Metabolomic Analysis of Human Breast Cancer

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Background: Despite vast research activities and achievements of the past decade, the reality of breast cancer has not drastically altered from that of ten years ago. While with the introduction of annual mammogram tests, early diagnosis undoubtedly contributes to the saving of women's lives, it has unfortunately created many controversies and dilemmas. At the center of these controversies lies a conceptual change for the management of breast cancer. The traditional treatment approach of mastectomy followed by chemotherapy and radiotherapy is no longer considered a standard protocol in light of the vast number of cases presenting at early stages of the disease. Alternatively, breast-conserving treatment (BCT) with and without adjuvant systematic therapies (AST) has become an approach that continues to gain acceptance in the U.S. Unfortunately, the traditional breast cancer pathology even with additions of new molecular biomarker tests still cannot provide adequate personalized disease information. Thus, researchers pursuing new directions that can contribute to earlier diagnosis and better patient prognosis are still urgently needed.

Patient Population: In this study, we analyzed human breast cancer intact tissue samples collected between 2003 and 2006 with high resolution magic angle spinning (HRMAS) followed by quantitative pathology. Approximately 360 samples were obtained from 197 cases, and among them 82 cases had matched cancer and benign samples that were analyzed. Currently, 271 samples from 175 cases, including 64 cases with matched cancer and benign tissues, have completed the entire spectroscopy and pathology analyses. Among them, 104 cases are from ductal carcinomas (10: Grade I, 47: Grade II, and 47: Grade III), and 13 cases are from lobular carcinomas (12: Grade II, and 1: Grade III), with the rest from mixed types. Among these completed cases, 35 patients were triple-negative for estrogen receptor (ER), progesterone receptor (PR), and HER-2/*neu.* Within these analyzed cases, 40 of them were pathological stage I (T1) tumors, 72: T2, and 19: T3 tumors; and 27 patients have been identified as having cancer recurrence as of July 2009, after their initial diagnoses. The age of this studied patient population at diagnosis was 53.3+/-13.2 years.

Results: Our individual metabolite data from the current patient group validated previously reported results including the linear correlations between the intensities of lipid signals and the quantified volume percentage (Vol%) of adipose tissues (r^2=0.66, p<0.0001), as well as the linear correlations between the total choline intensity and cancer Vol% (r^2=0.23, p<0.0001). Among the analyzed metabolite resonances, 38.1% (8 from 21 most common resonances seen in both cancer and benign spectra) of them demonstrated statistical significance after Bonferroni corrections. In addition, total choline intensities also presented statistical significance in differentiating ductal from lobular tumors (p<0.032). Furthermore, by applying principal component and canonical analyses on these measured common metabolite resonances, we observed the capacities for the metabolomic profiles obtained to differentiate tumor types (ductal vs. lobular, p<0.0001); tumor grades (ductal, Grades I &II vs. Grade III, p<0.0005; lobular, Grade II vs. Grade III, p<0.0013); lymph node involvement (p<0.0005); and tumor recurrence (p<0.012).

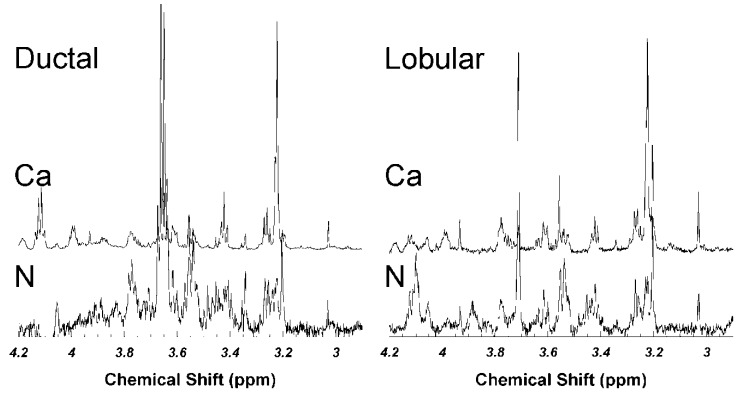

Fig 1. HRMAS 1HMR spectra of ductal and lobular carcinomas. Ductal samples were obtained from a G3, ER+, PR+, HER2 moderately positive tumor from a 53 y.o. patient diagnosed of T2N1 cancer. The cancer sample analyzed has: Ca 82.6%, Col 17.4%. Lobular samples were obtained from a G3, ER+, PR+, HER2 moderately positive tumor from a 54 y.o. patient diagnosed of T2N2 cancer. The cancer sample analyzed has: Ca 67.5%, F 7.3%, Col 19%.

Conclusion: Our understanding of these cancer metabolomic profiles will assist in our design of new MRS paradigms aimed at non-invasive diagnosis, characterization and monitoring of breast tumors. These paradigms will ultimately permit advancements in breast radiology and pathology to be wielded in tandem, optimizing patient survival and comfort, while allowing for the maximum reduction of health care costs.

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