Estrogen Metabolite Ratios: Time for Us to Let Go

by Jacob Schor, ND, FABNO

For the past 30 years we have relied on a theory that particular estrogen metabolites stimulate hyperproliferation in the hormone sensitive tissues of the breast and uterus and so increase risk of cancer development. Recent studies call this theory into question; it is time to assess whether we should still rely on these ideas for judging patient risk and more importantly for guiding patient treatment. Let us take a few moments to put this story in perspective.

The first mention of what we call the "estrogen metabolite ratio" theory was published in May 1982, in a paper by Jill Schneider et al. in the Proceedings of the National Academy of Science. Newly devised radiometric techniques allowed these researchers to accurately measure estrogen metabolites in 33 women with breast cancer and compare their levels with 10 women without cancer. Their data revealed a significantly higher rate of 16-hydroxylation in the cancer patients. These pathways can produce compounds that are potent estrogens, and Schneider et al. were the first to wonder whether this could have a bearing on the etiology of the disease.1

Metabolism of estradiol is oxidative and consists of an initial oxidation of a 17-beta-hydroxy group to yield estrone. Estrone is metabolized mainly through two alternate pathways, either hydroxylation at the C-2 or the 16-a position. These two pathways compete for substrate and yield products that, while both biologically active, have different properties. The 16a-hydroxyestrones are tissue stimulating, similar to estradiol. The 2-hydroxyestrogens, in contrast, have almost no estrogenic effect. Thus Schneider et al. theorized that "the relative amounts of specific estrogen metabolites rather than the quantity of the secreted parent substrate increase the risk for the disease [breast cancer] either by prolonging estrogenic activity or by virtue of the unique biological properties of a particular metabolite." They suggested that elevated levels of 16a-hydroxyestrogens could increase risk of breast cancer.

Two years later, Fishman along with Schneider and two other colleagues reported in the April issue of the Journal of Steroid Biochemistry that they had measured increased activity of the 16a-hydroxylase activity in women with breast or endometrial cancer. The increase in enzyme activity preceded clinical evidence of disease and so was seen as a significant prognostic or risk factor for estrogen dependent tumors.2

Two more years pass, this is 1988 now, and Fishman and Swaneck bring us the next piece to the story. They reported that 16a-hydroxyestrone binds in such a way to the estradiol receptors on breast cancer cells that it sticks, causing long lasting stimulation. As they put it, " … the estrogen bound extensively and irreversibly … "3

These early studies did not show up on my radar. The first that I read about the estrogen metabolite theory was in a 2002 article published in Alternative Medicine Review. The article was written by Lord, Bongiovanni, and Bralley, all working for MetaMetrix Clinical Laboratory.

By the time of their review, the evidence had grown stronger. Meilahn's prospective study published in 1998 in the British Journal of Cancer had measured estrogen metabolites in 5104 women aged 35 and older with a median follow-up time to cancer diagnosis of 9.5 years. Using the ratio of 2-hydroxyestrone to 16a-hydroxyestrone as a biomarker, they reported that those in the highest tertile compared with those in the lowest tertile showed a 30% lower risk of breast cancer. These differences however did not reach statistical significance (OR = 0.71, 95% CI = 0.29–1.75).4 Even so, they sounded good.

What was exciting about the Alternative Medicine Review is that Lord et al. not only brought this theory of how these metabolites could effect cancer risk to our attention, they revealed how we might ameliorate the potential threat that these "bad estrogens" posed through diet and supplements. Apparently all that patients would need do was to consume more cruciferous vegetables. It was all so naturopathic. According to the Lord article, these foods are high in indolymethyl glucosinolates, which in turn release indole-3-carbinol. In 2000 Kishida had reported that high doses of 1-3-carbinol fed to mice reduced 16a-hydroxyestrone.5 Thus, in theory, a woman could increase her 2/16a-hydroxyestrone ratio using diet and supplements, and so lower her risk of cancer.

This theory is well summed up on the popular website Natural News:
… the estrogen compounds called 2-hydroxyestrone and 16-a-hydroxyestrone are by far the most important for breast health. 2-hydroxyestrone is considered 'The Good Estrogen' because its presence doesn't seem to increase breast cancer risks, and MAY even be protective against it. However, 16-a-hydroxyestrone is considered 'The Bad Estrogen' because its presence seems to INCREASE breast cancer risk and has even been called a cancer CAUSING agent! All women have both estrogens, but each woman has a different RATIO, and this ratio is more important to health than the total AMOUNTS of the estrogens.6

This estrogen metabolite theory quickly became accepted and adopted into alternative clinical practice. It sounded good; it made sense; labs could test hormone metabolites; patients would buy supplements and, if they took them, shift the lab results.

There is a problem that we should mention: ongoing research has not supported this theory.

There have been at least seven decent clinical studies published over the years that have not found a significant association between these estrogen metabolites and breast

cancer. Significance is found for specific subgroups in some trials but these subgroup results lack consistency.

Lack of statistical significance in the association between metabolites and breast cancer risk in the Melihan trial from 1998 was already mentioned.

A paper by Muti et al. published in November 2000 in Epidemiology also failed to find significant association. Muti conducted a prospective nested case-control study of 10,786 women enrolled in the prospective Italian study "Hormones and Diet in the Etiology of Breast Cancer" (ORDET). After an average of 5.5 years of follow-up, 144 breast cancer cases and 4 matched controls for each case were identified among the participants of the cohort. Among premenopausal women, a higher ratio of 2-hydroxyestrone to 16a-hydroxyestrone at baseline was associated with a nonsignificant reduced risk of breast cancer: women in the highest quintile of the ratio had an adjusted odds ratio (OR) for breast cancer of 0.58 (95% confidence interval [CI] = 0.25–1.34). The odds ratio in postmenopausal women was 1.29 (95% CI = 0.53–3.10).7 Though nonsignificant, the trend could support the theory for premenopausal women but oppose it in postmenopausal women.

Cauley et al. also failed to report significant association when their study was published in 2003. Estrogen metabolites of 272 women with breast cancer were compared with 291 controls. There was no significant difference in the ratio of 2- to 16a-hydroxyestrone between the groups. The risk of breast cancer in women with the highest quartile of this ratio compared with those in the lowest quartile was 1.17 (95% confidence interval = 0.73–1.87).8 In this case, though nonsignificant, the trend was opposite of what the theory predicts.

Nor did the results of Wellejus et al., published in 2005, support the theory. Data were collected from a cohort of 24,697 postmenopausal Danish women. During follow-up, 426 breast cancer cases were identified. Higher 2-hydroxyestrone levels significantly increased incidence of estrogen receptor-positive breast cancer among current hormone replacement therapy (HRT) users. Higher levels of 16a-hydroxyestrone nonsignificantly lowered risk of estrogen receptor positive breast cancer.9 Again, these trends were opposite of what one would expect based on the theory.

Modugno et al. in 2006 did report a significant positive association between 16a-hydroxyestrone in women not taking hormone replacement therapy, especially if they had high BMIs. This was a nested case-control study using data collected from 200 women who developed breast cancer and 200 healthy controls. The 16a-hydroxyestrone levels were modestly yet still significantly higher in HRT users among breast cancer patients. But 2-hydroxyestrone levels were also substantially and significantly higher in HRT users among breast cancer patients. No associations between BMI, estrogen metabolism, and breast cancer risk were found for HRT users. For non-HRT users only, greater BMI and higher 16a-OHE1 levels were individually and jointly associated with

increased breast cancer risk (OR for women with high BMI and high 16a-OHE1 compared with those with low BMI and low 16a-hydroxyestrone = 3.51, 95% CI = 1.34–9.16). Estrogen metabolism differs according to both BMI and HRT use, potentially explaining the interaction between BMI and HRT in relation to breast cancer risk.10

A 2008 paper is also worth mentioning. Heather Eliassen and colleagues at Harvard's Channing Laboratory reported on their attempt to sort out the impact of these estrogen metabolites. They conducted a prospective case-control study using data and blood samples from the Nurses' Health Study. They tested for 2-hydroxyestrone and 16a-hydroxyestrone in blood samples collected between 1989 and 1990 and compared levels in 340 cases of breast cancer with 677 matched controls. Neither estrogen metabolite appeared to change breast cancer risk. Nor did the ratio between the two metabolites make a significant difference.

There was, however, a significant positive association observed for the 2-hydroxyestrone and the 2:16 ratio among women with ER-negative and PR-negative tumors. High numbers for either were associated with triple the relative risk for this small subgroup of breast cancer patients. Again these results are reverse from what the theory predicts. While these results don't support the basic hypothesis that 2-hydroxyestrone lowers breast cancer risk nor that the 2- versus 16-a ratio is predictive of risk, the significant link found with hormone receptor negative breast cancer is worth noting.11

Then there is Arslan et al. 2009: In this case 377 premenopausal breast cancer patients were compared with an equal number of matched controls. Again, " … no significant associations were observed between breast cancer risk and serum levels of 2-hydroxyestrone, 16a-hydroxyestrone, or their ratio."12

Examining the results of these various clinical trials led one recent reviewer to conclude, "On the whole, prospective epidemiological data do not support the hypothesis that the 2-hydroxyestrogen pathway is protective, and the 16a-hydroxyestrogen pathway harmful, in hormone-dependent cancers" (Zeleniuch-Jacquotte).

Perhaps the most important paper so far is a February 2011 meta-analysis by Obe et al. Data from nine prior studies comprising 682 premenopausal cases and 1189 postmenopausal breast cancer cases were combined. In comparing the "… highest compared with the lowest quantile of urinary EMR [estrogen metabolite ratio], nonsignificant associations suggested at best a weak protective effect in premenopausal but not in postmenopausal breast cancer (range of odds ratios: 0.50-0.75 for premenopausal and 0.71-1.31 for postmenopausal). … Circulating serum/plasma EMR was not associated with breast cancer risk. … Results of the prospective studies do not support the hypothesis that EMR can be used as a predictive marker for breast cancer risk."13 (emphasis added)

The data are no more supportive for endometrial cancer. A paper published in October 2011 in the British Journal of Cancer deserves our attention. Zeleniuch-Jacquotte et al. conducted a case-controlled study of 179 endometrial cancer cases and 336 controls. No significant association was observed for the 2- versus 16a ratio. Their results did not support the hypothesis that " … greater metabolism of estrogen through the 2-hydroxy pathway, relative to the 16a-hydroxy pathway, protects against endometrial cancer."14

Perhaps the most recent look at this estrogen metabolite theory comes from Mackey et al. published in August 2012. Data that came from 845 women with breast cancer were matched to 1690 control patients. Mackey reports a modest positive association between higher baseline levels of 2-hydroxyestrone and larger 2:16 ratio with breast cancer risk. Again, this is reverse from what the EMR theory suggests. With hormone replacement therapy, breast cancer risk was associated with greater increases in 2-hydroxyestrone and larger 2:16 ratio, but these associations were not significant. Increasing amounts of 16a-hydroxyestrone that resulted from hormone replacement therapy were not associated with breast cancer.15 A modest increase in risk for breast cancer was found in those women with a higher 2-hyrdroxyestrone level at baseline. Increased 16a-hydroxyestrone was not associated with greater risk. Read that over if you need to. This is reverse from what the EMR theory predicts.

These multiple large trials have not produced significant or convincing evidence in support of the good vs. bad estrogen theory.

At the same time that all this has been going on, there is some evidence that 16a-hydroxyestrone is actually protective in other ways. A 2009 study in the American Journal of Hypertension reported that there is an inverse association between 16a-hydroxyestrone and systolic blood pressure in women; that is, the higher the 16a levels, the lower their blood pressure.16

A July 2011 paper by Patel et al. reported that 16a-hydroxyestrone levels were affected by fiber intake. Soluble fiber has a greater impact than dietary fiber. Dietary fiber is higher in grains and beans while fruits and vegetables provide more soluble fiber. CYP1A2, one of the cytochrome P450 enzymes made by the liver and important in the formation of 16a-hydroxyestrone, is increased by soluble fiber in the diet. Patel hypothesizes that women who eat a lot of fruits and vegetables – because the soluble fiber in these foods increases CYP1A2, which in turn increases 16a-hydoxyestrone – will have lower systolic blood pressures.17

2-hydroxyestrone levels are affected by genetics and lifestyle factors including, weight, smoking, and consumption of hydroxybenzoic acid, anthocyanidins, wine, and caffeine. 18 Exercise generally doesn't increase the 2:16 ratios except in women with very low initial 2:16 ratios; for this subgroup, losing weight and exercising does seem to shift production toward greater 2-hydroxyestrone.19,20

Some would argue though that the "proof is in the pudding." In other words, that supplements which we have associated with "improving the ratio" (increasing the 2:16 ratio) lower breast cancer risk. Even this seems to be unraveling. One example is soy food intake. In a January 2012 study, Morimoto et al. reported that high soy intake (more than 2 servings per day) compared with low soy intake (< 3 servings per week) increased the 2:16a-OH E(1) ratio, a result of a nonsignificant decrease in 16a-OH.21

But a more recent paper, published in September 2012 and conducted by the same group on more participants for a longer time, did not find the same effect from high soy consumption: "Contrary to our hypothesis and some previous reports, the results from two well-controlled dietary interventions do not support an effect of a high-soy diet on a panel of urinary estrogen metabolites and the 2-OH/16a-OHE(1) ratio."22

Flaxseed consumption would not reduce risk of breast cancer according to this theory as it increases 16a levels, Sturgeon et al. reported in 2010. They fed 43 postmenopausal women 7.5 g/day of ground flaxseed for 6 weeks, and then increased the dose to 15 g/day for an additional 6 weeks. There was no significant change in 2-hydroxyestrone excretion in the urine. The urinary 2:16 ratio was lower at the end of 12 weeks compared with baseline. The authors write, "Based on the current paradigm of the effects of estrogen metabolism on breast cancer risk, the regimen of dietary flaxseed intake used in this study did not appear to favorably alter breast cancer risk through shifts in estrogen metabolism pathways in postmenopausal women."23 In other words, flaxseed meal shouldn't be good for breast cancer risk.

As naturopathic physicians, we are often ahead of the curve in translating new theories published in the scientific literature into clinical protocols for use with our patients. This "early adopter" tendency has its merits. We will sometimes find ways to help our patients when "regular" medicine has yet to develop a treatment. Because we limit our interventions to relatively nontoxic, low-risk therapies, we set the bar relatively low for our requirements of proof before experimenting with new ideas. We can justify our experimentation with a "might help and won't hurt" summation of risk analysis. If we were using more dangerous therapies, we would surely raise the bar, asking for stronger evidence before trying a new idea.

Thus adopting this estrogen metabolite theory early on before it was well proven did not threaten to hurt anyone if it eventually turned out to be wrong. Except that many people, patients in particular and also some practitioners, forgot that it was theory and considered it proven fact.

Being an early adopter does come with responsibility; if a new idea doesn't pan out, we need to abandon it and we need to let others know. It is easier for us to take on new ideas than it is to let go of them. In the case of estrogen metabolites, the theory that the 2-hydroxy form is good for women and that 16a-hydroxyestrone is bad is not holding up. Growing evidence suggests that there is little correlation between these hormones

and cancer risk; the situation is more complex than we at first thought. There may be other theories that will make sense of this. My colleagues, after reading the results of these studies, quickly scramble to find alternate theories, "… perhaps there's another metabolite that's the key, maybe the 4 hydroxy?" Maybe, but maybe not.

Sometimes you've just got to admit when you were wrong and move on.
It is past time that we let this particular idea go.

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Notes

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