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Circulating 27-hydroxycholesterol and Breast Cancer Risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) - Heidelberg Cohort

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Summary

27-hydroxycholesterol was the first identified endogenous selective estrogen receptor modulator. Selective estrogen receptor modulators bind to estrogen receptors, and exhibit agonist or antagonist activity depending on target tissues (e.g., breast, uterus and bone). As one example, the exogenous selective estrogen receptor modulator tamoxifen, approved for chemoprevention in high-risk women, exerts anti-estrogenic action in breast but has pro-estrogenic effects in the uterus. Results from animal studies show that 27-hydroxycholesterol promotes growth and metastasis in experimental models of ER-positive breast cancer. However, to date, little is known about 27-hydroxycholesterol and breast cancer in humans.

The primary aim of the thesis research was to provide the first study on pre-diagnosis 27-hydroxycholesterol and breast cancer risk overall, by hormone receptor subtype, and by menopausal status and hormone use at blood collection. To achieve this aim, a nested case-control study including 530 cases and 1036 controls was conducted in the well-characterized Heidelberg, Germany cohort of the European Prospective Investigation into Cancer and Nutrition. Serum 27-hydroxycholesterol was quantified in blood samples collected at study recruitment, and study participants have been prospectively followed for breast cancer incidence since recruitment.

The association between 27-hydroxycholesterol and breast cancer risk differed significantly by menopausal status at blood collection ($p_{heterogeneity}$=0.02). Among postmenopausal women, higher serum 27-hydroxycholesterol levels were associated with significantly lower breast cancer risk. Higher concentrations of circulating estradiol in postmenopausal women are an established breast cancer risk factor, and one of the most widely accepted hypotheses for the initiation of breast cancer is the activation of estradiol-estrogen receptor signaling. As an endogenous selective estrogen receptor modulator, 27-hydroxycholesterol can elicit conformational change of estrogen receptor α structure and effectively compete with estradiol for binding to estrogen receptor α in vitro, potentially counteracting the risk increasing role of estradiol in postmenopausal women. The associations between 27-hydroxycholesterol and breast cancer risk did not differ significantly by hormone use (p=0.19); however, a significant inverse association was only observed among women not using hormone therapy at blood collection. These results are in line with the finding that use of tamoxifen, a selective estrogen receptor modulator, may only have a chemopreventive effect among women not using hormone therapy.

Among women premenopausal at blood collection, no association between circulating 27-hydroxycholesterol and breast cancer risk was observed. It is plausible that 27-hydroxycholesterol is only associated with lower risk of breast cancer in the context of relatively low circulating estrogens, as observed in postmenopausal women not using

hormone therapy, and not in the context of higher circulating estrogens, as observed in postmenopausal hormone therapy users and premenopausal women. No heterogeneity by tumor hormone receptor subtype was observed overall, or in any menopausal status subgroup.

The secondary aim of the thesis research was to assess the within-person reproducibility of 27-hydroxycholesterol and other oxysterols over time, as there were no prior data on longer-term within-person reproducibility of these analytes. This study was conducted in a subset of 30 postmenopausal women with repeat blood samples taken one year apart. Results of this study show that a single measure of 27-hydroxycholesterol can reliably estimate concentrations over a one-year period (Spearman correlation=0.81). Other oxysterols of potential relevance to chronic disease risk (24S-hydroxycholesterol, 25-hydroxycholesterol and 7α-hydroxycholesterol, and lanosterol) also demonstrated relatively high within-person reproducibility (all Spearman correlation $\geq$0.66).

In this first epidemiological study on the topic, higher circulating 27-hydroxycholesterol was associated with significantly lower risk of breast cancer in postmenopausal women. These results are in contrast to those observed in experimental models, but in line with the actions of pharmacologic selective estrogen receptor modulators. Identification of the first endogenous selective estrogen receptor modulator associated with reduced risk of breast cancer in postmenopausal women may offer novel avenues for breast cancer prevention strategies. However, the findings observed here must first be replicated, and heterogeneity by tumor hormone receptor status should be addressed in a larger study. Finally, given the findings presented here and the established role of selective estrogen receptor modulators in the treatment of hormone receptor-positive breast cancer, future studies should investigate circulating 27-hydroxycholesterol and breast cancer survival.