Commentary

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or as treatment recommendations. Diagnosis and treatment decisions are the practitioner's responsibility.

Estrogen Metabolites

Estrogens are metabolized by two main pathways: (1) formation of the catechol estrogens 2-hydroxyestrone/estradiol (2-OHE1/E2) via the CYP1A1 pathway and 4-hydroxyestrone/estradiol (4-OHE1/E2) via the CYP1B1 pathway; and (2) formation of 16α-hydroxyestrone (16α-OHE1) via the CYP3A4 pathway.

2/16 Ratio and Hydroxylation pathways

2/16 Ratio - The clinical utility of the ratio of 2-hydroxyestrone (2-OHE1) to 16α-hydroxyestrone (16α-OHE1) – the 2/16 ratio or Estrogen Metabolite Ratio (EMR) – historically reported lower 2/16 ratio levels among breast cancer cases compared to controls (particularly in premenopausal women). Recent studies have been mixed: there appears to be no strong evidence in the literature that a higher urinary 2/16 ratio protects postmenopausal women from breast cancer, and only weak evidence of a protective effect in premenopausal women.

Higher 2-OH (E1+E2)/16α –OH ratios in males have been associated with reduced risk of prostate cancer.

2-OH (E1+E2) - While traditional 2/16 ratio clinical utility may not be as robust as previously thought, a majority of findings indicate that metabolism of parent estrogens through 2-hydroxylation (independent of any relationship to 16α-OHE1) may be considered as a benign or even protective pathway. (Of note: one study found increased breast cancer risk with higher 2-OH levels, but only in a small subgroup of ER-/PR- cases.)

Studies suggest that women with predominant metabolism through the 2-hydroxyl pathway have accelerated postmenopausal bone loss and lower BMD compared to those with predominant 16α-hydroxylation who appear to have reduced risk of bone loss. Increased 2- hydroxylation has been noted in women with a positive family history of osteoporosis suggesting that increased risk of osteoporosis in those with a family history may be related to inherited differences in estrogen metabolism.

16α-OH - Recent findings in the peer-reviewed literature are mixed, with some studies finding an association with increased risk (cancers of the cervix, breast, endometrium, and head and neck, as well as in people with tumors related to the human papilloma virus), but many finding no significant association.