and breast cancer risk within particular cultures? I was at first comparing the Asian women living in Asia with women living in the Western world, and we definitely know that there's a difference in risk there. But that could be due to many things involved in adapting to a new culture.

So what about within a culture what do we see? There are a number of studies. There are a couple of others besides these, but these are some of the main studies that have been done looking in

Asia and in Asian American women living in the United States to see what the relationship is between soy intake, soy food intake, and breast cancer risk.

You can see that one early study showed a odds ratio of .4 which means the risk was cut more than in half in premenopausal women consuming soy but not any effect in postmenopausal women.

Three of the other studies showed a nonsignificant, slight lowering, but not a significant effect. Then a study published in 1996 showed that there was a significant lowering of risk in Asian American women who were not born in the United States which is extremely interesting. And in Asian American women who were born in the United States there was no lowering, or a very, very slight, nonsignificant lowering.

So you can see that these studies were very difficult to do. Most of them were not designed to look at soy food intake. So the questionnaires may not have been designed properly to do that kind of study. So there are lots of limitations, but there's a hint that soy within a culture may lower risk of breast cancer, but it's clearly not a very, very strong effect from these studies.

In order to get around the limitation of the questionnaires, researchers more recently have looked at urinary excretion of phytoestrogens as an indicator of intake. They have looked at the relationship between urinary excretion of phytoestrogens and breast cancer risk.

Before going into the urinary excretion studies, a recent study published in 2001 looked at soy food intake during adolescence. They did a case controlled study of about 1,500 cases and 1,500 controls and they retrospectively asked what did these women eat when they were teenagers.

They also asked their mothers for the women whose mothers were alive the same questions. They found that adolescent soy food intake was inversely associated with breast cancer risk, a significant halving of risk, and the effect was significant for both pre- and postmenopausal women. When they looked at what the mothers had said, they found the same effect.

So whether the women answered the questions themselves or their mothers did, there was a significant lowering with retrospective adolescent food intake, and we'll talk in a few minutes about why that might be important.

Now let's take a look at the phytoestrogen studies. In 1997 Ingram published a study showing that increased excretion of urinary equol and enterolactone, two phytoestrogens, were associated with lowered breast cancer risk in Australia. Equol is a very, very interesting phytoestrogen it's only produced in about 30 to 50 percent of the population. The bacteria in our GI tract metabolizes, breaks down the phytoestrogens that we consume. Then we absorb those breakdown products and excrete them. Equol is one of those breakdown products that's only excreted in about 30 or 40 percent of the women. But it looks as though the women who excreted equol had a lower risk of breast cancer.

In a study in Shanghai, increased excretion of total urinary phytoestrogens was associated with lower breast cancer risk, a 50 percent reduction in the highest tertile and another study in Australia showed that breast cancer cases excreted lower levels of daidzein and a similar trend was seen with genistein. So these studies suggest that when you look at excretion rather than intake, there is an inverse association or a lowering of risk with phytoestrogen excretion. Most researchers assume that excretion is a good indicator of intake; possibly a better indicator than some of these questionnaires that have been used.

Now I'd like to spend a couple of minutes looking at some of the animal studies that have looked at the effects of soy or phytoestrogens on tumor growth in animals. One of the earliest studies was performed by Steve Barnes (?), and he actually leant me a few of these net slides, so I should credit him.

He showed in 1989 that a soy protein diet, this was soy chips, inhibits mammary tumors in rats. Here you can see either 5 or 20 percent of the diet given as soy chips lowered significantly the tumors per rat. The red is the control and the green and the yellow or the soy diets.

Another study published in 1998, very interesting. Goto (?) and others combined miso, a fermented soy product, with tamoxifen to look at the interaction because there is some concern that potentially soy could block the effects of tamoxifen. What they found was that when you compare the control with 10 percent miso, a significant lowering of tumors.

The tamoxifen, also they were about the same. When you combined tamoxifen and miso in these animals the tumor number was lower than with either one alone. So it looks from these data as though tamoxifen and soy together actually lowers tumors more than either of them alone.

The same researchers looked at animals that had already existing tumors, and when these animals had their tumors, they then divided them into three groups to look at what would happen to tumor size in the animals that already had tumors. They found that when the controls were looked at there was about a 60 percent increase in tumor size from the beginning of this part of the study.

The increase in tumor size was lowered in tamoxifen, but there was still an increase in tumors even with tamoxifen. But when miso and tamoxifen were put together, the tumors actually were reduced in size. So even in animals that already had tumors, it looked as though miso given with tamoxifen actually improved the effect of tamoxifen on these animals.

Now we've looked at soy foods, soy protein, soy chips, miso. More recently, studies have been done to look at the phytoestrogens themselves to see if the responsible component might be the isoflavones, the phytoestrogens. In 1996, Constantinou published a paper in which they gave rats genistein or daidzein intravenously. So this was not in a diet.

But they did find a significant lowering of tumors per rat in these animals that were given intravenous genistein. A more recent study in 2000 did the same thing with dietary genistein, and they found basically the same thing, that either dietary or intravenous genistein and intravenous daidzein lowered the tumorigenesis in these rats.

There has been a lot of interest recently, particularly from the Lamartiniere group in the potential effect of timing of exposure to phytoestrogens. I mentioned a couple of minutes ago that the study in China that looked retrospectively at soy intake in adolescents found that women who consumed soy in adolescence had a lower breast cancer risk.

There has been a lot of interest in the possibility that it may be that soy is important for prevention of breast cancer, and that the timing of exposure is important in that it needs to occur during the time of growth of the breast tissue.

So Lamartiniere has done a number of studies looking at this. In this study, genistein was given neonatally in new-born rats. What they found is that the animals who were given genistein had a much lower and significantly lower number of tumors per rat after 50 days. Of course, a carcinogen is given in these studies as well. So this neonatal exposure has a very significant lowering of tumors per rat.

Fritz (?) in 1998 published a study looking at genistein delivered perinatally in the mother's milk and they found again a significant lowering of tumors in the rats when they were exposed to genistein via the mother's milk.

So either perinatally, neonatally, and other studies have been done prepuberty in rats that have shown a reduction in tumorigenesis when the animals are exposed.

I'm not going to talk a lot about the mechanisms but I want to mention the proposed mechanisms. There have been lots and lots of very basic studies that have been done to look at this. These include tyrosine kinase inhibition, inhibition of DNA topoisomerase, inhibition of cell-cycle progression, induction of apoptosis, inhibition of angiogenesis, antioxidant actions, and antiestrogenic actions. Phytoestrogens, particularly genistein, have been found in cell culture studies to have all of these effects. Most of the research has been done with genistein, more than with any of the other phytoestrogens. It's mainly been genistein.

My laboratory has been interested in the hormonal effects and the potential antiestrogenic effects of phytoestrogens. So I just want to mention a little bit of the data that comes from my laboratory in that area.

A number of years ago we did a series of studies looking at the effects of a number of dietary flavonoids on the activity of aromatase enzyme. Aromatase enzyme is a rate-limiting enzyme in the synthesis of estrogen. So aromatase enzyme activity is considered a reflection of estrogen synthesis. So we could say that this slide is the effects of flavonoids on estrogen synthesis actually in adipose cells.

We looked at about a dozen different flavonoids, compounds that are either isoflavones or very closely related compounds that we find in foods. We saw that with many of these compounds there is a reduction in estrogen synthesis as you increase the concentration of these compounds.

Here I show a summary of some of the compounds, and the K_i reflects the potency. The lower the number, the more potent this compound is at inhibiting estrogen synthesis. Here you can see the K_i of amino-glutethimide which is a synthetic aromatase inhibitor that's been used clinically in the treatment of breast cancer. You can see that it's very potent, but there are some other compounds. Coumestrol is an isoflavonoid-like compound that's also found in soy; very, very potent inhibitor of estrogen synthesis. Biochanin A is a metabolite of genistein, and not as potent as amino-glutethimide, but also is an inhibitor of estrogen synthesis. Enterolactone is a lignan.

So we do know that these compounds in cell culture studies, in cell studies, so this is not in human studies, that they do inhibit estrogen synthesis, and if that happens in humans it's a potential mechanism that could be beneficial with respect to estrogen dependent diseases like breast cancer.

So now I'd like to show you a few slides that summarize some of the human data. There have been a number of studies, probably at this point maybe 30 studies, done in women consuming soy to look at hormonal effects. I'm going to summarize a look at a little bit of the data looking at premenopausal women where we've been interested to see when premenopausal women consume soy does it exert antiestrogenic effects that are reflected in alterations in the menstrual cycle length or altered hormone levels. So I summarized a few of the best studies in this area.

First let's look at estradiol, and you can see that the asterisks show significant effects, but in fact most of the studies have not shown significant effects of soy consumption on estradiol, and this is premenopausal women. But you can see that it looks like there's a trend toward a decrease, and it may be that our studies have not had enough subjects to show a significant effect, that we haven't powered them high enough, so that all we're able to see are trends. This is estradiol.

If we look at sex hormone binding globulin, we see no significant effects, but we do see a trend in the opposite direction from the direction we think would be beneficial. We would assume that an increase in SHBG would lower free levels of estradiol, and so the increase in SHBG would be in the more protective direction. But it looks like there's a trend downward when it comes to SHBG. None of these was statistically significant, however.

Progesterone, which a lowering would reflect potential anovulation weakened luteal phase which could be viewed as a protective effect. You can see that only two studies showed a significant decline but all of these studies showed a trend toward a decrease. So all the studies went in the same direction.

Only two of the studies looked at mid-cycle gonadotropins. One of them is a study in my lab, the Duncan study, and they both showed a significant decrease in mid-cycle gonadotropins which could influence ovulation and could potentially result in a weaker luteal phase.

Finally, a number of studies that looked at menstrual cycle length, epidemiologic studies have shown very strongly that increased menstrual cycle length is associated with reduced risk of breast cancer. It's thought to be because an increased menstrual cycle length reduces lifetime exposure to estrogen.

In these studies, only one of them showed a significant increase in length. But you can see that most of the others showed nonsignificant increases which when I looked at the data in this way, looking for trends, made me think that there very well may be something real that some of the studies have just not been able to detect because of problems with not enough subjects.

In our studies we also looked at estrogen metabolites, and the reason that we've been interested in estrogen metabolites, are any of you familiar with the 2 to 16 ratio of estrogen metabolites? So a few people are.

For a number of years, there has been interest in the possibility that certain natural metabolites of estrogen, compounds that we have floating around in our bodies due to breakdown of estrogen, that some of these compounds are potentially carcinogenic. So it might not just be the estradiol or even the estrone which is important, but perhaps some of these breakdown products as well.

The main ones that are thought to be potentially carcinogenic are the 16 alpha hydroxy estrones, and then the 4 hydroxy estrogens. Those are thought to be potentially carcinogenic. So a number of researchers have looked at either the levels of those compounds or the ratio of the 16 or the 4 hydroxy estrogens, the bad ones, with the 2 hydroxy estrogens which are considered to be benign estrogens.

In our studies, we've done that. I'm going to skip these slides here. I show the results from the premenopausal study, but we found very similar things with postmenopausal women. You can see that here we gave a controlled diet which actually contained about 10 milligrams of isoflavones because although we wanted it to be isoflavone free, the soy protein isolate when it's processed, they are not able to remove all of the isoflavones. So there were about 5 to 10 milligrams left.

The low isoflavones actually had about 55, and the high isoflavones about 130 milligrams of isoflavones. These numbers believe it or not are all significant; that there was a significant lowering of all the estrogen in the urine. There is urinary excretion. When we looked at the potentially carcinogenics, they also were lower. When we look at the ratios, the 2 to 16 ratio and the 2 to 4 ratio are all going in the beneficial direction. In other words, the potentially carcinogenic estrogens are at the bottom of the ratio. So they're all going in the beneficial direction.

When we look at this, the isoflavone intake increases these ratios in a beneficial direction. So all the estrogens in the urine were decreased but the bad ones decreased more than the other estrogens which is another potential mechanism by which soy could be beneficial with respect to cancer.

So that's as far as I'm concerned a summary of most of the evidence that suggests that soy may be beneficial, or isoflavones may be beneficial.

I want to mention a little bit of the negative evidence. I'm going to leave most of it to Bill Helferitz who is going to take that position in the next talk. But I'd like to mention a little bit of it just so that I can justify the recommendations I'm going to make at the end of the talk.

We did a number of cell culture studies in our lab looking at the effect of isoflavones on DNA synthesis in MCF7 breast cancer cells, and this DNA synthesis is thought to reflect cell proliferation or cell growth. What we found and others have found, I think Bill has done some of this research and other labs have too. What we found is that at low levels of exposure, and this is a cell culture study, there is actually an increase in DNA synthesis, and there is a decrease at very, very high levels.

When you look at these levels, the levels that are likely to be in the blood in women who are consuming soy are in this area right here, between 0.1 and 1 micromolar, right where there's an increase. So this really made a lot of us question whether with the natural circulating levels of these compounds if we're in a beneficial or a potentially negative kind of place.

I'll just mention very briefly some of the animal studies but I think Bill is going to be talking in much more detail about these because this is all his work. What he has found is that in mice who are already implanted with estrogen-dependent breast tumor cells, that dietary genistein or soy protein actually increases tumor growth.

So this is an animal that already has the cancer, as opposed to most of the other research which really looked at prevention. The bulk of it shows probable preventive effects in animals. But now there's a model looking at women who already have breast cancer, and suggesting that maybe there is some cell growth. One study looked at perinatal exposure to genistein and saw an increase in mammary cancers, and that contradicts one of the studies that I showed before.

These are all in animals. There are only a couple of studies in humans that have looked and found effects on the breast itself. In 1996 Petrakis published a study showing that the volume of nipple aspirate fluid which is thought to affect an estrogenic effect on the breast would increase in premenopausal women consuming soy. In postmenopausal women there was no effect.

Hargreaves in 1999 showed from a 2-week study of women consuming soy that there was an increase in the PS2 protein and a decrease in the apolipoprotein D in the breast. These two effects are thought to reflect an estrogenic effect. It's a weak estrogenic effect, so both of these studies show a possible weak estrogenic effect on the breast of premenopausal women.

But that's it for any human data showing a possible negative effect. There is no other human data that I'm aware of besides these two studies. So in my view, the bulk of the data show a beneficial effect, but there is some recent data that showed some reason for concern from animal. So now I'll share my conclusions.

Epidemiological studies suggest that both consumption of soy and excretion of urinary phytoestrogens are associated with reduced breast cancer risk. Animal models have shown that both soy and isoflavones prevent breast cancer. They've also shown that genistein inhibits the effects of tamoxifen.

On the other hand, cell culture studies have shown that isoflavones stimulate breast cancer cell growth at concentrations near circulating levels, and a few animal studies have shown that genistein stimulates breast tumors when given after tumors are established. And two human studies show that soy consumption causes weak stimulation of breast cancer cells.

I'm going to skip that point because I skipped over those slides.

So the timing of soy exposure may be crucial. It may be cancer preventive when consumed before cancer develops, and exposure to young animals may yield the largest preventive effects. After cancer the effects of soy are less clear. Because of concern stemming from animal and cell culture experiments, soy should probably not be part of a cancer treatment plan.

Now I'd like to share my recommendations. For women who have had breast cancer, there may be cause for concern, though at this point in my view the concern is theoretical because there have been no studies that have connected soy or isoflavone consumption with cancer in humans, but there is theoretical concern.

All high-risk women should avoid phytoestrogen supplements, the pills, because we know very little about their actions. All the studies in humans have been done with soy protein isolate or soy foods. We have no information about what happens when the pills are consumed.

Finally, for women who want to consume soy, consume an amount of soy in the range of typical intake in Asia, no more than one or two servings a day. In my view, it's very unlikely that that would be harmful even in women who are at high risk of breast cancer.

That's it. Thank you. Is there time for a couple of questions?

AUDIENCE: -----

DR. KURZER: A serving would be for example a half a cup of tofu would be a serving; 4 ounces, a half a cup.

MODERATOR: I'm going to ask if you have a question to come up to the microphone.

DR. KURZER: Yes?

AUDIENCE: Can you comment on whether the apparent difference in response to genistein or other kind of isoflavones may be related to the status of the receptors?

DR. KURZER: Yes, it's a good question, and I don't think we know a whole lot about it except that there are some data to suggest that the inhibition of cell proliferation by genistein may not occur through the estrogen receptor, that there may be other mechanisms besides the estrogen receptor.

So for example in our studies we saw the inhibition of cell proliferation at very high levels in both estrogen-dependent and estrogen-independent cells. But the cell growth that we saw at lower levels only occurred in estrogen-dependent cells.

So there does seem to be a difference, but I don't think that we have a lot of data to answer that question.

AUDIENCE: There are some situations where tamoxifen becomes stimulatory to the tumor. I was wondering whether there have been any studies done on the cells that have been cultured and shown to be stimulated by tamoxifen instead of the opposite effect. In other words, have you found anything in terms of the effect of soy on those cells ----- if they have a common receptor?

DR. KURZER: On particular cells that have been stimulated by tamoxifen?

AUDIENCE: Yes, or some of these tumors that have been grown in mice, whether there is any evidence that soy affects that the same way that tamoxifen does.

DR. KURZER: I'm not aware of that data.

AUDIENCE: For example, have you done any studies looking at the type of genistein in MD231 cells that are ER negative?

DR. KURZER: In MD231, yes. That's what I was saying, is that in the proliferation studies that we did we find that both MD231 and MCF7, so estrogen independent and dependent, both are stimulated at lower concentrations, but only the MCF7, the estrogen dependents, are inhibited at the higher concentration. So we don't see the inhibition in the MD231.

MODERATOR: This will be the last question, and then we're going to take questions at the end.

AUDIENCE: I'm here from ----- magazine which is the national women's cancer magazine. A lot of our readers who are breast cancer survivors are concerned about their younger relatives, the female relatives and are there any recommendations about how much young girls and infants should consume, and whether people in higher risk families may have a different relationship.

DR. KURZER: That's a great question, and I would say that some of my colleagues would probably recommend that all of those young women be consuming soy because of the strong data suggesting that there's prevention. I am very conservative. In lots of other ways I'm not. But around this kind of stuff, I would hesitate to make that recommendation. Though as I said, I think that if people are consuming the amount of soy in a typical diet which would be one or two servings of soy as a soy food, it's unlikely to be harmful, and it's potentially beneficial.

So to me the risk-benefit ratio goes in the direction of doing that, but just the amount -- like one or two servings a day at the most is what I would recommend. But I don't think we're at a point of actually saying do it, everybody. It's a little scary to make that recommendation because we don't know about the possibility that in some groups there could be some harm.

For example, I mentioned that in Asian American women born in the United States, there's a different effect than Asian women born in Asia. So maybe in Westernized populations it's different. We just don't know.

AUDIENCE: There has been some discussion about prepubescent girls and adolescent girls and that being an important time. Is there any data on infants and young children, that as an important time?

DR. KURZER: Yes. In the animal studies, the exposure was prenatal, neonatal, and prepubertal, all showed a benefit, all showed a reduction.

MODERATOR: Thank you. Now I'm going to introduce Dr. Helferich. He received his Ph.D. from the University of California in nutrition. Following his Ph.D. he was an NIEHF postdoctoral fellow in environmental toxicology. He was in the faculty at Michigan State University from 1988 through 1997. Since 1977 he has been an associate professor of nutrition in the department of food, science, and human nutrition at the University of Illinois. His research focuses on dietary soy estrogen and breast cancer, and I'm excited to hear his slant.

DR. HELFERICH: I mentioned to Mindy that I probably could have taken her slides and given the same talk. I think it's more important that we both give sides but that we don't polarize. I'm going to present a lot of our data that is in animal models, so the focus I'm going to do this afternoon is I'm going to just do a real general outline. I'm going to go through some of the background. I won't have to go through it very extensively because Mindy did a very good job with it.

I'm going to introduce this term paradox, and I think that that's a word that I like to use when I talk about genistein, and a word that I think is an appropriate word to use when you're talking about estrogen is a dilemma. "Time" magazine had -- on the cover of "Time," and it was several years ago. They had it in big bold letters, "**Estrogen: Every Woman's Dilemma.**" I think that's a real true statement. Without estrogen, a lot of the things that you enjoy as being a woman wouldn't occur, and with estrogen a lot of the things that you don't like wouldn't occur.

So it puts a bit of a dilemma, and these phytoestrogens actually present a real major paradox. The paradox that I'm going to talk about is the ----- effects and the estrogenic effects. Then what Mindy alluded to was there's a difference between ----- prevention and treatment, and I think that's a real issue because when you read most of the information that's out about soy is looking at ----- prevention, and most of the work that's done in nutrition regarding cancer and diet and cancer is all focused on preventing.

That is important because there's a lot of potential to prevent, but I think it's really important that there are very few people that actually do studies looking at what kind of diets should a woman with breast cancer do. Let me tell you, there's no lack of people out there making recommendations, and it's a serious issue to me because the recommendations are all over the place.

In general, it's Luke Skywalker and Darth Vader. When they pick our data, it's always they're making out like Darth, and when they pick up the positive data it looks like Luke. You don't find the positive data and the negative data in the same articles. It's always a very positive article or a very negative article, and that doesn't help the public.

So I think in this forum, I think Mindy was very, very balanced about the way I would have presented the talk. I don't think that you're going to see that we really have very many disagreements.

Asian women have a lower instance of breast cancer than when compared to those in Western cultures. Mindy made that very clear, and she made the point that the incidences approaches that of the host country if there's a second generation. So that if an Asian woman is here for one generation, they're protected. The second generation is almost similar to that of what an American would have, or a U.S. person would have.

In general though, Asian women consume less fat, high vegetable containing diets, and they consume soy as a dietary staple. This is the part that gets most of the focus.

----- the devil's advocate here. If you wanted to use a marker of a healthy diet, would consuming soy be a marker of a healthy diet in Asian women? This is the devil's advocate because there's a lot of the data out there, and the urinary excretion data suggests that when you have equal or isoflavone metabolites in the urine that the risk for breast cancer goes down twofold to 50 percent. That may be just a simple marker of the fact that these individuals have a good, healthy diet. To be somewhat flippant about it, you don't really see people consuming biscuits and gravy and soy.

It's not really what you would perceive. I think the data on soy is solid, and I think soy is a healthy food, but I think what you have to do is you have to be sure that you're not trying to convert an unhealthy diet to a healthy diet by eating something that doesn't taste good. It isn't that simple.

I think that that's the part that I see as an issue with regard to dietary supplements and the fact that the stuff can be advertised any way you would like and get it marketed.

The one thing that's been is Mindy has got a lot of my stuff covered. Mindy has exactly the same slide with a few different things on it, but the potential anticarcinogens in soy are the protease inhibitors, phytates, saponin, photosterols, all of these have lots of papers on them showing prevention of cancer, and in particular breast cancer.

The part that gets the most interest lately has been the isoflavones, and in the last decade about a thousand to two thousand articles have been published about genistein and its ----- effects. If you go back three or four decades, there's probably fifty articles published about it being a phytoestrogen.

This is what I would consider a paradox, that you have a phytoestrogen that is known to cause proliferation; estrogens are known to cause proliferation; but yet it also is an antiproliferative agent. Mindy's curve where she showed that upside down U, you have low concentrations of proliferative with high concentrations of antiproliferative, I think you can explain the issue there a little bit based on the dosage.

You have to get really high concentrations in the cell culture dish to be able to get the inhibitory effects, so that the issue of phytoestrogens occurred at very low concentrations.

So this was the paradox that I just alluded to is that you have a phytoestrogen that's antiproliferative and estrogenic, and that seems to be in direct contraction and that's what the paradox is, is an apparent contradiction.

The apparent contradiction can be resolved first by dosage. It can also then be resolved by the timing of exposure. I think what's nice is I'm going to hammer that point home, and Mindy already made. So I think you can leave with that message pretty effectively. A paradox is anything exhibiting an apparently contradictory nature, and I've bolded the term **apparently**.

This is where I think genistein was alluded to earlier. If you look at genistein by nutritionists or the health food fanatics, and I don't know how everyone would characterize that, they look at genistein as a cure all.

The EPA has characterized genistein as one of their model endocrine disruptors. If you go back about 25 years, the National Academy of Science had two books published and they listed naturally occurring toxicants in foods, and in each of the two publications that they had, one was in 1973 and one was in 1978, they listed genistein as a phytoestrogen that actually is an estrogenic compound in food and it's been shown to cause reproductive failure in sheep, it's been shown to cause male sheep that have been castrated, they'll produce milk, and ----- produce milk. So these compounds are fairly estrogenic, at least they mimic estrogen in a fairly aggressive manner. So again, cancer, and genistein is an issue of dosage and timing.

If I were to ask the audience what you think of estrogen, looking at estradiol or if you're looking at DES, all that comes about though is regarding breast cancer and it's almost all negative. If you start looking here if you got chemo prevention of NMU, and this is chemically induced carcinogenesis, is prevented by pretreatment with ----- and progesterone.

This was done by a person named Grubbs (?) who is a very well-known person with the initiation promotion model. He's actually at the University of Alabama. I think that will become important here in the next slide.

What was done in 1992 is neonatal DES administration prevents mammary adenocarcinomas in rats. I don't think there's a person in this room that would associate DES with chemo prevention of breast cancer. The work that was done, was done also at the same place that Grubbs worked. It was done at the University of Alabama. It was published in 1992, and I think the study that Mindy showed, and this is probably the study that started a lot of the chemo prevention issue with genistein is that genistein suppresses mammary adenocarcinomas in rats.

This was also done at Alabama. It was also done by the same researcher that showed that DES was the preventative in rats. And in the very first paragraph of the introduction he alludes to the fact that

they came upon this hypothesis fortuitously from their work with DES. So in a way he states that the genistein actually can work as an estrogen to prevent breast cancer.

How does that work, I think Mindy alluded to that, in terms of the way that it causes the ----- to develop. These are the actual curves. Mindy showed these. I have these up.

The part that's interesting here, these are tumors per rat. The part that I think is a little bit misleading here in terms of prevention, about 80 to 90 percent of the animals get tumors. So you're getting seven tumors versus three tumors. So there's a 50 percent reduction in tumor number, but still you got a high enough dosage of the carcinogen that animals almost all get tumors.

So you're looking at a decrease in the number of tumors, and you're not preventing the tumors being formed. The other thing that's a little bit unsettling about some of this is they didn't characterize all these tumors for whether they're benign or malignant. That's an important issue regarding breast cancer.

So what's the hypothesis that was put forth by Martinaires? What he put forth was that you're giving estrogen to an animal early, prepuberal so the estrogen actually can mimic a pregnancy in some way. What you get is you get the ----- differentiate. A differentiated cell doesn't proliferate as much. If it doesn't proliferate as much it's not as susceptible to DNA damage.

That's a mouthful of words, but what it's saying is that like pregnancy, it's protective because the mammary gland is developed and you're not going to get the initiation of cancer because the gland is not proliferating as much.

This individual followed this up with another study that was done by injection, and then a follow-up study that Mindy showed with the dietary administration of genistein. In that study he used relevant dietary dosages which is really important. Those data actually fit then with the consumption ----- early in life, and that may be why when Asian women move to this country it takes two generations because if they're born in Asia they got early exposure. There's a lot of positive information out saying that early exposure is protective.

So our question became a little bit more of an issue, what happens after the cancer exists. Most of the dietary supplements are out there, and they're out there and they're focused mostly on relief of menopausal symptoms. Those would occur in women usually over 50, and that's the group of women that are at the highest risk for breast cancer.

I can go through these slides very quickly again because Mindy had the same things. This dietary genistein estradiol. You can see that she had more on the slide that she had, but these compounds are actually very good mimics of estradiol. They bind to the estrogen receptor. This is data where you actually take ----- estradiol, bind it to the receptor, and then you compete it with either estradiol or you compete it with genistein. You can see that estradiol will displace ----- estradiol as will genistein. The difference here is about a hundredfold which suggests that genistein is a weak agonist and it takes about 100 times more to get the same level of binding to the receptor.

I don't know what occurs at the level of the cell because you have metabolism going on, but in general they get the same effect in the cell. It takes about between a hundred and a thousand times more genistein to get the same effect that you get with estradiol. These are confirming that the effects are estrogenic. This is the same gene that was on the slide that Mindy showed about Hargreaves that they looked at. This is PS2. It's a very estrogen responsive gene.

We treated MCF7 cells which are estrogen responsive cells in a low estrogen environment with DMSO and got no expression, a modest amount of estradiol and got pretty good expression. Then we got an enhancement of expression of PS2 with genistein at 1 and 10 micromolar. The 1 micromolar is a

dose that a woman would have if they're on a ----- diet. So these are fairly relevant dosages that can stimulate the estrogenic effects.

What we did then is we looked for cell proliferation and, again, as Mindy alluded to, at the lower concentrations you get an enhancement of cell growth, at the higher concentrations you get an inhibition of cell growth. The point being here is that the concentrations that are causing stimulation of these tumor cells is in the range of .1 to 10 micromolar.

These are human breast cancer cells. They were isolated from a woman that was postmenopausal and had an estrogen responsive tumor. These are the cells that have been used to do the majority of the work on endocrine associated breast cancer. These are the cells that tamoxifen was developed with, and so that they are a very, very well-characterized cell line, and they're used pretty extensively.

The real issue then comes in a cell culture dish it's real easy to add more. If you don't get the effect you want, you just add more, and you keep adding it up to the point that you get effects that you can characterize, you can do the mechanisms. It's real easy. You can have multiple plates and in an afternoon you can literally run hundreds of experiments ----- time points.

What's really essential when we're looking at dietary compounds is that they're administered in the diet. To be in the diet you've got to go to an animal model. This was actually the animal model that Dr. Fair had used when he had mentioned about an hour and a half ago that the cancer cells that they would remove from his I believe it was colon, that he actually was able to work with a person at the laboratory and they actually put his tumor cells into this mouse and he was actually able to look at the treatments that he had alluded to.

To this animal model is very effective at taking human tumors and putting it into it. So you can actually put a human tumor into the mouse, and then you can use the mouse as a four-legged incubator that can eat and digest and excrete. Then you can actually use human gene products to look at expression of various genes in this animal model.

So it's a very well-characterized model. It's also a model that was used to develop tamoxifen. It was also shown in this model that if you put uterine cells in and administer tamoxifen they grow. So it does have a lot of strengths in mimicking what happens in humans.

Again, it's an animal model, so it has all the limitations thereof, and I think that the one thing that's nice is we can do things in a preclinical setting that we can't do with humans, and so that's a real advantage. So what we've tried to is we tried to work out dietary dosages that are relevant and show whether or not they will or will not stimulate growth in the animal model.

Then you could make a prediction, that's all, of what would happen if women had the same level, and they had the same type of tumor. Those are two big ifs, but I think what it does is, to use Mindy's words, it raises the cause for concern. It doesn't say don't do this.

So what we have is we have four tumors in these animals, and then we administer dietary genistein. We use genistein as a pure compound because we were able to synthesize that about 6 years ago. That allowed us for the first time to be able to these studies in animals because animals eat a lot and chemicals are expensive. At the time we did this, genistein was a dollar a milligram.

These animals were each eating about \$7 a day at the time, and these studies went on for 3 or 4 months. So if we had to buy this compound, it would have cost us probably \$200,000.

So we took actually 4 months to synthesize it, but what that allowed us to do then is we implanted the tumors 3 or 4 weeks earlier, the tumors began to grow, and just as a visual, if you look at your hand, when the tumors are about the size of your little fingernail, we started the treatments.

So the tumors were about the size of your little fingernail here. We moved estradiol and the tumors quit growing. We gave a reimplanted estradiol pellet, and the tumors began to grow. So they're stimulated with estradiol until they get to the point that they're the size of your little fingernail. Then at that point we took them off all the estrogen and then dietary genistein. We used the level of genistein of 750 parts per million. We used that level because that's the level that gives a dosage in the blood of 1 micromolar, and that's relevant to a dosage of women consuming a high to modest amount of soy.

What you see is the tumors begin to grow. They don't grow as rapidly as with estradiol, but this is a pharmacological dosage of estradiol. This would prevent pregnancies in probably a thousand women if it was divided up. There's 2 milligrams here, and the amount that's in a birth control pill is the low microgram amounts.

So this is a whopping dose of estradiol. You would expect it to make the tumors grow very fast. This is a weak estrogen in the diet, and you can see that it does stimulate.

At the numbers that are relative to the 100, the tumors are about the size of your thumbnail. So they're dramatic when you're looking at these animals. It takes a little bit of stomach to be able to these kinds of experiments. We do monitor the animals to make sure that they're healthy all the way through because if they're not, the data is meaningless. So we do this extremely carefully.

The next thing that is an issue is what we did is we synthesized genistein. It's ----- it's a pure compound, and it probably is of more benefit to a pharmaceutical company than it would be to a cancer patient. I just used this as a prompt. It's not a product I endorse. I don't even know what's in this bottle, because I don't think the people that make it know what's in there. This was about 10 years ago, and I think what it is is a soy flower that probably has 2 or 3 milligrams of isoflavones per tablet.

Now it's different. There is really quite effective extraction procedures out for getting very high dosages out there. But the point is that what exists in the plant is a glycoside. Just to give you a brief introduction, this is what genistein looks like. If you take this hydroxyl, this hydroxyl can have a glucose hooked to it. So actually if you put this glucose on here, this compound is not going to be bind to the receptor and be ineffective. You got to remove this glucose to make it effective.

So we actually were able to get 30 grams of this stuff, and at the time this stuff was \$15 a milligram. So, again, here's another retirement if we could sell it, so we then feed it to mouse. Exactly the same experiment. We put the tumors in when they're about the size of your little fingernail, we take the estradiol away, and they regress. We reimplant estradiol and, again, it's a pharmacological dose. They grow very rapidly. We give the glycoside form and they grow like this, we give the aglycon and they grow like this. So there is virtually no difference in the glycoside form or the aglycon form.

So the availability of whether it's the natural product or whether it's something that we synthesized from a bunch of precursors, it gives you the same biological effect. When we take the genistein way, the tumors regress. Again, at this point here they're about the size of your thumbnail. They're going down here where they're half the size of your little fingernail. So removing the compound from the diet in an ----- animal that has a low estrogen environment is very, very effecting these tumors to regress.

AUDIENCE: What kind of tumors are these?

DR. HELFERICH: These are human breast cancer cells isolated from a postmenopausal woman that had an estrogen responsive tumor.

I'm not supporting this product. I'm putting it up to make a point. This is something that one of my students pulled up on the Web, and it's endearing, but this is a soy food, but it's not a soy food. It's actually a soy food that has an extract added to it. Each one of these servings has a 150 milligrams of isoflavones in an 8 ounce drink.

I had a call from a woman about 3 months ago. She was consuming two of these a day. So she was getting 300 milligrams of isoflavones a day and she wanted to know if she had poisoned herself. I didn't know what to tell her, but she had been through two pregnancies and two lactations.

So she had consumed this stuff constantly for 6 months. I don't know what that would do in that aggressive hormonal environment that would be during pregnancy and lactation, but this is a product that's out there. It's easy. It looks like it's a food, but it's a supplement.

Then they put in bold letters that it's nongenetically modified which I think is kind of interesting because they seem to be more concerned about that rather than the fact that it a pharmacological dose, and I don't think Mindy would dispute the fact that 100 milligrams is an issue.

What happens when you do the soy proteins and the soy isolates? You can take soy protein and you can extract it to the point that it's what would go in infant formula and has very low isoflavones, or you can process it to the point that it has a lot of isoflavones.

We were able to get isoflavones containing isolates that low, medium, and what I would consider isoflavone content per gram of protein. We mixed those into the diet of the mice and we replaced that with we took the casein out and put the soy protein in.

We made the diets isocaloric and isonitrogenous. Again we started the tumors at the same size as the little finger, put the estrogen back and they grow; take the estrogen away and they regress.

The low soy isolate had 15 parts per million which would be virtually none I think in many cases, and I think it's the same isolate that Mindy used. Again, there is no difference in the soy protein isolate in terms of tumor growth in this animal model.

This level had 150 parts per million, this level had 300 parts per million. This study went on for about 30 weeks, almost 8 months. It's a long time in the life of a mouse that lives 2 to 3 years. These are low levels of isoflavone chronically exposed from a soy diet.

I don't really know what that means in a human. If you have breast cancer at age 55, and we fed it for half an animal's life, you fed it for half a human's life, you would be dealing with the issue maybe when you're 110.

So maybe it's not an issue; maybe it is an issue. I think the point that needs to be made from this slide is that it really in my mind doesn't matter if it's a soy food or not if it's hammered with isoflavones, and you can hammer it with isoflavones by adding isoflavones back from the extract.

I hope Mindy and I are on the same page as this. This is not saying soy foods are bad. What this is saying is they're not all the same, and maybe you do have to be cautious about how much you consumer. Maybe it's worth it to read the label and equate the isoflavone content to what's there.

This is exactly the same study done in a matched set of animals with the casein-based diet and genistein added as a pure compound, and these curves are virtually identical. So it's really the isoflavone contact that is doing it.

I can real quickly go with this slide. The issue that I think is important is as you increase the dosage in the diet, a lot of individuals want to get the dosages so high that you can actually mimic what goes on in the cell culture dish. These are very high concentrations so you can get the antilipidor (?) effects which is rare.

Most of the literature has been focused with regard to genistein. Since we had a lot of genistein, we actually went at levels of 0 up to 6,000 parts per mission which is 6 grams per kilogram, a unit making it ourselves which was the experiment to do.

You can see even at the highest dosage levels they're only given 7 micromolar, and the majority of that is conjugated to glycuronide to one of those hydroxyls, and there's one 1 to 2 micromolar free.

But even at these lower concentrations, you're dealing with somewhere between 100 nanomolar up to about 1.5 micromolar of the free genistein. Again, from the cell culture studies that we did and Mindy has done, and much as I hate to admit it, some of these studies were actually done in 1978, but they were done at this concentration here.

You can see that those concentrations of the aglycon are right in this range here, that if you make the assumption that what goes on in a culture dish is what goes on in the blood at the same concentrations, that there's sufficient aglycon available to bind the receptor and then transactivate it. I think that's all I had. I think that was it.

Let me get my summary slides which are really quite straightforward. I think what I'm going to do is prompt you for an answer that I'm going to give when I get a bunch of questions because I really don't know what to recommend. I think in a way I do appreciate that Mindy has been very conservative in what she's recommending.

There are people out there that are recommending no more than 100 milligrams a day, and I have faculty colleagues that are saying they consumer 90 milligrams a day. When you hear a professor at a university like the University of Illinois saying that they consume this much, whether it is or is not an endorsement, it is an endorsement, and I think that that's a significant issue.

I think just in summary the things that really concern me the most are that there are soy foods that are wholesome. They're supplements that look like food, they're marketed like food, they're in a container that looks like Carnation Instant Breakfast drink or Slim Fast or whatever, but yet it really is a supplement.

Both Mindy and I have young children. We have a 15-month-old daughter who loves milk. Do I want her to drink that Soylicious (?) stuff? I think not, but maybe it is good for her. I don't really know.

I do not like the approach of treating an individual for prevention of one disease, because overall what we want, we'd like to be able to get those free lift tickets at Vail when we're 75. When I ask my students what your ultimate goal is, what you want to do is they let you ski for free when you're 75, and I want to get there. But what's going to happen when I get to be 75, it's going to be like social security, it's going to -----

I think what I'd like to do is to just have you address the questions to both Mindy and I. I'm sensitive to the fact that you guys are getting hungry, and they're not going to delay the afternoon sessions, they're going to cut your lunch short.

DR. FAIR: I have nothing very profound to say. You may even ask why a urologist is up here speaking about the role of soy in breast cancer. However, as I think Bill started off with his slide and said

estrogen is every woman's dilemma, testosterone is every man's dilemma because a lot of these things that you're talking about, you could have easily put testosterone up there and had the same questions.

The other thing that occurred to me when you had that slide, sometimes it's good, sometimes it's bad, I was thinking you could put teenagers up there too and it would be pretty much the same thing.

But I just had a couple questions that I would address to both of you because I can't be as eloquent as you were. The business of when to treat, the same thing is true with testosterone, you can imprint on mice depending on when you give them the testosterone as to whether or not this might have an effect on the subsequent of prostate cancer, or nondevelopment.

So I had two questions relative to this. Number one, we heard a lot about soy as a food and then soy as a supplement. I've always thought that those two may not necessarily be equivalent. Is that correct? When you talk about soy, is that whether you give soy as part of a diet, like in Japanese women it's incorporated I tofu and so forth? Or is that the same as having an American diet and then taking Soylicious or something along with it? Do we know that?

DR. KURZER: There are two parts to that. One is whether the more purified compound will have the same effect as when it's present in the food, and we don't know.

Some effects, for example, the effects on cholesterol lowering, we don't see with the extracts even though we do see it when soy protein is given. So there is something in the protein which is necessary for that. We know much less about the hormonal and cancer effects of extracts.

The other effect is what Bill was just talking about, the dose effect. That is, with the extracts or the supplements you can get huge doses, and we just don't know. We haven't done human studies at those doses to know what the effect is going to be.

DR. FAIR: Another question along that line, you had mentioned very nicely about the urinary excretion. If one increases the dietary intake by supplement, does the urinary excretion necessarily parallel that, Bill?

DR. HELFERICH: In the study that we did with the blood levels, the blood levels actually go up in exact linear fashion, as you increase the dose, you increase the amount in the blood. As I think as Mindy made the point, the urinary exposures are probably very, very good indicators of dietary exposure. Whether or not the urinary excretion is linear like the blood levels, I'm not sure.

DR. FAIR: Has anyone looked at the effects of soy supplementation in the VRCA1 gene or anything like that? You have to take someone with biopsy with cancer and then give the soy I guess and see what would happen. Has that been done at all?

DR. HELFERICH: I'm sure that it's on the horizon for somebody. My point of view is, and this is somewhat harsh, but if the data that we have with genistein was to be approved as a food additive, it probably never would get to the point of being added to the food at the level it's at.

So I think what we have is you can actually do this experiment. Whether or not it's appropriate or not in women that are a high risk to breast cancer is an issue to me, but it really doesn't matter because women are voluntarily taking it. So the experiment is going on, but no data is being collected.

It's a concern, but I think what would bother me more than looking at that specific gene is that if you're going to do that kind of experiment you need to separate the women into responsive as you were making the point, looking at nonresponsive tumors to estradiol and those that are responsive. Then I think

you'd have to take it even further and then separate those that are responsive to highly responsive and poorly responsive.

The poorly responsive estradiol actually can respond to tamoxifen pretty effectively, but I don't think you're going to see personally, and I guess ----- let me qualify it, it's my impression that in a poorly responsive tumor, a weak agonist isn't going to be very effective at stimulating the growth of those tumor. But in a highly responsive tumor, I think that that would be the issue.

So what concerns me if they do the kind of study that you're talking about and they lump all these tumors together, what they're going to get is high variability and no effect. No effect is a good thing for the supplement industry because it says there's no difference, so ----- take it because that can't harm me, and that's I think a potential issue.

I think this is a pretty significant. I want to make sure you and I agree on that.

AUDIENCE: Yes.

AUDIENCE: I agree.

DR. HELFERICH: I think the work that we do, people want to pick it up and they want to make me look like Darth. I don't really like that, but I think what we do do, the work that we do indicates that there's a pretty good likelihood that if a woman has a highly responsive breast cancer and she's postmenopausal with a low estrogen environment and she's not supposed to take HRT, she's on tamoxifen, I don't know, do you really want to be taking 150 milligrams of isoflavones to negate some of the side effects that are associated with tamoxifen like the hot flashes and vaginal dryness?

That is a question that goes back to the dilemma. If it's an estrogen, it's an estrogen. If you take advantage of the fact that it can prevent based on its estrogenic action, maybe you need to take into account that it's an estrogen where you're looking at growth.

But, again, it comes down to the point that if you're informed and you're making the decision on your own, I think that's appropriate. But most of the people are taking it thinking that it's preventing cancer, so it's going to be good for me. There's a difference between the mechanisms that prevent and the mechanisms that grow, even though they work by the same receptor, at least in the responsive tumors.

AUDIENCE: It's probably the 19-year-old kid in the health food store telling them that it's good, and that's often unfortunate ----- science behind it.

DR. HELFERICH: The same thing is, they're articulate, they're good looking, and they have complete confidence in what they're doing.

AUDIENCE: Absolutely.

DR. HELFERICH: I knew more nutrition when I got my first degree than I will ever know again.

AUDIENCE: That's probably true.

DR. HELFERICH: Because I was naive. I could tell my parents that this is dogmatic. It's funny, I'm now like our cat looking at something unusual ----- bad conscience trying to back off because I don't want to make a recommendation, because all of a sudden people are listening to me.

DR. FAIR: I do have to compliment both speakers. When we set this program up, the idea was have someone speaking pro-soy and then someone against soy. It was hard to find anybody that would really come out and say that soy is bad for you, but I think you both deserve congratulations for giving such a balanced picture.

One final question, because I get asked this all the time because soy is big now in prostate cancer. There was a study from Hawaii I guess that you and I talked about before about if you take soy, particularly middle age you might get some softening of the brain and decreased cognitive function. Is that a real worry? Do you bring that up with patients?

MR. KURZER: I'm not worried about it. I think there have been a lot of criticisms of those studies from the epidemiologists. I'm not an epidemiologist so I don't want to get into it. One of the studies, as I recall, the tofu consumers got dementia earlier than the nonconsumers.

So instead of getting dementia at 90, they got it at 88 or something like that. The difference was really not as dramatic as some of the press made it out to be. But there have been a lot of criticisms of those studies, so I'm not really worried about it.

DR. FAIR: That concludes my comments. Again, I congratulate you.

* * * * *