Alterations to breast tissue chemistry in women at risk of cancer: 2D MR spectroscopy in vivo study

Jessica Buck[1], Saadallah Ramadan[1], Leah Best[2], Judith Silcock[3], Jameen Arm[2], Scott Quadrelli[1], Gorane Santamaria[1], Kin Men Leong[2], Peter Lau[2], Peter Malycha[1], David Clark[1,3], and Carolyn Mountford[1,4]

[1]Centre for MR in Health, University of Newcastle, Newcastle, NSW, Australia, [2]Calvary Mater Hospital, Newcastle, NSW, Australia, [3]The Breast and Endocrine Centre, Gateshead, NSW, Australia, [4]Centre for Clinical Spectroscopy, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Target Audience

Clinicians, radiographers, radiologists

Purpose

The clinical management of women at an increased risk of developing breast cancer through strong family history or a previous personal history of breast cancer can be challenging. This is due to a lack of personalised medicine based approaches, and differences in screening recommendations across different areas. However, many studies of cell lines and biopsy samples have provided evidence for the existence of premalignant conditions. If detectable in a non-invasive way, this could provide an objective means for women to monitor changes in their breast tissue and make informed decision on interventions such as prophylactic mastectomies. Recent evidence has shown that women carrying BRCA gene mutations have different breast chemistry as identified by Magnetic Resonance Spectroscopy (MRS) when compared to healthy controls[1]. This study investigates whether women at an increased clinical risk of developing breast cancer, but who do not carry BRCA gene mutations, have alterations to breast tissues that may constitute potentially premalignant condition(s).

Materials and Methods

In vivo Two Dimensional Localized COrrelated SpectroscopY (2D L-COSY) was recorded at 3T on a Siemens Skyra or Prisma using a 16 channel breast coil, in women at increased clinical risk of developing breast cancer (N=32), and healthy controls (N=10). Participants underwent standard diagnostic contrast enhanced breast MRI and breast ultrasound. The 15x15x15mm^3 spectroscopic voxel was placed in the lower outer quadrant midway between fibroglandular and fat tissues in the breast. The L-COSY sequence was applied with a TE initial of 30ms, TR 1.5s, 8 averages per increment, bandwidth 2000 Hz, t1 increment 0.8 ms, vector size of 1024 points, RF offset frequency was set on 3.2ppm, and increments were 64. The "WET" method of water suppression was applied. Processing was undertaken using previously reported parameters[1]. Cross and diagonal peak volumes were measured using the Felix software, with the (CH2)n diagonal peak at 1.30 ppm as the internal chemical shift reference. Due to the absence of a reliable internal concentration standard, the ratios were calculated for all peaks with respect to the following peaks: (2.75,2.75)ppm; (1.30,1.30)ppm; and (4.25,4.25)ppm. The peak volume ratios of the L-COSY spectrum of each patient were examined individually to determine which chemical changes were present in each patient. Four peak volume ratios were found to be altered in the whole group analysis. For each of these, each patient was categorized as fitting the "healthy control" or "chemically changed" profile, and a score was given indicating the number of chemical changes present in that patient. Scores of 0-2 changes were categorized as "MR spectroscopy Low Risk", while those patients with 3-4 changes were categorized as "MR spectroscopy High Risk". Statistical significance was calculated using the Mann-Whitney two-tailed non-parametric test.

Results

No abnormality was recorded in the breast tissue by MRI or ultrasound, with all images rated BI-RADS1 or BI-RADS2. L-COSY recorded four changes in the breast tissue of women at increased clinical risk for breast cancer, two of which were statistically significant (P<0.05). These changes were used as biomarkers to subcategorise the clinically increased risk group. The cohort was subdivided into an MR spectroscopy Low Risk subgroup, which was found to be statistically the same as the control group; and an MR spectroscopy High Risk category based on their chemical profiles. Chemical changes in the MR spectroscopy High Risk group when compared to healthy controls included increases in the composite metabolite resonance containing choline, glycine and myo-inositol substrates of 133% (P=0.009); the composite metabolite resonance containing glycerol, glutamine/glutamate and glucose (131%, P=0.004); the composite metabolite resonance containing inositol, glucose and histamine of 138% (P=0.003); and the composite metabolite resonance containing glycerophosphocholine (GPC), asparagine and creatine of 55% (P=0.039). Increases in lipid unsaturation (25%, P=0.013) and cholesterol levels (67%, P=0.004) were also recorded. There was also a reduction (32%, P=0.023) in the terminal methyl group on the fatty acid chain in the MR spectroscopy High Risk group. No statistically significant differences were found between the healthy control and MR spectroscopy Low Risk groups.

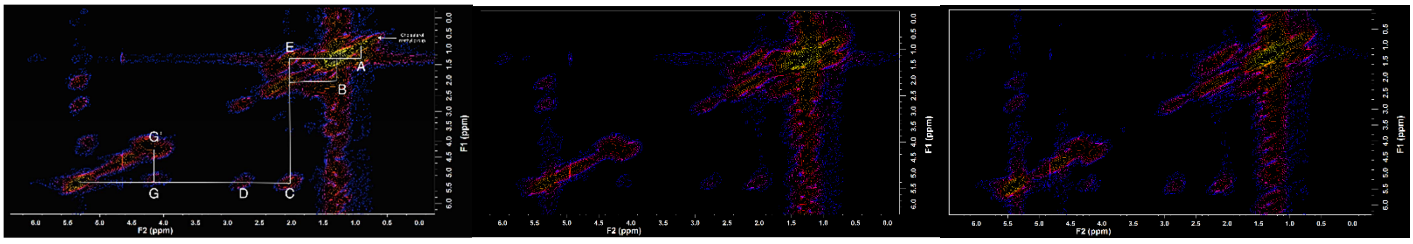

Figure 1: Representative L-COSY spectra presented at 96 increments for improved image quality of: A) Healthy control (44 years old) with crosspeaks assigned "A-G" along with the cholesterol methyl group; B) A patient at clinically increased risk from family history but MR spectroscopy Low Risk from tissue chemistry (42 years old); C) A patient at clinically increased risk from family history and MR spectroscopy High Risk from tissue chemistry (52 years old).

Conclusion

In vivo L-COSY identifies premalignant changes not seen by routine imaging, and allows women to be identified as MR spectroscopy Low or MR spectroscopy High Risk according to changes recorded. Changes in the MR spectroscopy High Risk group include deregulation of lipid pathways and increased levels of metabolites. If these changes are confirmed in larger populations, it is possible that the information provided by L-COSY will allow women at increased clinical risk for breast cancer an objective means to monitor changes that may be important that are taking place in their breast tissue. Despite no evidence of an abnormality with current imaging modalities, in vivo 2D L-COSY MR spectroscopy documents alterations to the breast tissue chemistry of women at increased clinical risk of developing breast cancer.

References

1 Ramadan, S. *et al.* Lipid Deregulation in Women Carrying the BRCA Mutations: Non invasive evaluation by two-dimensional Spectroscopy. *Proceedings of the International Society for Magnetic Resonance in Medicine* **22**, 1038 (2014).