



EXCLUSIVE NEW BOOK EXCERPT

NATURAL HORMONE REPLACEMENT REDUCES CANCER RISK

BY JONATHAN V. WRIGHT, MD and
JOHN MORGENTHALER

Members of the “baby-boom” generation have learned to expect medical solutions to medical “problems,” and menopause is no exception. Growing up with birth control pills, our generation is the first’ generation in human history with the option of spending the entire fertile life span taking hormones to control reproductive function. Why should postreproductive, “menopausal” life be any different?

Indeed, why should it? The major medical solution to menopause for more than three decades has been a variation of birth control pill technology known (somewhat inaccurately) as “estrogen” replacement therapy, or ERT. The logic behind ERT is quite simple. If a lack of estrogen is causing body systems to malfunction and making life generally miserable, why not just replace the missing estrogen?

The promise - and apparent simplicity - of ERT is attractive: a life free from hot flashes, vaginal pain, and other discomforts of the perimenopause. And, after menopause, ERT seems to offer crucial protection against at least two major causes of death

and disability in older women: cardiovascular disease and osteoporosis.

So attractive is this promise that one form of “estrogen”* Premarina (which is derived from the urine of pregnant bones!), has been among the most frequently prescribed human) drugs every year since the early 1970s. In 1996, more than 22 million prescriptions were written for Premarin in the United States (about twice as many as those for such popular drugs as Prozac© and Zantac©, which was worth nearly \$370 million to its manufacturer, Wyeth-Ayerst Pharmaceuticals.

A Disturbing Undercurrent

Despite the overwhelming clinical and marketing success of Premarin and other forms of patentable “estrogen.” there has been, almost from the start, a disturbing undercurrent of doubt about the safety of conventional “estrogen” replacement therapy. That doubt can be summed up in one word: cancer.

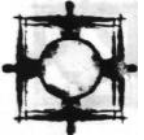
The increased risk of endometrial cancer from “ERT” is largely eliminated when women take a patentable “progestin” or natural progesterone along with their “estrogen” (making it “HRT”), but the risk of breast cancer remains highly controversial.

Scores of large, sophisticated, expensive studies have been done over the years to try to answer one key question: Does replacement horse

* Premarin® isn't exactly the same as human estrogen, which is why I've put the “estrogen” in ERT in quotation marks. This is an extremely important point that I will come back to repeatedly.



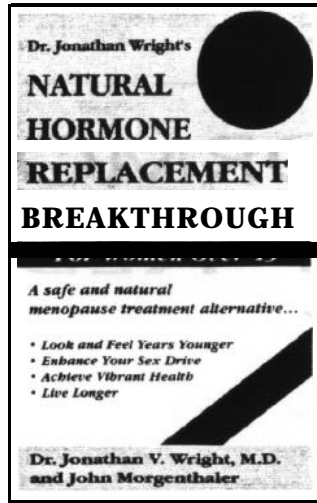
Co-authors John Morgenthaler and Jonathan V. Wright, MD



Natural

Hormone
for Women
over 45.

Smart
Publications,
will be
released by
May and will
be available
for \$9.95
through LIFE
enhancement
or your local
book store



estrogen cause human breast cancer? (I'm NOT making this up!) You, I, and any reasonable high school science student would want to know if replacement human estrogen causes human breast cancer. But then, you, I, and reasonable high school students don't own patents and make huge amounts of money selling horse estrogen.)

Despite all the time and money thrown at (some might say, wasted on) the problem of "HRT" and human breast cancer, the answer still remains elusive. There's no direct proof HRT causes breast cancer, but at the same time, it's not possible to say that it doesn't. In the face of this uncertainty, though, three facts remain indisputable:

In nearly all the large scale studies that have examined the relationship between estrogen replacement and cancer, the "estrogens" used have been estrone + equilin (Premarin), estradiol, or ethinyl estradiol.

The results of many studies in laboratory animals and cell cultures have confirmed that estrone, equilin, estradiol, and ethinyl estradiol can all cause cancer in endometrial and breast tissue.

Some researchers think estriol - the major component of human estrogen - has virtually no propensity to cause cancer, and that it reduces the carcinogenic activity of other estrogens and other carcinogenic chemicals in breast tissue. Others, especially those working with estriol in "unnatural" ways in experimental animals, believe estriol may have carcinogenic potential.

No large studies have been done in a human population to examine the possible risk of cancer associated with estriol (or triple estrogen, the combination of *estriol*, *estradiol*, and *estrone* in their natural proportions). However, a large amount of clinical and laboratory evidence dating back to the mid-1960s has been collected that addresses the issue of estriol and cancer.

This research strongly suggests that estriol has less cancer-causing potential than estrone, equilin, estradiol, and ethinyl estradiol, and that estriol may actually inhibit the carcinogenic activity of these other "estrogens."

How Some "Estrogens" May Cause Cancer

One of estrogen's primary roles is the stimulation of growth and proliferation of cells of the endometrial lining of the uterus and cells of the breasts in preparation for pregnancy and lactation. Estrogens accomplish this by stimulating estrogen receptors located on cells at these sites.

In the endometrium, the tendency of "estrogens" to induce proliferation is opposed by progesterone (or patentable "progestins." In breast cells, the picture is much less clear. It appears possible that "estrogen" stimulation of already cancerous breast cells is much less opposed by progesterone (or "progestins") than "estrogen"-induced stimulation of endometrial cells.

Built-in Cancer Protection

Unlike other "estrogenic" treatments, such as horse estrogens or 100% estradiol, there is no evidence that estriol at reasonable doses stimulates excessive proliferation of endometrial cells, which is a precursor to endometrial cancer. Estriol actually may antagonize the proliferative activities of other estrogens, probably because it competes for and benignly occupies estrogen receptor sites that would otherwise be occupied by the other more proliferation-oriented estrogens' (Fig. 1). Thus, it appears that Nature may use estriol to partially block these powerful hormones before they can do harm.

Studies in experimental animals have shown that the proliferative dose of estriol is at least twice as high as it is for horse estrogens (equilin + estrone) and estradiol, and 60 to 75 times higher than that of the synthetic estrogen ethinyl estradiol. This translates into a reduced or even negligible risk of endometrial cancer from estriol.

If Henry Lemon, MD, is correct, estriol may be Nature's own built-in cancer protection. During the 1960's and 1970's, Dr. Lemon, a long-time physician, medical researcher, and former head of the division of gynecologic oncology at the University of Nebraska College of Medicine, studied the apparent ability of estriol to protect women against breast cancer.

Work published prior to Dr. Lemon's had already demonstrated that estradiol and estrone were both capable of promoting abnormal cell proliferation, including endometrial and breast cancer. It was also well-known that the body treats these two hormones with extreme care,



Continued on page 24

Continued from page 23

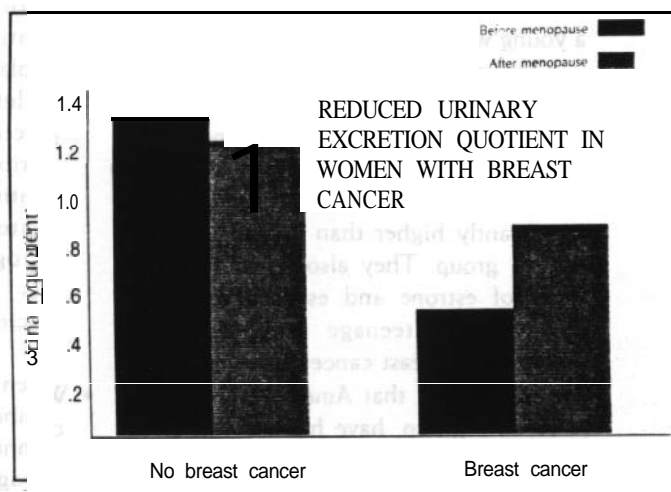


Figure 2

converting them to estriol rapidly and irreversibly. Estriol, however, had no carcinogenic tendencies, as far as anyone knew.²

“Was it possible,” asked Dr. Lemon, “that some women who develop breast cancer have too little estriol relative to estradiol and estrone circulating in their bodies?” While there had long been suspicion that estrogen was somehow related to breast cancer, until Dr. Lemon came along, no one had thought to look at the levels of each of the three primary estrogens separately to see how each one related to cancer.

To answer his question, Dr. Lemon ran a preliminary study in which he employed a urinary estrogen quotient (Eq), which was simply a measure of the ratio of estriol to the total of estradiol + estrone in the urine over a 24-hour period; the higher the quotient, the more estriol there is relative to estradiol and estrone.³

In 34 women with no signs of breast cancer, Dr. Lemon found the Eq to be a median of 1.3 before menopause and 1.2 afterward, with only 21 % of the women below 1.0 less estriol than estrone plus estradiol).

$$\frac{\text{Estriol (ug/24hr)}}{\text{Estradiol + Estrone (ug/24hr)}} = \text{Eq}$$

The picture was quite different in the 26 women with breast cancer. Their median Eq was 0.5 before menopause and 0.8 afterward, with 62% below 1.0 (Fig. 2). Thus, the women with breast cancer seemed to be making substantially less estriol relative to the other estrogens than women without breast cancer.

Dr. Lemon’s results raised many questions. Does this apparent hormone imbalance open the door to breast cancer? Is it a reliable biologic marker of breast cancer risk? Could it

be used to predict which women were vulnerable to the disease but had not yet developed it?

And most importantly, could restoring the natural hormone balance prevent breast cancer and perhaps even treat ongoing disease? These are intriguing questions that still need good solid scientific answers.

Some researchers have published work disputing Dr. Lemon’s findings, while others have published research supporting him. The issue is complicated by the fact that a woman’s level of estriol when breast cancer becomes apparent may not be as

HORMONE REPLACEMENT

important as a deviation from the norm in her estriol levels as a young woman as a young woman.

One group of researchers found the levels of estrone and estradiol (the known procarcinogenic estrogens) in the blood of 150 sisters and daughters of women with breast cancer to be significantly higher than in a matched control group. They also found blood levels of estrone and estradiol to be higher in 36 teenage daughters of women with breast cancer. They noted studies showing that American women (who, as a group, have higher rates of breast cancer) have lower levels of estriol than Asian women (who, as a group, have lower levels of breast cancer), especially at the time the studies were done. The researchers pointed out that Asian women in Hawaii - whose breast cancer levels were midway between those of Asian women in Asia and American women - also had levels of estriol midway between American women and Asian women in Asia. Clearly, much more research, including large-scale, long-term human trials will be necessary to answer the many unanswered questions regarding estriol's role in cancer.

Despite the absence of these large expensive clinical trials, much of the evidence that is already available is encouraging. Dr. Lemon's preliminary results make sense in the light of several findings reported by other researchers, as well as by Lemon himself:

Laboratory animal studies totaling more than 500 rat-years have demonstrated that estriol is the most active protective estrogen ever tested against cancers of the breast induced by several potent carcinogenic agents,⁷ including radiation.⁵

- Few animal studies have shown estriol to have any significant carcinogenic activity - unlike estrone and equilin, estradiol, ethinyl estradiol, DES, and other patentable "estrogens," which are

routinely found to be carcinogenic. Estriol, given in high doses, given continuously (every day), or implanted under animals' skins in pellets has been found to be carcinogenic. However, when estriol is given in pulses, or in non-continuous doses (which approximates the natural pattern of estrogen secretion), it was much less carcinogenic or not carcinogenic at all.

- When estriol is given to rats and mice combined with estradiol and estrone, it inhibits the ability of these other estrogens to stimulate uterine growth.⁶
- Estriol gives the immune system a boost by enhancing the activity of certain cells known as phagocytes whose job it is to consume foreign invaders, such as bacteria and viruses, and cancer cells.
- In a group of premenopausal women with noncancerous breast diseases, including fibroadenoma, sclerosing adenosis, and intraductal hyperplasia, estriol excretion was found to be subnormal in 60's.⁷
- Dr. Lemon observed low estriol secretion in three women who had not yet developed cancer but had precancerous changes of the breast.⁸
- During pregnancy, a woman's body increases its secretion of estriol by 1,000-fold. After pregnancy, estriol levels drop but usually remain higher than they were prior to pregnancy. This may help explain why women who have never given birth have a higher risk of breast cancer than women who have borne a child.⁹

On balance, the evidence arising from modern scientific research favors estriol (when used in physiologic doses according to natural timing patterns) as a noncarcinogenic, anti-carcinogenic, or

Continued on page 26

HORMONE REPLACEMENT

Continued from page 25

at worst, lowest risk estrogenic substance. When modern science isn't crystal clear, it's always safest to mimic Nature as closely as possible, which is why NHR employs the three human estrogens in exactly the patterns established in women's bodies over tens of thousands of generations. This is undoubtedly safer than using horse hormones, other patentable estrogens, or incomplete, wrongly dosed, or poorly timed natural estrogens, such as estradiol.

Progesterone and Breast Cancer

Unlike synthetic "progestins," which have an uncertain influence on breast cancer, two important studies employing natural progesterone have demonstrated a clear protective benefit. In one publication, researchers

at the Johns Hopkins University Medical School reported on more than **1,000** women being treated for infertility who were followed for more than **20** years. The women were divided into two groups, those whose infertility was caused by a deficiency in progesterone and those whose progesterone level was normal. With all other possible influences accounted for, the women who were progesterone-deficient had a 5.4-fold greater risk of premenopausal breast cancer compared with the women whose progesterone was normal. Even more startling was the finding that the progesterone-deficient women had a 10-fold higher rate of death from cancers of all kinds. ¹⁰

The other study, conducted in Taiwan, focused on the proliferation of breast epithelial cells removed from women who had undergone a lumpectomy for breast cancer. About 10 to 13 days prior to their surgery, the women were randomly assigned to apply a topical gel containing either estradiol, progesterone, estradiol + progesterone, or a placebo each day. When the researchers examined postsurgical breast tissue from around the lump, they found increased proliferation of breast epithelial cells in the samples from the women who had used the estradiol-only gel compared with placebo. By contrast, cell proliferation was significantly reduced in the tissue samples from the women who had used either the estradiol/progesterone gel or the progesterone-only gel. ¹¹

What about Ovarian Cancer?

The risk of developing ovarian cancer as a result of "hormone" replacement has not been investigated nearly as intensively as breast or endometrial cancer. It should be. A large, prospective study recently conducted by the Emory University School of Public Health in Atlanta, Georgia, reported about more than

240,000 peri- and postmenopausal women studied for seven years. The results indicate a significant risk associated with “estrogen” replacement. During the course of the study, 436 of the women died from ovarian cancer, and their risk of dying increased significantly with the length of time they had been taking “estrogen” replacement. Women who had used “estrogen” for six or more years but had stopped using it were found to be just as much at risk as current users.¹²

let's Remember ... and Research the “Forgotten Estrogen”

In a 1978 editorial in the *Journal of the American Medical Association* titled, “Estriol, the Forgotten Estrogen?” Alvin H. Follingstad, MD, bemoaned the lack of large clinical trials on estriol that would earn it an FDA stamp of “approval.” Do we as clinicians have to wait the years necessary for the completion of these trials before estriol becomes available to us? he asked. “I think not. Enough presumptive and scientific evidence has been accumulated that we may say that orally administered estriol is safer than estrone and estradiol.”

Two decades later, we are still waiting for those clinical trials, and what Dr. Follingstad said then is even more true today. There’s nothing to be gained by waiting. If a woman is concerned about her risk of cancer from estrogen replacement (and who isn’t?), then the logical choice (considering both modern scientific research and hundreds of thousands of years of human experience with producing and metabolizing estrogens) is estrogen containing a majority of estriol, or in some cases, estriol alone.

References

1. Hisaw FI, Velardo JT, Goolsby CM. Interactions of estrogens on uterine growth. *J Clin Endocr.* 1954;14:1 34-1143
2. Hamilton. TH. Control of estrogen of genetic transcription and translation. *Science* 1968: 161.649-661.

3. Lemon. HM, Wotiz HH, Parsons. L, Mozden PI. Reduced estriol excretion in patient with breast cancer prior to endocrine therapy *JAMA* 1966.196.112-120.
4. Lemon HM. Oestriol and prevention of breast cancer *The Lancet* March 10, 1973:546-547
5. Lemon HM, Heidel JW, Rodriguez-Sierra JF. Principals of breast cancer prevention 1991, Paper presented at Annual Meeting of the AACR
6. Hisaw FI, Velardo JT, Goolsby CM. Interactions of estrogens on uterine growth *J Clin. Endocr.* 1954, 14:1134-1143
7. Bacigalupo G, Schubert K. Untersuchungen uber die oestrogen ausscheidung im urin bei mastopathie *Klin Wochr.* 1960, 38: 804-805.
8. Lemon, HM, Wotiz. HH, Parsons. L, Mozden. PI. Reduced estriol excretion in patients with breast cancer prior to endocrine therapy. *JAMA* 1966; 196 112 - 120.
9. Siiteri PK, MacDonald PC. The utilization of circulating dehydroepiandrosterone and fate for estrogen synthesis during human pregnancy. 1963, .2:713-730.
10. Cowan LD, Gordis JA, Tonascia JA, Jones GS. Breast cancer incidence in women with a history of progesterone deficiency. *J. Epidemiol* 1981, 114-209-217.
11. Chang KJ. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo *Fertil Steril* 1995; 63 785 - 791
12. Rodriguez C, Calle EE, Coates RJ, Miracle-McMahill HL, Thun MJ, Heath CW. Estrogen replacement therapy and fatal ovarian cancer. *Am J Epidemiol* 1995, 141:828-835.