

Preventing breast cancer recurrence through reducing dietary intake of oxidized cholesterol: An analytical tool.

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Abstract

Oxysterols are a group of signaling molecules that are derived from cholesterol through auto-oxidation during cooking (e.g. 25-OHC, 7-KC) or by enzymatic synthesis (22R-OHC, 24S-OHC, 25-OHC, 27-OHC, 24,25-EC). Some of these cholesterol oxidation products accumulate in breast cancer tissue and are elevated in the circulation of individuals with metastatic breast cancer and other conditions that risk factors for breast and other cancers (obesity, metabolic syndrome, hypercholesterolemia). Importantly, oxysterols are emerging as functional drivers and circulating biomarkers of breast cancer and *in vitro* experiments reveal they enhance metastasis and chemoresistance. Oxysterols may therefore be therapeutic targets in ER+ and TNBC disease and simple dietary or pharmacological interventions could improve disease free survival.

In this pilot grant, we set out to develop and apply a Liquid Chromatography Mass-Spectrometry (LC-MS/MS) method to detect a panel of oxysterols in human breast tumours. An important objective was that the sample requirements (size/volume of tissue, storage, processing conditions) should be compatible with existing surgical, diagnostic and analytical procedures. Secondary aims were to measure the concentrations of oxysterols in different breast tumour subtypes and assess oxysterol content in a panel of cell lines. Our method was able to detect 5 out of the 6 proposed oxysterols in primary tumour samples obtained from the Leeds Breast Tissue Bank and in a panel of breast cancer and fibroblast cell lines. Importantly, the tumour volume requirements were optimised so that analysis of 10 different sterols could be performed on tissue equivalent to less than 20% of a single needle core biopsy (*circa* 10mg of tissue).

We now intend to apply the LC-MS/MS method to a fully powered cohort of tumour samples with matched blood samples. In subsequent work we will ask the following questions: i) Is the oxysterol mixture quantitatively or qualitatively different between ER-positive and ER-negative breast tumours, ii) Are oxysterols predictive biomarkers of relapse/response to therapy, iii) Are oxysterols from non-cancer "host cells" driving cancer initiation/progression, and iv) Can dietary repression of eswaoxysterol signaling reduce primary or secondary breast cancer incidence?

Dissemination so far

The data generated by this pilot grant have been or will be presented soon, at national and international conferences. BCUK is acknowledged as a main funder of the research.

- Oxysterols and Phytosterols alter chemotherapy resistance in Triple Negative Breast Cancer. **2017**. An invited talk to the Breast Cancer Research Action Group Patient and Cancer survivor charity.
- Cholesterol hydroxylation products confer resistance to anthracyclines in Triple Negative Breast Cancer. **2017**. Hutchinson SA, Kane D, Røberg-Larsen H, Vaghela K, and Thorne JL. The Nutrition Society Winter Meeting, London (Dec).
- Towards a robust molecular understanding of how plant sterols could prevent metastatic relapse in Triple Negative Breast Cancer patients. **2017**. Hutchinson SA, Kane D, Hsu N, Røberg-Larsen H, Pajares NP, Hughes TA, Thorne JL. Translational Research in Human Nutrition: Nutrition and Cancer. Clermont-Ferrand, France. **Winner of first place prize for best oral communication**
- Are oxysterols Selective Liver X Receptor Modulators in Breast Cancer? Hutchinson SA, Røberg-Larsen H, Kane D, Vaghela K and Thorne JL. **2017**. 7th ENOR Symposium: Oxysterols and sterol derivatives in health and disease, Brussels.
- Could the dietary advice for cardio-vascular disease prevention also reduce breast cancer relapse rates? **2017**. Hutchinson SA, Røberg-Larsen H, Hughes TA and Thorne JL. Yorkshire Breast Cancer Symposium, York.
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