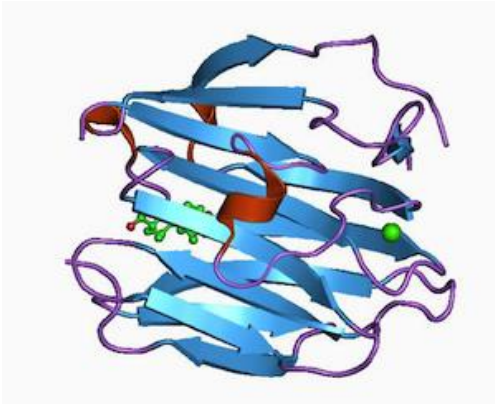


Breast cancer battle: SHBG to the rescue?

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The crystal structure of sex hormone-binding globulin (tetragonal crystal form).

Postmenopausal women with elevated levels of serum sex steroid hormones including estradiol, testosterone, and estrone, are at increased risk for developing breast cancer. Currently, medications to inhibit or block estrogens are the mainstay of treatment for women with hormone receptor-positive breast cancer. However, data on the association between circulating sex steroid hormones and prognosis in breast cancer survivors are limited. To address this question Drs. Catherine Duggan, Anne McTiernan, and colleagues, evaluated the association between sex hormone-binding globulin (SHBG), and circulating levels of free (non SHBG-bound) and total estradiol, estrone, and testosterone, with breast cancer-specific and all-cause mortality. This association was explored in the Health Eating Activity and Lifestyle (HEAL) study, a multiethnic cohort of breast cancer survivors, diagnosed with Stage I– IIIA breast cancer. They reported their results recently in *Breast Cancer Research and Treatment*.

The study included 358 postmenopausal women, not taking hormone replacement therapy at the time of blood draw, diagnosed with stage I-IIIa breast cancer between 1995 and 1998. Women were followed through December 2012. The investigators measured levels of estradiol, estrone, testosterone, and sex hormone-binding globulin (SHBG), in serum collected on average 30 months after diagnosis.

Then using Cox proportional hazards models, a statistical technique for exploring the relationship between the survival of a patient and several explanatory variables, the authors examined the associations between these hormones and breast cancer-specific and all-cause mortality. Over a median of 14.5 years of follow-up, 102 deaths occurred; 43 of these were due to breast cancer. In

models controlling for ethnicity/study site, age, body mass index, and tumor stage, increased levels of SHBG (log transformed) were associated with reduced risk of both breast cancer-specific mortality (hazard ratio, HR 0.48; 95 % confidence interval, CI 0.26–0.89) and all-cause mortality (HR 0.64, 95 % CI 0.43–0.97). There were no statistically significant associations between levels of estradiol, estrone, or testosterone for either endpoint. In subgroup analyses, after correction for multiple testing, increased estrone was significantly associated with reduced risk for breast cancer-specific mortality among participants with ER-negative tumors (HR 0.16, 95 % CI 0.05–0.63) but not among participants with ER-positive tumors.

Dr. McTiernan notes, "The most striking thing in the data was that the pattern we usually see of cross-the-board increase in breast cancer risk with increasing estrogen and testosterone levels was not seen here at all. Rather, the trend was to no associations with survival, or to improved survival with higher estrogen and testosterone levels. This suggests that there are differences between carcinogenesis and the processes that lead to fatal disease." One theory the authors cite for the observation that elevated levels of SHBG are associated with reduced risk of breast cancer-associated and all-cause mortality, is the fact that bioavailable concentrations of estrogens and its access to target cells are regulated by SHBG. In addition SHBG may have direct effects on cells, mediated by its unliganded binding to a cell-membrane receptor. Activation of the receptor–SHBG complex by binding to estradiol induces a number of downstream effects, including inhibition of progesterone receptor expression, increased apoptosis, and regulation of cell growth.

Dr. McTiernan elaborates, "It was interesting to see that increased levels of SHBG were associated both with breast cancer specific and all-cause mortality. We and others have shown that SHBG can be modified by diet and exercise. We've shown that it increases significantly with weight loss of just 5% of starting weight and increases even more with 10% weight loss. It also increases significantly with a regular moderate intensity physical activity program. So this could be a potential way for breast cancer survivors to improve their health."

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Citation:

[Duggan C, Stanczyk F, Campbell K, Neuhaus ML, Baumgartner RN, Baumgartner KB, Bernstein L, Ballard R, McTiernan A.](#) 2016. Associations of sex steroid hormones with mortality in women with breast cancer. *Breast Cancer Res Treat.* 155(3): 559-567.