

PROSPECTIVE STUDY OF ESTROGENS DURING PREGNANCY AND RISK OF BREAST CANCER

**Pentti K. Siiteri, Robert I. Sholtz, Piera M. Cirillo,
Richard D. Cohen, Roberta E. Christianson,
Barbara J. van den Berg, William R. Hopper,
and Barbara A. Cohn**

Public Health Institute

psiiteri@aol.com and crwch@emf.net

Breast cancer prevention and control may benefit by elucidation of natural protective mechanisms. Pregnancy is an excellent model for studying protective mechanisms under conditions of promotion, when women are exposed to a variety of growth factors and hormones. The purpose of our research was to test the hypothesis that maternal serum levels of steroid hormones can explain novel protective associations that we recently reported for placental characteristics.

The study population is a subset of the Child Health and Development Studies, with more than 40 years of follow-up on 15,000 women. Women entered the study during pregnancy between 1959 and 1967, were members of Kaiser Foundation Health Plan and resided near Oakland, California. Extensive data were assembled through interviews, and examinations, including a standardized placental examination. Serum samples were stored, frozen at -20 degrees C. The design was a prospective case-cohort study with follow-up conducted via linkage to the California Cancer Registry. Cases are defined as invasive breast cancer diagnoses or deaths as of 1997. The first study pregnancy resulting in a live born, singleton birth was eligible. Pregnancy hormones were assayed for subjects with placental data (N=204 cases and 434 subcohort members). Pregnancy steroids were assayed following celite column chromatography for estrone and testosterone or by direct assays, which were validated by celite column chromatography, for estradiol and estriol. We verified the integrity of steroid assays in stored samples.

We found a protective association for the percent of estrogens present as estriol and this association had a significant linear trend ($p<0.01$). The protective association increased monotonically by quartile of estriol percent. Breast cancer risk was reduced by 58% for the 4th quartile of estriol percent compared to the 1st quartile of estriol percent (95% CI=26% reduction to 77% reduction). The estriol percent was higher in both Asian and Hispanic women, who are known to have reduced risk of breast cancer.

Our findings are consistent with an earlier hypothesis that estriol, an estrogen largely of fetal origin that rises 1,000-fold during pregnancy, protects against maternal breast cancer by antagonizing the effects of the active estrogen, estradiol.

If confirmed, these results could lead to breast cancer prevention or treatment regimens that seek to block estradiol action using estriol, similar to treatments based on the synthetic anti-estrogen, tamoxifen.