



Media Roundtable Transcripts

FLASH! The Latest News and Research on Menopause Management

Dr. Jaffe: I'm Robert Jaffe and we have an audience both here in the room and calling in. I'm a practicing reproductive endocrinologist and investigator from the University of California, San Francisco, and I've had a markedly increased number of menopausal women in my practice since the WHI results were published. More importantly I'm the immediate past President of the Hormone Foundation and I'm currently the Chair of the Foundation's Women's Health Taskforce.

The Hormone Foundation was established in 1997 as the public education affiliate of the Endocrine Society to be a resource for the public by promoting the prevention, treatment and cure of hormone-related conditions. Since its inception, the Foundation has reached over 200 million people with important information on a wide variety of hormone-related conditions and biological events, including thyroid, diabetes, pituitary disorders and the subject for today's media roundtable, menopause and its management. I'm delighted to welcome you to the Foundation's media roundtable, "*FLASH! The Latest News in Research and Menopause Management.*"

The publication of the Women's Health Initiative, the WHI, was a watershed, both for women and their caregivers. There's been a great deal of confusion about how to interpret the data from these studies and that confusion has not only been on the part of the patient, it's been on the part of the caregivers and the media. Hopefully, during these presentations we can clarify this confusion for media representatives here today. We hope to provide you with information that will be informative, concise, clarifying and we look forward to a very exciting program.

Let me just briefly introduce our very distinguished speakers with us today. Judy Foreman who is a syndicated writer of Health Sense for the *Boston Globe* and for many, many years served as a writer on the *Boston Globe* and she, like our other

speakers, has a very impressive CV. Sundeep Khosla who is now at Mayo and was here in Boston for many years, is a specialist on bone disease, one of the topics that we'll be covering today, and also happens to be the program chair for the Endocrine Society's Annual Program Steering Committee. Richard Santen who is a Professor of Medicine at the University of Virginia, is an expert in breast disease and breast carcinoma, and he'll be speaking to us on that topic. Nannette Santoro who is the Professor and Director of the Division of Reproductive Endocrinology at the Department of Obstetrics, Gynecology of Women's Health at Albert Einstein in New York, is a major figure in this area, and is also the Director of the Women's Health Across the Nation Study, or the SWAN Study. Meir Stampfer is MD/PhD and the Chair of the Department of Epidemiology and Professor of Epidemiology and Nutrition at the Harvard School of Public Health, and a Professor of Medicine at Harvard Medical School, and has been involved in the analyses of the Women's Health Initiative study, the Nurse's Health Study and a wide variety of studies that are related to menopause. And finally, Cynthia Stuenkel, who is Clinical Professor of Medicine at the University of California, San Diego, and she too has studied extensively and reported extensively on clinical trials on menopause and has been a great teacher and a great clarifier of some of the issues that arise in menopause.

So without taking any more time, let me introduce our speakers and what I would like you all to do is hold your questions until all of our speakers have presented their very brief talks. We're purposely keeping them brief so that there will be time at the end for all of you to ask all the questions you wish. Incidentally, when you do ask questions, please identify yourself. I should say that all of the content of this talk was provided by the speakers and me, and although we are extremely grateful to Lilly and Wyeth for sponsoring this program, they had nothing to do with either the selection of the speakers or the content of what's going to be presented here today. And I would appreciate as each speaker comes up to talk if she or he will also identify any support that they get from the industry.

So our first speaker, who will give us a brief history of clinical research in menopausal women, is Cynthia Stuenkel from the University of California, San Diego. Cynthia.

Dr. Stuenkel: Well, good morning. I appreciate the opportunity to be here. I feel like, a little bit like Stephen Hawking giving A Brief History of Time, but in a very short time. So I think most of this will be a review for those of you who are very familiar with this topic, but I thought it would be helpful before we talk about the clinical trials that have come up in post-menopausal women and women's health, that we just review very briefly a little bit about what distinguishes one study from another and why it's so important to keep that in mind.

I wanted to start with this hierarchy of evidence that's been put forth by the Oxford Center for Evidence-Based Medicine because I think it's helpful just to look at how these things are ranked, if you will. And it's a little bit humbling to

see at the very bottom of the totem pole some clinical experience, expert opinions and consensus opinions. Nevertheless, if that's the only option and the only information that we have, that's what we have to go on.

Now in the realm of menopausal women's health, there've been times when we've had some very interesting laboratory information, like looking at breast cancer cell with various hormones added, animal studies in the way of particularly primate and monkey studies, and various small trials of human physiology. And these are very interesting to help support hypothesis and to help us plan the next direction, and for many years in menopausal health we relied on the findings from observational studies. Probably the largest, most familiar to you would be the Harvard Nurses Study that gave us some very good ideas about associations between things like hormone therapy and various outcomes, but one of the concerns was relying completely on observational data and planning therapies is that there can be biases introduced in observational studies, such as which women might have been prescribed hormones by their physicians, which qualities of the women might make sense, continue to take hormones and while good investigators can be very clear about trying to control for these and sort these out, that always is one of the concerns.

So that brings us to the randomized controlled trials and for many, many years these were just lacking in menopausal women's health. Finally over the last decade there have been a number of trials and I'm going to go through those briefly and perhaps at some point we'll be to the point in menopausal women's health when we can actually combine various clinical trials in meta(?) analysis. So the strongest and most powerful data would be the clinical trials, the weakest and again most humbling would be looking just at our clinical, anecdotal clinical experience. Unfortunately, a little bit in the realm of menopausal women's health, for a long time clinical experience was the best thing we had and I'm calling that traditional. And I think it's been a little bit of a challenge or a little difficult for some of our practitioners to accept some of these new findings that I'm calling new age for the lack of a better term, but just to get us all on the same page to accept evidence-based medicine.

I've created this timeline and it's really a pretty short timeline if we would compare this to things like the history of cardiovascular trials, for example, and more general health issues. And so really it was in the '70s that the first trials were done, looking at vasomotor symptoms and just trying to see what was happening with different hormone therapies for symptom. Then in the '80s, in the mid '80s, particularly, there started to be some small and usually relatively short clinical trials looking at things like what happened to bone mineral density, what happened to lipid changes. And as I mentioned, the observational studies really started becoming very clear and very intriguing in the mid '80s and continuing on really to the mid '90s. This was the strongest data we had and the constellation of some of the trials selling lipid benefit from hormone therapy, various other benefits, and the very positive observational studies that said it looks like

hormone therapy isn't quite beneficial from a cardiovascular standpoint, really regulated our clinical practice.

Now the PEPI trial was put together in 1989. This was an NIH funded study. This was the first large randomized clinical trial in post-menopausal women and PEPI asked the question, what really are the effects of various hormone therapies on cardiovascular risk factors? So this was a huge step forward. While PEPI was underway though, I think there were a group of investigators that realized that PEPI would be helpful, but really would be just getting us more in the way of intermediate and surrogate end-points and then what we really want to know about post-menopausal therapies is are they going to prevent heart attacks? Are they going to prevent death? What happens to fractures and what might be the downside, if any, from the standpoint of breast cancer?

A friend in the WHI let me have this slide which I really liked. The gentleman is counseling his patient, he goes, "Well, we have studies of fruit flies, mice, cancerous bugs, monkeys and men, but medical research using women as subjects just never really occurred to anybody." And I like to remind people that one of the first heart trials using hormone therapy was done in the coronary drug project in men in the 1970s. So we do have a long way to come.

So the HERS trial was initiated in 1993 and interestingly, the WHI was also initiated about that same time. Now the PEPI trial came out a couple years later and the PEPI trial, in general, was very reassuring and told us that there were good news from the standpoint of cardiovascular risk factors. But then the HERS trial came out and this was a most disappointing and upsetting finding that hormone therapy not only didn't prevent heart disease in women with heart disease, but it also might have increased it.

About this same year, the RUTH where lots have been used for the heart trial, was initiated and so that was a little tricky talking to women about those potential benefits. And over the next several years, there were a number of added clinical trials looking at either cardiovascular events or looking at anatomic changes in the way of coronary, angiograms and/or carotid endometrial thickness. But for the most part, were consistent with the HERS findings.

Now the WHI combined hormone therapy initially was published in 2002. The estrogen alone therapy was published in 2004 and then over the last several years have been a number of papers published with some refinements of those findings, so I've listed 2006 on here as well. The WHI, and I'll just remind you because I know you're probably familiar with these data, I think is best expressed when we put it in terms of absolute risk. How many events of heart disease or stroke will occur in women on a combined hormone therapy or estrogen alone? And the WHI basically showed us that at least in the population that was studied, we did not see prevention of heart disease, prevention of stroke. We did see a reduction of hip fracture across the board. And then it also showed us that there were some

differences between combined therapy and estrogen alone – in the way of colon cancer results, we have breast cancer results and in the way of heart disease results. And so based on some of the intrigue, considering the potentially estrogen alone in younger women might have benefits, there have been a number of other trials initiated that are currently underway looking at younger, more post-menopausal women to see if various combinations of estrogen might be helpful in reducing heart disease.

Now the RUTH trial was just completed this year and it has not been published yet. We've been told in press releases that raloxifene therapy did not increase or decrease the risk of heart disease, but a second primary end-point of the RUTH trial was breast cancer.

And I just wanted to segue for a moment just to remind you that while we're largely focusing on those studies looking at heart disease and hormone therapy, that in the last few years, there have been quite a lot of trials in women looking at breast cancer prevention with Tamoxifen, with raloxifene and more recently with aromatization inhibitors that from the fracture standpoint – and you'll be hear more about these as well – there've been a number of trials looking at the bisphosphonate therapy, calcitonin therapy, PTH and then finally, the question of cognition. What happens -- we really have been able to only take a bit from HERS on the WHI. The MORE trial looked at cognition with raloxifene as well, but I think cognition is kind of falling into a spot like the heart disease that these trials have not shown benefit in the older women that were evaluated. But the question remains as to whether or not younger women who initiate therapy close to menopause might have benefit.

So in conclusion, the randomized trials with clinical end-points are a relatively recent phenomena in women's health research, having emerged only in the past decade. The WHI is the largest, longest and really broadest trial from an end-point standpoint that has ever been conducted exclusively in women. And the decision regarding safety and efficacy of hormone therapy in menopausal women should be based upon findings in the WHI until more data regarding other populations of women, perhaps younger women, other formulations of hormone therapy, lower doses are available. Thank you.

Dr. Jaffe: Thanks very much. We're going to turn now to four speakers who are going to address specific areas in which hormone therapy has impact. We're going to talk first about the breast, then we'll talk about osteoporosis and bone, and cardiovascular disease and then a facet that wasn't covered in the Women's Health Initiative, how do you take care of the patients with problems? Our next speaker is Dr. Richard Santen from the University of Virginia, an expert in breast disease and he'll be talking about that in relation to hormone therapy.

Dr. Santen: So I'm going to focus almost exclusively on new data and by new data I mean over the last two months. The patients that I see tell me that "I'm worried about

my risk of breast cancer, is there something I can do to prevent it?" So let's talk about breast cancer prevention data. The STAR trial was published June 9th, 2006. This was a trial, basically, to compare Tamoxifen to raloxifene with respect to efficacy to prevent breast cancer in high-risk women and to compare severian(?) side effects and toxicity.

The women in the STAR trial were all post-menopausal and they had an estimated risk of breast cancer of greater than 1.6% at five years. They were stratified at the age risk and race and we had 9,706 women were randomized for Tamoxifen for five years, a similar number randomized for raloxifene for five years. The bottom-line, basically, was that there was a 50% reduction in breast cancer with either of these two serums. Now since this is not a placebo controlled trial, we know that Tamoxifen reduced the risk of breast cancer. And this study, one could calculate the risk of the number of patients that would develop breast cancer over a five-year period, 312 women. In the Tamoxifen group, 163 and in the raloxifene group, 167. So a calculated risk reduction of 50%, but similarities in prevention of invasive breast cancer with either modality.

The average annual rate and number of uterine cancers was reduced by 38%, but this was not yet statistically significant. Strikingly, the number of hysterectomies for non-cancer reasons, 244 in the Tamoxifen group, 111 in the raloxifene group, or a 55% reduction. We don't quite understand this because it really was patient care are not part of the trials that drove this.

Now there was a very surprising finding in this study and that is that invasive breast cancer was reduced equally with Tamoxifen and raloxifene, but raloxifene did not seem to cause the reduction in noninvasive breast cancer. We don't have a good physiologic explanation for this difference. So it will be interesting to see the RUTH trial when it comes out to see if it supports the same observation.

Now as I read the initial reports in the media, most conclude that raloxifene is superior because of similar efficacies of fewer side effects and toxicity. And in fact, the NSABP chose raloxifene over Tamoxifen for this reason. But I would give you a caveat here and the "however" is that Tamoxifen actually appears superior for the prevention of noninvasive breast cancer, whereas raloxifene appears superior with a 30% fewer thromboemolic event, 38% fewer endometrial cancers, 21% fewer cataracts, 84% reduction in uterine hyperplasia and 55% fewer hysterectomies.

This was partially confirmed, I think, by the RUTH trial. The RUTH trial is only available to us as a press report on April the 12th, but basically the RUTH trial is 10,000 women approximately treated randomized to raloxifene or placebo. And results of the two primary end-points were that raloxifene decreased invasive breast cancer over placebos, confirming the STAR trial, and raloxifene neither increased nor decreased heart disease.

So my opinion is based on the STAR trial is that raloxifene, I believe, will probably achieve a therapeutic niche for women at high risk of breast cancer who have concomitant low bone density, osteoporosis or osteopenia and/or an intact uterus. This is subject to some debate.

My patients also ask me, “What is my risk of breast cancer if I take menopausal hormonal therapy?” Of course we all know from the Women’s Health Initiative Study, estrogen plus progestin over a period of seven years, there was a 26% increase in relative risk of a breast cancer and this has been confirmed in other studies. And would suggest that there’s about a 5.5% increase in relative risk of breast cancer per year over a 10-year period for women taking estrogen plus a progestin.

Now this patient hasn’t had a hysterectomy, “What is my risk for breast cancer if I take estrogens alone?” I’m going to raise a new concept here today and I think it’s a rather controversial one, but it’s provocative. The old concept based on observational data was that estrogen caused a one percent increase in relative risk of breast cancer for each year of use. So in the Nurses Health Study, if you took estrogen alone for 25 years, you had a substantially increased risk of breast cancer. The new concept is based on the Women’s Health Initiatives Study and I’m going to call this the estrogen paradox. The concept is that short-term estrogen alone, perhaps, reduces the risk of breast cancer, whereas long-term use clearly increases that risk.

So let’s look at the short-term data. The update of the Women’s Health Initiative estrogen-alone trial came out April the 12th in the Journal of the American Medical Association (JAMA). Basically what it showed was that after five years of use, there was a 20% reduction in breast cancer risk in women receiving estrogen alone. This was not statistically significant and thought perhaps to be due to chance. Well, in the Women’s Health Initiative update the subgroup analyses showed that for women with localized breast cancer, there was a 31% decrease in breast cancer, which was statistically significant, for ductile invasive cancer a 29%, which was statistically significant and for women who adhered to the therapy – which was only about 50% of the women who were studied – a 33% statistically significant reduction in breast cancer risk. So the Nurses Health Study, which was published in May of 2006, it showed that estrogen alone for five to nine years showed a non-significant 13% decrease risk of breast cancer. But for obese women, this was a 26% decrease and statistically significant. Long-term, the recent Nurses Health Study, showed that for more than 20 years of estrogen alone use, 41% increased in breast cancer for all women and a 77% increase in lean women, both statistically significant.

So I would introduce the term the estrogen paradox where estrogen alone perhaps prevents breast cancer early and causes breast cancer if taken long-term. How in the world do we come up with some physiologic explanation for this? Well, my hypothesis, and that’s all it is, is that based on extensive autopsy findings, 5 to

10% of women have breast tumors at the start of estrogen therapy, these are found on autopsy. They're too small to be picked up by mammography. There's about 15 studies that say this. In these women, estrogen alone kills breast cancer cells. It actually gets rid of them. However, long-term estrogen use causes mutation in genes that result in breast cancer.

So what are the data to support this hypothesis? Well, there are model systems, both in xenograph models and in cell culture and it's suggested if you take breast cancer cells and you deprive them of estrogen long-term – mind you the WHI estrogen alone study, these women were 53 years old, average age of menopause 51 – so if you deprive estrogen, breast cancer cells of estrogen long term, what happens is that estrogen actually kills cells through a process called apoptosis so it occurs both in cell models and in xenograph.

So one hypothesis, and I think probably the most reasonable one potentially to explain this, is that this early reduction in breast cancer risk might, in fact, be related to the cells killed. And of course, long-term use from the Nurses Health Study particularly, looks as if there is an increase later on. So this is very similar to the timing hypothesis, estrogen short term prevents our(?) disease, long term, perhaps, does increase it.

So my conclusions are that raloxifene will perhaps be better accepted than Tamoxifen for breast cancer prevention in women with concomitant bone disease and with an intact uterus. And then short term use of estrogen alone as menopausal hormonal therapy does not seem to be associated with an increase of breast cancer, but paradoxically, the data are beginning to be accumulated that bring up they can decrease this risk. And with that, I thank you very much for your attention.

Dr. Jaffe: Our next speaker, who will be talking about bone disorders, Dr. Sundeep Khosla from the Mayo Clinic.

Dr. Khosla: Thanks. So I was going to just review the area of osteoporosis and how its management is evolving in the post Women's Health Initiative era. And just by way of definition, as you know, this is a disease characterized both by low bone mass and by actual structural deterioration of bone tissues that lead to increased bone fragility and increased accessibility to fractures. And the classic osteoporotic fractures are those that involve the hips, the spine and the ribs, although women with osteoporosis fracture at multiple other sites.

Just a few words about the prevalence of the disease. It's a major public health threat for an estimated 44 million Americans and this comes to about 55% of the people 50 years of age or older. Then in the US it's estimated that 10 million already have the disease and almost 34 million more are estimated to have low bone mass, which places them at increased risk for osteoporosis. Eighty percent of these are women, so it really is a disease of women, although men are affected

also. And it's estimated that 1 in 2 women and 1 in 4 men over the age of 50 years will have an osteoporosis-related fracture in his or her remaining lifetime. So the morbidity from this disorder really is quite significant.

Now there's really not a whole lot new in terms of estrogen and bone. This actually is a study that was done more than 20 years ago showing that when women undergo oophorectomy, which would be an accelerated form of menopause, that you see similar things with the natural menopause – that at the vertebra there is a dramatic loss of bone over two years that can be prevented with estrogen replacements. At the radius, which contains a somewhat type of bone than the vertebra -- the vertebra is more trabecular bone, the radius is more cortical bone -- you also lose bone and this is prevented by estrogen. And these findings have been replicated in many studies over two decades, and have really held up and, in fact, also held up in the Women's Health Initiative. So these are data from the fracture outcomes in the WHI. You can see if you look at hip fractures, vertebral fractures, other osteoporotic fractures or total fractures, in each case the estrogen plus progestin arm had fewer fractures than the placebo arm, and the hazard ratio, which would be the relative risk of developing a fracture was reduced by anywhere from about 25 to 35%. So the findings with regard to bone have been very consistent over the years. This just shows the cumulative hazard or risk of developing a hip fracture over time in the WHI, you can see here's placebo and a clear reduction with estrogen and progestin.

So the debate in terms of treatment for osteoporosis has really come not so much about estrogen being good or not for bones, but its use being limited by the potential other side effects in terms of breast cancer risk and cardiovascular risk and so forth. So what do we counsel women about treatment today? Certainly adequate calcium and vitamin D. There's been some controversy about the importance of this. I think at the end of the day, it still plays a role. It probably alone is insufficient to completely prevent bone loss or fractures. I think estrogen or hormone therapy still is an option for some women, especially those that are symptomatic for whom you may wish to use estrogen for other reason. You get the added benefit that it's going to protect their skeleton.

The mainstay of treatment in 2006, really, are bisphosphonates. There are now three drugs approved that have gone through extensive clinical trials, alendronate, risedronate and etidronate(?). They're all very effective in preventing bone loss and fractures. Now they're not a panacea because there are potential concerns about long-term use. There is data evolving about side effects. There's a lot of press recently about osteonecrosis of the jaw that is present, which occurs at a very low frequency, but we don't understand that disease very well.

Calcitonin is an old drug. It's given as a nasal spray and it also an effective drug, although it's less effective, certainly, than bisphosphonates or estrogen. Already in place is raloxifene, the selective estrogen receptor modulator that Dr. Santen talked about and there are newer ones coming out. These have beneficial effects

on bone and fracture risk reduction, but it's reduced the risk of breast cancer and appear to be neutral as far as cardiovascular risk is concerned. So I think as more potent agents become available – right now raloxifene works, but it's probably not as potent as estradiol in terms of preventing bone loss or fractures, but as we've become more potent in terms of bone effects, they're going to be used even more.

And the first therapy, all of these drugs prevent loss of bones. Parathyroid hormone or Forteo is the first drug that's become available that can actually reverse bone loss. And this is sort of in the class of anabolic agents, and that's become available. So I guess the point here is that 15 years ago, all we had was calcium or estrogen and now we have a whole class of other drugs to choose from. So the management of osteoporosis, I think, has really evolved over the past decades and that's really been to the benefit of our patients.

So what's on the horizon? There are new bisphosphonates, more potent drugs, drugs that can be given less frequently, that are more convenient to use that are going to be developed. These are going to be incremental changes. They're going to be sort of improving on what we have, but that's not going to be a dramatic new development.

In the clinical trial process, and potentially being approved by the FDA in the next several years is a drug that targets RANK ligand. It's an antibody so it's a biological that will target this key molecule that leads to a development of osteoclast, or the cells that absorb bone. And this can be given as an injection under the skin every six months. So you can see this would be a very convenient option for women to prevent osteoporosis. There is a new class of drugs, _____ cathepsin and K inhibitors, which target certain enzymes involved in the bone resorption process, and serves as a Holy Grail for a number of companies is finding newer drugs that actually reverse bone loss, like parathyroid hormone that actually stimulate bone formation. And I suspect we'll be seeing a whole class of these in the near future.

So what do we do today for primary and secondary prevention? For primary prevention it's recommended that a bone density test using DEXA, which is painless. It's low amount of radiation, but it gives you the best measure of the risk of osteoporosis, that all women aged 65 and older have a bone density test to assess their risk of osteoporosis. That younger women who are postmenopausal and have one or more other risk factors, other than being white, postmenopausal and female, also consider having a bone density test. And postmenopausal women who present with fractures, these women are already at high risk of fractures and a bone density should be obtained to assess their risk.

And secondary prevention is also very important because if a woman has already got a fracture, irregardless of her bone density, she is at a very high risk of having subsequent fractures. So these women, in particular, need to be targeted for

aggressive diagnosis and treatment.

What's next? Well, the whole area of the diagnosis of osteoporosis is evolving. Many of you are familiar with T-scores, which is what you get out of the bone density test. The World Health Organization and National Osteoporosis Foundation are, in fact, updating the guidelines for prevention and treatment, and the concept is to not so much give a woman a T-score, which is you're minus 2.2, which is an abstract concept that's hard for the woman the practitioner, but using a bone density and a combination of risk factors to actually tell the women that "Based on your age and the fact that you have a family history and that maybe you had or didn't have a prior fracture and so forth, that over the next five years, you've got a 10% chance of having a spine fracture or a 5% chance of having a high fracture." So with those absolute kinds of numbers, I think physicians and women will be able to make better decisions about whether or not they want to take a particular medication. There's certainly newer treatments, as I mentioned, based on a better understanding of the mechanisms and bone loss.

And finally, what's really needed are long-term safety studies. All of these drugs we have are very effective, but as for the bisphosphonates, for example, where we learned about this issue about the osteonecrosis of the jaw and are trying to understand this better, even though that's a rare side effect of these drugs. We need to continue to be vigilant and monitor all of these patients, and perhaps, actually include subsets of women in long-term clinical trials to be sure that they are no long-term adverse effects to these drugs. So I'll stop there.

Dr. Jaffe: Thanks very much Dr. Khosla. Next we turn to what may be the hottest topic in relation to hormone therapy and that is cardiovascular disease. Those of you who have been attending the Endocrine Society meetings may have heard the first plenary session at which Dr. JoAnn Manson, a colleague of our speaker today, Dr. Meir Stampfer at the Harvard School of Public Health, entitles her talk, "Timing is Everything" to highlight the implications at the age of the start of treatment on cardiovascular disease. And there's – that's a very important message, I believe..

Dr. Stampfer: For anybody who went to JoAnn's talk, all of these slides are probably going to be a total rerun since – although I have no drug company support, I do have support from Dr. Manson who loaned me all these slides. But a little review can't hurt. So just to pick up on Cynthia's historical view of hormones, this is sort of where we were in 1995. This is a review I put together with Francine Grodstein, looking at hormone therapy and coronary heart disease and looking at either ever users or never users. And what you can see here is combining results from over 40 observational studies, very consistent results, especially from population-based cohorts of a significant reduction in risk of coronary disease. And these are populations, not only in the US, but around the world in different circumstances and it was fairly substantial reduction and risk.

And it was findings like these, plus the results of clinical studies looking at the

impact of hormone therapy on risk factors that led to the HERS trial, which was a trial of secondary prevention. That is, women who already had heart disease would hormone therapy reduce their recurrent disease or death from coronary heart disease? So this is a very different population. This is a population that there was no observational data for at all, essentially none. Because most of the time the women are given hormone therapy at the time of menopause, they're healthy, they don't have much coronary disease. So why did they do this? Why take a completely different population? And the answer is efficiency. And this is the reason that most of the heart disease studies up to around this time were done in men rather than women. It wasn't completely malevolent on the part of men, but it was a matter of a bang for the buck. So, I didn't say completely malevolent, maybe there was a little bit. But most of it, maybe all of it, was for efficiency because heart disease is much more common. Men at younger ages, we need a certain number of end-points to get a result, so you target a high-risk group. And obviously the high-risk group is the people who need it the most anyway, so this kind of made sense, at least prospectively. If hormone therapy is protective for younger women, well, what we do in older women who already have hormone therapy? So the big surprise to everybody, and I haven't found anybody who makes the claim that they predicted this finding, was the increase in risk and first year – and this had not been really reported in observational studies and it came as a complete shock. In later years there was a trend toward decrease in risk, but there was this early increase.

So the Women's Health Initiative, as you've seen, the combination of estrogen and progestin actually there was a decrease in risk and there also was a 29% increase in coronary disease observed. Again, these are not old women, but they're older than the typical hormone therapy patient, so these are – the mean age was 63. Two-thirds of the women were over age 60, many years after menopause. So again, very different from the type of women that we see in our observational studies. The estrogen alone, overall, it seemed to be roughly balanced and coronary disease was null, but it didn't show any benefits. And again, same age population.

So why this apparent discrepancy between what I showed you earlier? All of the vast majority of observational studies apparently showing the benefit and the trials now showing the benefit? Well, the most popular explanation that had been advanced in the early years, after WHI, was “Well, it just shows you that the hierarchy of evidence is correct and the observational studies got it wrong and why don't they just grow up and quit griping and face the truth?” So this is what we were told and – feel a little beat up on, but so that's science. Of course you want to face the truth and evaluate the evidence.

So the basis for the claim that observational studies got it wrong was that these are observational studies, women and their doctors choose hormone therapy and that maybe healthier women are being put on hormone therapy and what we're seeing is not a cause and effect relation, but just confounded. Well, we

epidemiologists actually, we care about the confounding, it's our bread and butter, but still, you always worry about leftover confounding residuals _____. So one thing we put together – this is a review that JoAnn put together comparing observational studies with the Women's Health Initiative and observational studies -- mainly our own studies, the Nurses Health Study and what you see is little dots, basically, observational studies results or Women's Health Initiative results and you can see that they track almost perfectly. It's eerie, actually, how close they are to one another, except for coronary disease. Now if you make the argument that healthy women are being chosen for hormone therapy and, therefore, this is all compounding, how can you explain the stroke findings? The stroke findings are basically on top of each other, exactly the same, and if you have confounding with healthy women, then you also have seen there's big protection for stroke. And we do. So there's something unique about coronary disease. (inaudible)

Dr. Stampfer: So this idea of timing began to take hold more firmly when people took a closer look at the Women's Health Initiative, to look at the subgroup of women who are closer in age or time since menopause to the observational studies. Observational studies, again, just based on what people actually do in clinical practice. So in the E+P trial you can see when you'd subdivide by years since menopause, there's a trend across time since menopause, with higher risk with longer time since menopause. And this higher risk is concentrated, again, in the very early period of initiation of hormone therapy, just as it was in HERS. In the estrogen alone group, it's even more striking -- this is by age and you can see that women who started hormone therapy closer to the time when most women in clinical practice start hormone therapy, you see a relative risk, .56, very similar to what we see in the Nurses Health Study. Not quite statistically significant, but it's quite noticeably different from the relative risk of 1.0 for women who initiated therapy at an older age.

In the Nurses Study, we went back to look at the few women who initiated hormone therapy many years after menopause and we see the same kind of trend. There are very few such women, because it's not common clinical practice, but among those women...in the first four years you do see a significant reduction, either estrogen alone or E+P. So the data are starting to make some sense.

What about animal studies? A lot of the results come from animal studies that help support the initial concept and these are data from Tom Parson's group who showed that in primates given estrogen therapy, there was a 70% reduction in plaque area, a huge reduction in this for atherosclerosis in this randomized trial in our cousins. But the monkeys who had an atherogenic diet to promote atherosclerosis before initiation of hormone therapy, they actually had no reduction in risk. So this is equivalent to a substantial period of time after menopause when we're eating American diets, atherogenic and this is analogous, roughly, to the situation of WHI hormone therapy is initiated a number of years after menopause with no benefit with HERS, with therapies specifically initiated

after diagnosed coronary disease and there you actually see the harm, whereas in observational studies and what we do in clinical practice, is initiated here early when women have little coronary disease.

So, just to conclude, it seems that things are a little more complicated than we thought and in particular, there is an adverse effect of hormone therapy to raise the risk among women who already have established disease. So most of those women 10 years postmenopause, if you did an angiogram you'd see plaque and there's experimental evidence suggesting that hormone therapy can increase plaque instability and increase the propensity for plaque rupture. But at the other side, it's reducing atherosclerosis. So it's having two different effects and depending on when you give hormone therapy, one or the other can predominate. If you start it when women already have some plaque, you're likely to cause harm, at least in the early years. If you start it when women have relatively (?) coronary, they're likely to have reduced risk.

Dr. Jaffe: Thanks very much, Dr. Stampfer. One of the things that hasn't been covered in the Women's Health Initiative is, how do you take care of the patients? And Dr. Nanette Santoro from Albert Einstein College of Medicine is going to talk about management of menopause symptoms, the benefit and risk counseling for menopausal women.

Dr. Santoro: So, I wanted to talk about a little bit of the practical issues involved in treating women. For the most part, symptoms aren't going to go away, and menopausal symptoms are often what drives women to a doctor's office to get treatment. They don't always know about osteoporosis. They are no longer concerned with much of that cardiovascular risk because we've made a little bit of a disconnect between that and the process of menopause, so the symptoms are often a driver and in 2005, the NIH and the Association for Health, AHRQ and I can't remember what that stands for – Health Research Quality? Convened a panel of experts to examine medical evidence on linking symptoms to menopause and what treatments made the most sense. And this may not shock anybody in the room, but the best evidence was found to attribute that following symptoms to the menopausal transition.

And number one on the list vasomotor symptoms is that 85% of women will report having them as they go through the menopause – vaginal dryness is reported in about 30 to 40% of women and sleep disturbances are relatively common. Symptoms that have failed or mixed evidence, even though they were reported by many menopausal women, the ability to link them to menopause is not as clear. On mood disturbances -- and there's a variety of different studies that have shown some linkage – some improvement with hormone treatment for mood disturbances, some changes in cognition, memory loss, the development of Alzheimer's disease, partially address by the Women's Health Initiative and other clinical trials, but not completely so, and urinary symptoms, which used to be widely believed to be attributable to the menopausal transition, are now believed

as having mixed evidence. Similarly for sexual dysfunctions, since sexual dysfunction is such a prevalent complaint in women, linking an increase to the menopausal transition is not so clear. And some symptoms are actually found to have poor or inadequate evidence – body pain and joint aches, which are again, in the office setting, a very common complaint of women, not necessarily linked to the menopause. It may be true that your joints start to give you trouble after a certain age, happens to coincide with menopause. And changes in skin and body fat distribution, which may, again, just be the aging changes per se, have widely been attributed to menopause, but probably without evidence.

So when we're in a clinical office setting and a doctor is balancing the risk to benefits of the patient, quite often symptoms are the focal point and it's very important to understand that no long-term study has ever been designed to specifically examine benefit-risk ratios in symptomatic women. Women with symptoms will assign a value to the relief of their symptoms by treatment, whether it be hormones or anything else, and that value is going to alter that risk benefit equation. So it's we saw some nice scales presented by Dr. Skuenkel and Dr. Stampfer – this is another thing that needs to be factored in and right now we're in a very subjective area when we talk about symptoms, but they are becoming important.

In relatively asymptomatic women, such as the Women's Health Initiative population, and other population studies such as the SWAN study, quality of life, as measured by a variety of different ways, seems, at most, to be minimally impacted. So the group moves in a way, it doesn't show a big degree of discomfort. Yet within that group, there are women who are fairly massively unhappy as they go through the transition, and really request and ought to be treated.

So, given that these vasomotor symptoms and hot flashes are the number one menopause symptom, I just wanted to review a little bit about that, and only estrogen, basically, exists as the FDA approved compound for that. So hormones in many forms, as well as estrogen plus testosterone combination, are FDA approved. I believe Bellergeral, which had a Phenobarbital derivative in it, was formally approved, but had its indication removed. And indications have never been sought for many of the newer generation of alternative medications that are not hormonal. And it's unlikely that pharmaceutical companies are going to seek specific indications for them.

So you've seen much on the pros and cons of estrogen. When we treat symptoms with estrogen, it is the most effective treatment. Relief happens quickest, it is most complete and it is most long lasting. Estrogen also relieves vaginal dryness, in addition to relieving hot flashes, and again, it's number one on the list there for symptom relief, and has these other benefits that have been discussed. And even though we spend a lot of time arm wrestling about the risks and benefits of estrogen, it actually has a long track record of efficacy and well characterized

risk, which makes it – gives clinicians a great deal of comfort with it. And the negatives we've already talked about. You have to add progesterone in women with a uterus and for symptomatic patients, that's not always great.

All other treatments don't give as rapid or complete relief and the risks are not nearly as well characterized for these other treatments. There are many fewer women years of use. And we have some significant side effects with them. When one treats flashes with an SSRI or SNR medication, loss of libido is a very prominent problem. Antihypertensive drugs can lead to low blood pressure, women falling out of bed at night and someone who can feel attunded(?) or sleepy if they're given agents like Gabapentin, Bellergal. So everything has got its risks and benefits.

So the current FDA recommendations have been essentially recapitulated by everybody that has looked at this in consensus -- the North American Medical Society, the American College of OBGYN and International Menopause Society - - that when we treat symptoms because they come and go, the most sensible approach is to use the lowest possible dose when hormones are used, for the shortest possible time.

And the preparations that I think that you will see, as a media person, I think you're going to see bewildering arrays and new preparations, because while the Women's Health Initiative showed us well characterized risks and benefits of conjugated estrogens and Provera, medroxyprogesterone acetate, now the ballgame is wide open. So the best way is to treat symptoms with the least risks are really what we're seeking and of all of these preparations that I've got up here -- and I want to leave time for questions and answers so I'm not going to read them off to you -- there are some assumptions that we may want to make about them being safer or better because they're a lower dose or because we're giving them through the skin or because they're being given vaginally. But those things have not been proven yet. So we really need to take a long hard look at all of these different ways to give them, and at the wide dose range. This is almost a 10-fold dose range. And again, here in transdermal estrogen, to see which are really the best for individual women.

So a number of questions in this field are appropriate to ask. What is, in fact, the lowest appropriate dose? Different women obviously require different approaches, and when symptoms are treated because they're subjective, the woman is the arbiter of success or failure of the treatment, so that clearly we're going to need to learn more about dose requirements. What is the shortest appropriate time to treat a symptomatic woman? You get a big question. Symptoms are known to vary over time. If someone is made comfortable for a month, is that good enough? Can she go back out and stop her hormones? Is three months enough? When should one try to reevaluate? An often forgotten group is the 10 to 15% whose menopausal symptoms never go away. Again, when one looks at a large group, you never see these women. They vanish out of a larger

cohort, but they are people who would be very difficult to get them to give up a treatment that's working and to have symptoms come back. So keeping it all in perspective is really the job of the clinician in the office and we rely on our colleagues to help us do that.

And in order to leave some time, I actually ended early. How do you like that?

Dr. Jaffe: Thanks very much, Dr. Santoro. The rest of the program will be under the direction of Judy Foreman from the Boston Globe. Judy first is going to talk about menopause in the news and then open it up for discussion to her colleagues, both here in the room and those calling in. Judy.

Ms. Foreman: Thank you. Well, I've been covering this issue for way too long. So the whole hormone replacement issue has been an incredible nightmare to cover because it's such a moving target. Maybe I should ask the other speakers to come up while I talk so that by the time we get to questions they will already be in place. As you all know, it's been back and forth. One huge problem for reporters is that the data has really come out piecemeal, so everybody gets mad at us. It's always the shoot-the-messenger situation. And why can't you guys interpret it right? Why can't you guys get it straight? And then we get mad at the scientists. Why can't you give us this information in a coherent way so we can get the message out to people, whatever the right message is supposed to be? It's really been very, very confusing and we've swung – we've swung ourselves, and we've also been spun like crazy. People that I used to trust totally, scientists I used to trust totally, now I don't trust so much, because they're all so invested in their own findings that when other scientists criticize those findings, the people you used to trust get very defensive and in their attempt to defend their work, kind of confused things further. So it's been really difficult for the press. I know nobody has great sympathy for the press, but you should, because we are actually the good guys in all – and we have no vested interest in any particular point of view, we just want to get your accurate stories and hope they wind up on page one.

One question we're trying to ask more often and put the answers in our stories is, where does the money come from for the different pieces of the research? And one thing that's true about journalists that may or may not be true about scientists is, we don't get paid – we practically get paid by nobody. Our salaries are not huge, and we get paid by our news organizations, not by any drug company. So in that sense, we're truer than Cesar's wife. Anyway, with that plug for journalism, I think I should open this up to questions. I don't know how in this audience are journalists and who are scientists, but if the journalists with questions would go up to the microphone in the middle of the room, that would be great. And I guess we alternate between live people in the room asking questions and people on the phone lines. So I would ask a question. Can you just raise your hand if you're a journalist so I know how many people are journalists?

One thing, and I'm not sure who to ask, while we're waiting for somebody to be brave, nobody really mentioned much about bioidentical hormones, which is a huge issue and it sort of gets into this transdermal hormones versus oral. Wyeth, which, as everybody knows makes Premarin, has asked the FDA to regulate the compounding pharmacies which make these bioidentical hormones, so-called bioidentical hormones, for women. And it's become a big kind of political football because a lot of women – apparently the FDA has gotten like 40,000 emails and letters from, mostly from people against Wyeth's petition, that these are women who want bioidentical hormones to be available. So let's see, who would be willing to take on that whole issue? Go ahead.

Dr. Santoro: I'm happy to start. Bioidentical hormones exist in FDA approved preparations. So the concept of bioidentical hormones is one where the transdermal estradiol and micronized progesterone, one would be giving bioidentical hormones. And having it given in a preparation that's FDA regulated is to the benefit of patients because it is much better controlled, the quality control for the amount of hormone in the patch and the pill is much better than what a patient would be relying on if she were to go to a compounding pharmacy. She is essentially doing an experiment with an N of 1 on herself by going to compounding pharmacy. May or may not be getting something effective. Some of the excipients that are used in creams that are applied to the skin don't allow a hormone to be absorbed. So there isn't really an effective way to monitor it. The concept that it's customized and the presentation of the bioidentical hormone purveyor is sort of a mom-and-pop shop, leads to an assumption of safety that is not warranted. And that's the reason for concern.

Ms. Foreman: I completely agree. In fact, I switched about a year or so ago from Premarin to estradiol patch and I specifically went to the FDA-approved one because I could count on it more. Anybody else want to make a comment about that?

Dr. Santen: I would. I see a lot of patients that want bioidentical hormones and they really don't understand that the compounding pharmacies basically give estradiol, estrone, estriol, which are hormones that are available clinically with transdermal preparations. And I spend a lot of time distinguishing the compounding pharmacy from bioidentical hormones. I think that's one major issue. Those of you that have read Suzanne Sommer's book, which I've had to do because my patients always ask me about it, there's a lot in there that's right and there's most of it in there that's wrong. The part of it that's right, I believe, is that difficult patients, if one measures estradiol levels in the blood, it's like every other drug that we give, we're aiming for a level. Now we don't know precisely what level is appropriate, but for difficult patients we can actually give 17 beta estradiol, that's bioidentical to the hormone made by the ovary, it's what circulates in the blood, and we can measure it. And in patients that are difficult, we can actually titer (?) our dose to levels of estrogen that we can measure in the blood.

Ms. Foreman: What's your definition of a "difficult" patient?

Dr. Santen: Well, in my referral practice is patients that the other physicians in town can't manage their menopause appropriately and they either have too many hot flashes, they have side effects or they're not getting along with their medication properly. And my start in that individual, really, is to use estradiol, which is the circulating estrogen. I usually do it by patch, because this is very stable. We call it a zero order kinetics, but it doesn't go up and go down, it just stays very stable. And we know that the average estradiol level – my premenopausal women varies tremendously, but averages about 130. And with the low patch it's about 30 and with the .1 patch it's about 11. So one can actually get some objective information of what the hormonal milieu in the patient is. Most patients don't need this, but a few patients really need careful tailoring. Now, Suzanne Sommer's book does that, in fact, and I think that's part of her book that's right.

Ms. Foreman: I have more questions about that, but I think we should go to one of the questions on the line. Will the first caller speak up? Do I have to do something? Is there anybody on the line? Any questions from the room? Go ahead.

Reporter: I'm Cathy Kristiansen from *Endocrine News*, published by The Endocrine Society. I'd like to ask a question about bisphosphonates. These are very new and one wonders if in a few years we'll have some study come out that show side effects that were not expected, like the WHI. May seem safe, but what could we do about reassuring women – is the dose too high? What studies are ongoing to try and get at the safety factor?

Dr. Khosla: Yeah, I mean that's a good question. They're very effective drugs and they are a large number of women who benefit greatly from having taken them. There are data with alendronate after 10 years and at least in that particular...

Ms. Foreman: That's Fosamax?

Dr. Khosla: Fosamax – that it was well tolerated, that there seemed to be a consistent effect on fracture risk reduction and at least in that trial, there weren't any really adverse effects that were noted in terms of the jaw osteonecrosis or delayed fracture healing and so forth, although the study may not have been large enough to pick up some of the rare side effects. So I think, again, in the absence of those kinds of data, it becomes a matter of clinical judgment and hopefully ongoing surveillance for these problems over time. And many of us are – in the past, they were largely used in much older women, but as fewer and fewer women are using estrogen, more are likely to be candidates for bisphosphonates or other related drugs. And I think most of us are taking the position that if we start a younger women, let's say in her 50s or 60s on a bisphosphonate, that we would aim, perhaps, to treat for about five years and sort of think in five-year windows because there are going to be newer drugs available, we'll be learning more about the potential side effects. So I don't think any of us is comfortable committing a person to 30 years of therapy with a bisphosphonate.

Ms. Foreman: What happens if a woman has been on it for five years and then stops?

Dr. Khosla: Right. So to some extent, it depends on which bisphosphonate, because stopping Fosamax or alendronate may be somewhat different (?) from stopping Actonel or risedronate because they have different potencies, they've got different retentions in bones. In general, over time, when the time is variable, depending on which drug you've been on, the bone resorption markers, or the bone breakdown markers tend to sort of come up and you may start to see recurrence of the bone loss. But, having said that, I think increasingly people are treating for five years and then maybe stopping for a year or two to let the bone kind of recover from the effect of the bisphosphonate, just because of these kinds of concerns.

Dr. Jaffe: Dr. Khosla, Q: Sundeep, I'm getting a lot of calls from my patients about the jaw necrosis, far out of proportion to the frequency that it occurs. How do you respond to your patients when they call?

Dr. Khosla: Well, first of all I tell them that the cases that have been reported, that 95% or so have been in women who have been given fairly high doses of these drugs for treatment of cancer metastases to bone and so there likely is a dose response. And it's less than 5% of the cases have been reported in women who are taking oral bisphosphonates for osteoporosis. So that subgroup is at fairly low risk for this. The patients that have cancer and have been getting high doses of this, they're at significant risk, I mean depending on which series you look at, maybe up to 10% or more so if the patients may be at risk for developing that.

Ms. Foreman: Why does it show up in the jaw as opposed to the elbow or something?

Dr. Khosla: Yeah, that's a very good question. I don't think anybody knows the real answer, but one can speculate that the jaw is – the membrane that separates the bones in the jaw from the oral cavity is a very thin membrane and there is a lot of bacteria in the mouth, so that maybe we all are getting transient infections in the jaw bone, but are able to sort of clean them out and heal them fairly easily. But if you're on a bisphosphonate, that completely shuts off, or largely shuts off the breakdown of bone, that if you get a small nidus of infection, the ability to access that and repair it may be impaired. But there are other possibilities. Bisphosphonates have some effects on the growth of blood vessels, for example, and that may play a role also. But many people are thinking that this may start off as sort of a sub-clinical infection that doesn't heal and then that goes on to death of part of the bone.

Ms. Foreman: Is there a caller on the line? You hear it rattling. Yes, go ahead.

Dr. Santen: So Judy, I would like to not really take issue with something that you've said, but I think in the early days of reporting of the Women's Health Initiative Study and many of these other studies, what the media did, basically, was to focus on relative risk. The WHI came out and you saw my slide, 26% increase in breast

cancer risk. My wife looked at me that night and said, “I’m on Prempro, do I have a 1 out of 4 chance of getting breast cancer because of this?” And I think, my sense is that it’s a lot easier to have a story get on the front page if there’s a greater risk than if there’s a smaller risk and I think that drove a little bit of the reporting. Now my sense is that people like Jane Brody and Gina Kolata began to get into the milieu that we really need to focus on not absolute risk even, but it’s relative – it’s attributable risk. Now...

Ms. Foreman: You really do mean absolute risk.

Dr. Santen: I don’t, I don’t mean absolute risk. So if I have a thousand patients in my office (I’m very busy as a physician), and they’re average age 60, let’s say 50, and they say, “What is my risk of getting breast cancer?” It’s basically 18 of those women out of a thousand will get breast cancer over a period of five years. Now they say, “Well, what’s going to happen if we all take estrogen and a progestin?” There now will be 22 women in that room that will have breast cancer. Now you’re going to make a decision about whether you’re going to go on estrogen or not, so it’s really not the 18 or the 22, it’s how many excess cases of breast cancer, that’s the attributable risk. And I think when you saw the study of treatment of prostate cancer with radical prostatectomy, the *New York Times* the next day characterized the attributable risk beautifully. And I think still in places like Oshkosh, Wisconsin the media there still doesn’t get this concept.

Ms. Foreman: I completely agree with you and I also agree that it was the *New York Times*, it was Gina Kolata and Jane Brody who were way ahead of the rest of us in using absolute risk and saying, “Yes, there’s a 26% increased chance of breast cancer on hormones, but that translates to an extra 8 women per 10,000 women years or something.” And when you put it that way, it’s much less scary. So I’ve been trying to do that lately too, and there’s a couple of really good researchers, Schwartz and Lisa – what’s her name – up in Dartmouth, who have a whole course on interpreting statistics for journalists and one of the things they really emphasize is using absolute risk because it gives you a much better idea of if you’re going to be (inaudible background comment) 1, an extra 8 women for 10,000 women years of taking a drug, the chance of you not being in that 8 are pretty good. And it’s a whole different way, and much less frightening way of looking at statistics. And advertisers, I might say, when they’re advertising their drugs, “Twenty-three percent more effective than blah-blah-blah,” they use a relative risk, which is the flip side of this whole thing. Do we have any call on the line? Go ahead.

Ms. Foreman: Okay. Got a question.

Reporter: Hi Judy, this is Adam Martin from *Health Magazine*, we’ve spoken on the phone a couple of times. My question concerns plant compounds and I’m not sure whether your panel really has much to say about this or cares, but some of the sources we’ve spoken with at *Health Magazine* about treating women with these

symptoms, have suggested that some women may benefit from certain plant compounds – soy, black cohosh – without really getting into whether the studies show that there's effectiveness or not, just sort of a blanket statement that some women might. And I guess my question is, really, how do you, as a doctor, how do you decide when you're talking to a woman, whether she ought to try something like that and how do you characterize the chances of the treatment being effective versus the hormone treatments, which you basically know will be effective? And I wonder if there's really a way that you can sort of do this in a systematic way, or it's just patient by patient, depending on whether the patient is interested in that treatment. I hope that makes sense. And by the way, *Health Magazine* is owned by Time Warner. We accept lots of ads from pharmaceutical companies, but on the editorial side, where I am, we have nothing to do with the pharmaceutical company. Thank you.

Ms. Foreman: So this is a question about alternative remedies. Do you want to take that on? You can all have a shot at this.

Dr. Jaffe: Yeah, it's a very important question and it was very clearly asked. First of all, one of the things we need to remember to do as physicians is ask our patients if they are on other agents that we haven't covered, because fully half of them are taking black cohosh or are taking St. John's Wort, and the problem is that we never know about those. And there are very few objective data about any of them and so far. Those that have been studied, by and large, have not been found objectively effective. Now a number of schools, medical schools now, are developing departments of alternative medicine where they're doing systematic studies of these alternative forms of therapy. And hopefully, some objective answers will be forthcoming. In the meantime, what I have to say is, we don't have published evidence in medical journals for most of these, and those that are so far, have not been found helpful. However, it doesn't stop people from taking them.

Ms. Foreman: Actually, I just finished a couple months ago a column on alternative medicine websites that have relatively decent information on some of this stuff, because the information is all over the place. And it was fascinating. You look up something like -- black cohosh was one of the examples I used -- and *Consumer Reports* has a pretty good site where they have a huge pharmacological base. HerbalGram which is a partially industry supported group, the American Botanical Council also has good information. And the information completely splits. The National Center for Complementary and Alternative Medicine (NCCAM) at NIH has good summaries of the stuff. But basically, it's a mish-mash. I mean it's not all terrible data, but by and large, it's much shakier than most doctors are used to in mainstream medicine.

Dr. Santoro: Well, I think we do have some information and the good things about some of these alternatives is that they have a very wide margin of safety, so that for the most part, for use of up to two years, little harm has been shown ever for things like black cohosh and for soy. They're relatively inexpensive, which is also a

good thing and makes them attractive to patients. And in almost all the studies there's at least a transient placebo effect, where symptoms get better for a month or two and then they tend to revert back to what they were before. But if that month or two helps my patient and it's not ridiculously expensive, I'm okay with that. And that may be a reasonable intervention for that person, especially if her symptoms abate and then she doesn't have them for awhile, may want to go back on it intermittently, it may be a reasonable safe alternative. Typically in practice, women who are very symptomatic will not get relief. So most of the time these are for mild to moderate symptoms in someone who is really very proactive and has the layered clothes, sits in front of the air conditioner, does what she needs to do. Adding this may help.

Dr. Santen: Just a comment. You were asking, "How do physicians handle this?" And I think most of us go back to the first principle, is *primum non nocere* – the first thing you do is not harm the patient. What Dr. Santoro was saying is that most of these agents over short term are not harmful. But what's the science in this? I think the science is that these agents are really serums, they're selective estrogen receptor modulators. They have some estrogen effects on some tissues, they have anti-estrogen effects on other tissues and they're mixed. And if you try to study these agents, particularly when there are many of them mixed together, it becomes a mish-mash of really studying what's happening. So can we harm patients with these agents? There's one example that I think we can and these are patients that are on tamoxifen, that are on very high doses of soy. Do we get human data to support what I'm saying? No, but if you put a breast cancer in a nude mouse and treat that mouse with high doses of soy, you'll stimulate that tumor to grow. You then try to block the tumor from growing with tamoxifen and you can't, so this is a situation with products that are being used in pure soy and fairly high concentrations – Genestine and diazine – that really can be harmful. So I think when we approach patients, the first principle is, don't do any harm. The second is, take the science into account, knowing that these agents are partial agonists and antagonists and then based on limited data – we always have to make decisions on limited data. Based on limited data, try to decide whether it's going to do harm or not. If it's not going to do harm, it's reasonable for patients to choose this, to use it for a period of time.

Ms. Foreman: Dr. Stampfer would you like to add something?

Dr. Stampfer: In thinking about alternative therapies, it's instructive to think about the term, "alternative." Alternative to what? So we have scientific data and then what is it? It's sort of magical. And people have this notion that somehow natural products are safe and what comes out of drug companies is harmful. Obviously there are a lot of bioactive materials in plants. The most deadly carcinogens that we know of are natural: asbestos, tobacco. These are natural. So this concept of natural versus unnatural is really not informative for practicing medicine, and I think when you think of alternative, if we're talking about something where there's evidence versus something where there's hope, I think that delineates the issues.

Ms. Foreman: I get so many emails from people promoting natural products and it's all chemical. Everything, water is chemical. Everything is chemical. It really makes me crazy. I know we've got a few – oh, you want to say something?

Dr. Stuenkel: Well, I just wanted to say that I think is a little naïve to think that women who come in are just, kind of, an open book. And very often women will come in and be very clear about what it is that they want to do. And whether they derived this from medical reading that they do, whether this is what the women in their book club are doing, or their bridge club, or in their office, they often will be quite clear about what they'd like to try. And I think that as long as – I think women who have had a history of breast cancer, we have to be a little more cautious with, but if they're otherwise a healthy, postmenopausal woman who – and I think in some ways, we've also given women a little bit of insecurity about the science and the estrogen and with time they're feeling a little uneasy with some of the data that's come out, that I think that it's okay if she comes in and says, "I'd like to do a trial of black cohosh," for example, that it's good to work with them on these _____. (background talking). As Dr. Santoro said, they may not be terribly symptomatic, but have some clear ideas of their own of the way they want to go. I think there's still some art in this practice of menopause symptom management.

Ms. Foreman: We only have a few minutes left and I want to end with a cardiovascular question for Dr. Stampfer, but first some more general questions. There are doctors in Boston and elsewhere who will get women to come into their office and measure their hormones every few months. And my understanding is that this is ridiculous, that hormones vary so much that there's no point in trying to do that. But what do the experts think about this?

Dr. Santoro: I think that's called practice enhancement. It's a financial term.

Ms. Foreman: Ah, that's what I thought. The heart question, Dr. Stampfer, so tell us, first of all, I don't understand why they did WHI with women, starting hormones at 63. That makes no sense. But you can answer that or we can consider that water under the dam. But what should women who are now becoming menopausal do in terms of this issue.

Dr. Stuenkel: They should enroll in the KEEP Study.

Ms. Foreman: Well, they can't all enroll...

Dr. Stuenkel: We're recruiting now. Sure they can here in Boston, there's one in New York.

Ms. Foreman: Well, both of these, but that's a _____ for us. I mean what should women who are every month turning menopausal do with respect to the heart?

Dr. Stampfer: Well, first let me just say about why I think it did make sense back then, because if you look at rates of heart disease, they're extremely age related. They double every five years. So the big burden of heart disease is not at the age group of the time of menopause. I mean it's terrible when it happens then. It's a tragedy. But in terms of numbers, the big mass of risk is in the older age. So faced with observational data in primary prevention that women taking hormones at menopause might benefit, I think it did make sense to do a trial in that older age group to see if women who really bore the brunt of the burden would benefit. If they have done the trial to test what we saw in observational studies, the trial would have been about four or so times the size and the cost, and also would have taken longer. So it's just not feasible.

Ms. Foreman: Well, but that information that doesn't apply – is it doesn't fit with the way most women _____.

Dr. Stampfer: Right. Exactly right. But, suppose it had been the other way. If hormones had been protective in older women through the trial, then you could see that would have caused a huge shift in practice. So it was a hypothesis that was worth testing, so I don't think they should be badly faulted for that. But to get at what you asked – what women should do who become menopausal. I'll give my own personal response, based on the data, which I think is that it should be driven more than it has been on quality of life. Because that's the individual end-point at that time for that woman. So I think for breast cancer, for heart disease, the risks at the time of menopause are very low, so if you have a woman of typical average risk, she's having bad symptoms, I would say, "Sure, go ahead, try hormone therapy for a few years and then reevaluate." And I think what we need to constantly reinforce in this type of thinking is that when you start on hormone therapy, you're not saying, "I'm starting on hormone therapy now for the rest of my life." You start on it, you see how it goes, then you reevaluate a couple years later, taking into account all the evidence that the risk of breast cancer is going to be marching up if you're on estrogen plus progestin. And I think that's also a very key distinction in risk, because there you really do need to be concerned much earlier if they have a uterus and they're on progestin as compared to estrogen alone.

Ms. Foreman: So should we all have hysterectomies and go on estrogen alone?

Dr. Stampfer: No

Dr. Santoro: I think it's important to point out that while there may be many compelling reasons why estrogen alone and estrogen plus progestin differed, the women themselves differed and they differed in substantial ways. So the women who have hysterectomies may be biologically different so that they may process estrogen a little differently. So it may not just be the progesterone.

Dr. Stuenkel: I wanted to just go back to one part of your question, Judy, about why on earth were these trials done on these particular groups of women, because I think we've

developed a collective amnesia about how we were practicing then and it wasn't just for symptomatic women. We had cardiologists in their office giving women estrogen who'd had heart disease to prevent further heart disease, because there were observational data that suggested that. And we had women in their 60s going on hormones to protect their hearts and to protect their bones. So the WHI really wasn't about, "Will my patient feel better on these hormones?" The WHI was trying to find out, will these hormones present some of these long-term chronic disorders. And so I think the point that the observational data was largely generated from younger symptomatic women, is important, but that was really the reason why we went about some of the clinical trials the way we did, was because it was being used and even mandated in some insurance and HMO plans, that a postmenopausal woman must be put on hormones for prevention. And we didn't really have that data clear.

Ms. Foreman: Thank you. I think we should wrap it up, because we're a little bit over our time already. Are there any other questions from the floor? If not, we will call it a morning. Thank you very much. Thanks.