Breast Cancer and Hormone Replacement Therapy-the Truth Behind the Numbers

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TO TAKE OR NOT TO TAKE-that is the question millions of women across the country are asking. The recent release of a new study has forced women and their physicians to revisit the issue of whether hormone replacement therapy increases the risk of breast cancer, and whether these risks are substantial enough to warrant stopping these medications, or never starting them. Unfortunately, the media has over-sensationalized these results, leaving the public unsure what to believe. Are their physicians really allowing them to use a medication which has a 27% increase in breast cancer occurrence?

Why is hormone replacement therapy all over the news today? Recently, a study called the Women's Health Initiative trial has received much attention in the media. This was a landmark study in that it is the first randomized, controlled study of hormone replacement and its long-term effects to be performed. The main focus of the study was to evaluate the effects of hormone replacement therapy on cardiovascular disease. Data obtained were then used to balance the risks and benefits of hormone replacement in terms of coronary heart disease, stroke, pulmonary embolism, breast cancer, endometrial (uterine) cancer, colorectal cancer, hip fracture and death due to other causes.

The study was designed to look at 2 hormone combinations and compare their effects with placebo, or no drug at all. The 2 drugs studied were Premarin, which is synthetic estrogen, and Prempro, a combination of estrogen and medroxyprogesterone acetate (MPA). MPA is a manufactured type of progesterone. Women who have an intact uterus, or have not undergone hysterectomy, need to take both estrogen and progesterone in order to protect themselves from developing uterine cancer. The study was scheduled to run until 2005, thus determining the effects after 8.5 years of treatment.

The reason for the recent media buss is that part of the study was concluded prematurely. The investigators had set predetermined limits in order to ensure that no serious adverse effects were occurring to patients who had enrolled in the study. The investigators found an increased risk of coronary heart disease and breast cancer in the women who were on Prempro. The results were not duplicated for the patients taking Premarin alone, thus that portion of the study is still underway.

With any possible risk, why would anyone take hormone replacement therapy? There are many reasons physicians may offer their patients estrogen. First and foremost are the bothersome symptoms associated with the change of life, namely hot flashes, night sweats, difficulty sleeping, severe mood changes, sexual dysfunction and vaginal dryness. Despite the multitude of complaints that can be relieved by the administration of estrogen, most physicians, especially gynecologists, support the use of hormone replacement therapy for other reasons that may be undetectable to patients. The primary prevention of osteoporosis is undisputed, as well as favorable effects on the cholesterol profile, prevention of colon cancer, and decrease in the incidence of Alzheimer's disease. Estrogen also restores the vagina, keeping the tissue healthier, and eliminates bladder urgency, frequency, and incontinence.

Despite the known positive effects of hormone replacement therapy, there has continued to be a constant negative influence by the media, supporting myths about its usage without concurrent opinions to the contrary. Information released by the medical community is sensationalized, producing dramatic headlines but often out of context. What makes it more difficult for the general population is that often "experts" are quoted in these articles, leaving it to appear that there is no doubt that physicians have certainly been prescribing medications that are sure to cause cancer and other poor outcomes.

What is a patient to believe? Let's first begin by reviewing what we knew prior to the release of the Women's Health Initiative study. Breast cancer risk has been linked in the past to prolonged exposure to estrogen produced by a woman's own body. For example, early onset of

menstruation, late onset of menopause, and obesity, a condition that naturally raises one's internal estrogen levels, have all been associated with increased risk. The detection of the risk factors prompted the investigation in what effect the administration of post menopausal estrogen would have. To date there have been over 50 studies looking at estrogen use and negative health outcomes. Premarin has been commercially available since 1940, and it is probably one of the most well studied drugs ever used. To that means, any adverse effect due to estrogen should be readily apparent by this time.

This is, however, certainly not the case. In fact, review of the literature leaves even the well-trained statistician unsure what to think. There are as many studies, if not more, which prove that use of estrogen is not related to any increase risk of breast cancer. Those studies that do show an increased risk find a slight increase only, and mainly only with prolonged usage, generally greater than 5 or 10 years. It is difficult to determine whether these risks are actually associated with estrogen, progesterone, or both.

So what about the Women's Health Initiative and its negative findings? Does that mean we finally have definitive evidence of the potential dangers of hormone replacement? Not necessarily. Although designed in a manner to finally get answers to some important questions, there were some significant flaws with both the study and the design.

For starters, as mentioned above, only two drugs, Premarin and Prempro, were studied. There are now a large number of other commercially available drugs today used in menopause that contain neither Premarin nor Provera. There are also a variety of all-natural compounds that may be prescribed in a similar fashion. Obviously, one cannot with any certainty apply the outcomes of this study to any hormone preparations, dosages, combinations or routes of administration.

Secondly, the participants of this study averaged an entry age of 63. That means that most of the women enrolled in the study had been menopausal at least 10 years prior to treatment.

This happened because the majority of women just reaching menopause find their symptoms so distressing that they did not want to take a chance they would not receive real hormones and risk not feeling better. It is therefore likely that these women had an increased adverse risk profile to begin with, because they were less likely to have been receiving gynecological care up to that point. Indeed, almost 8% of participants reported pre-existing CHD, 50% smoked, 70% were obese, and 20% were over 70 years old. Breast cancer is known to increase with increasing age.

The study claims to be well designed because it is randomized. What that means is that when a patient is enrolled, their risks factors are analyzed and they are separated into groups such that both women getting hormone and those getting placebo share similar backgrounds, age, race, medical history, smoking history, etc. That is fine but one needs to consider that the type of patient who enrolls in a study like this may not actually be representative of the average person in the population. That is, they may not have received the same care prior to enrolling in the study and their risk factors may not apply to the general population. One of the prerequisites for being in the study was that one could not have taken hormone replacement in the past, or needed to be off hormones for a given length of time before joining the study. Therefore, it is impossible to tell if the outcomes measured would have been the same if patients had started treatment at the usual time of onset of menopause.

So what does this all mean? According to the media's interpretation of the WHI study, there is a 27% increase in risk of breast cancer from combination HRT. Well, in reality, there are 38 cases of invasive breast cancer per 10,000 women in the Prempro arm, versus 30 cases in the placebo arm. That is, 8 more women per 10,000 who developed breast cancer, or an excess of 0.8%. Overall this is still a low absolute risk. Furthermore, when analyzed statistically, these results were found non-significant and therefore inconclusive. These differences were not found until treatment had continued past 4 years.

This data is actually consistent with prior studies documenting a lack of any significant increase in breast cancer risk with duration of treatment less than 5 years. Two such studies, the Collaborative Re-analysis and the Nurses' Health study have received little attention from the media. Also, studies have indicated that while some estrogen users may have a higher incidence of breast cancer, they are found earlier and more amenable to treatment. It may be strictly that more the tumors grow more rapidly on HRT so in comparison are found earlier, which falsely raises the incidence ratio. That is, it makes it seem that there are more cases, when actually they are just found earlier and thus in any given time frame, have a higher detection rate.

The other main point of interest is that women taking Premarin alone are still enrolled and being studied. That means that they found no equivalent increase in events leading them to stop this part of the study. That tends to point to progesterone, or in this case Provera, as the place the problem may lie. If this is the case, it is difficult to predict whether other forms of commercially available progesterone would have the same effects or not.

Probably the most important omission from the HWI was any comment on quality of life. Most menopausal of perimenopausal patients will tell you that their symptoms are so severe that they would do anything to feel better. There are significant improvements in all of the symptoms mentioned earlier in women taking estrogen products. Even some women with a history of breast cancer would say that they would accept a small increase in risk of recurrence in order to alleviate their symptoms, and improve their quality of life.

What is reasonable to conclude from the recent information? According to Dr. Utian who is the founding president of the North American Menopause Society, there are a few probable conclusions that can be made. First is that combination hormone replacement in the form of Prempro is of no value in reversing established coronary heart disease of preventing it in apparently healthy women. Secondly, that the use of this medication may in fact increase the risk of heart attack and development of blood clots, especially in the first 1-2 years after

beginning therapy. Third, there is a slight increase in breast cancer occurring at about 4 years of usage, with a slight decline in number of events later. This may confirm that the hormone replacement therapy actually causes an increase in growth of breast cancer that already exists, rather than being the causative agent per se. With the premature conclusion of the study, however, this question was not adequately answered.

Next, all of the above problems are more likely to be due to the effect of Provera on Premarin, since those women taking only Premarin in this study did not have the same outcomes. Finding ways to give estrogen with either lower doses of progesterone, different formulations of progesterone, or cyclical and not daily administration may in the future hold promise for women to still receive the benefit from estrogen. Also, there is substantial evidence that there is early benefit shown for women on combination hormone therapy in terms of reduction in hip fracture and colorectal cancer. Finally, estrogen alone may very well be proven to have a favorable benefit ratio, as opposed to being more detrimental than no hormone at all.

In conclusion, whether or not to take hormone replacement therapy is a very individual decision. Women making this choice have to weigh many factors, including their own risks for later development of breast cancer. Family history may play a role in this decision. It seems highly doubtful that short-term, less than 5 year treatment with even combination hormone replacement therapy will ever prove to be a highly significant risk factor for development of serious health issues. The prevention of menopausal symptoms is often enough impetus for many women to start and continue HRT.

Women who are considering stopping or starting hormone replacement need to speak with their own physicians in order to determine if they are good candidates for these medications. One can obtain the best information for their own personal benefit from a health care provider who has knowledge about their risk/benefit profile. Those women who are currently on hormone replacement are urged not to discontinue their medications without prior consultation with their physicians.