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Meeting abstract

The effect of sulindac on growth differentiation factor 15 and 13,14-dihydro-15-keto prostaglandin A_2 in nipple aspirate fluid

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Use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated in several large epidemiologic studies with a lower risk of epithelial cancers including breast though no randomized, placebo controlled phase III studies have been conducted to date. NSAID use was associated with a significantly lower risk of breast cancer among participants in a multiethnic cohort, though the nearly 50% reduction in risk was limited to women with estrogen receptor positive tumors; an observation previously reported by Terry et al., and supported by Gierach et al., and findings of Harris et al for cyclooxygenase-2 (COX-2) inhibitors. These findings in epidemiologic studies are supported by work in human mammary tissues and cell culture where overexpression of COX-2, one of two cyclooxygenase targets of NSAIDs, acts as an early event in the transition of normal breast cells to malignancy. Further, COX-2-associated prostaglandin E2 (PGE_2) production has been shown to increase aromatase activity in mammary epithelial cells possibly explaining the observed benefit of NSAID use in hormone receptor positive disease and the recent observation of lower circulating estradiol levels among regular users of NSAIDs. Thus, there exists sufficient rationale for the use of NSAIDs for the prevention of breast cancer.

While the best studied target of NSAIDs is the COX isoenzymes, the anti-tumor activities of each of the NSAID agents via 'non COX' pathways remains unknown. Sulindac, a non selective NSAID with well recognized COX-independent induction of apoptosis has remained a strong candidate for chemoprevention largely because of its broader anti-tumor activity. Growth differentiation factor 15 (GDF-15), a potent proapoptotic molecule in the TGF-β superfamily and potential tumor suppressor is upregulated by several NSAIDS independent of its activity as a COX inhibitor. Sulindac sulfone, a metabolite of sulindac and a COX-independent mediator of apoptosis, has been shown to be a potent inducer of GDF-15 at pharmacologically relevant doses whereas Celecoxib, a COX-2 specific inhibitor, has low GDF-15 induction potency even at toxic doses. Other NSAIDs such as aspirin and indomethacin as well as a number of candidate dietary chemopreventives including resveratrol, indole-3-carbinol, 3,3' Diindolylmethane (DIM), and lycopene as well as the PPAR agonists troglitazone, and 15-deoxy-$\Delta^{12,14}$-prostaglandin J2 all show potent induction of GDF-15 leading to the suggestion that GDF-15 might serve as a complementary molecular target to COX-2 for cancer chemoprevention and serve as a surrogate biomarker of apoptotic response.

To better understand the effect of NSAIDs in the breast, we conducted a phase 1b dose study using sulindac as a representative drug of the non selective NSAIDs with known activity to induce GDF-15 and inhibit COX-2. To assess sulindac and its metabolites and their effects on a stable

COX-2 derived prostaglandins 13,14-dihydro-15-keto prostaglandin A_2 [PGEM], and the NSAID inducible growth differentiation factor (GDF-15) in nipple aspirate fluid (NAF), we randomized 30 women at increased risk for breast cancer to 150 mg once daily or twice daily sulindac for 6 weeks. Sulindac and sulfide were detectable in 57.7% of NAF samples with sulfone detectable in 11.6%. Sulindac was associated in a dose independent manner with a nonsignificant decrease in NAF PGEM levels ($p = 0.1$). Serum levels of sulindac, but not NAF sulindac, were correlated with a decrease in NAF PGEM levels ($p = 0.03$). GDF-15, showed a borderline significant trend towards higher levels in NAF with 300 mg daily sulindac ($p = 0.07$). This study suggests that COX inhibition in the breast may be achieved at 150 mg sulindac once daily while a higher daily dose is needed to exhibit activities via COX independent pathways. The study also suggests that NAF levels of PGEM and GDF-15 could be considered as drug effect biomarkers for future early phase chemoprevention trials.