Altered fatty acid profile of periprostatic adipose tissue in prostate cancer patients: an MR spectroscopic study

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Target Audience: Results presented in this study will be of interest to a wide variety of audience - clinical oncologists specializing in prostate cancer, cancer biologists investigating the role of adipose in promoting cancers, scientists studying metabolism in obesity, and MR spectroscopists.

Purpose: Obesity is considered to be an adverse prognostic factor for prostate cancer (PCa). Several clinical studies suggest that periprostatic adipose (PPA) may promote PCa growth, and elevated adiposity shows a positive association with more aggressive disease. In a study using transrectal ultrasonography, increased thickness of the PPA was positively associated with both the overall presence of PCa and the presence of high grade disease [1]. However, the molecular mechanism by which increased adiposity stimulates PCa progression remains unclear. We hypothesized that in addition to its increased mass, the composition of adipose tissue in the tumor microenvironment might be a prognostic marker for PCa aggressiveness. To verify this, we measured the fatty acid (FA) composition of the PPA and abdominal subcutaneous adipose (SQA) tissues from PCa patients using *ex vivo* MR spectroscopy (MRS), and determined the potential of MR measures to predict a pathological criterion of PCa aggressiveness.

Experimental Methods:
Tissue collection: PPA and SQA were collected from 30 PCa patients undergoing radical prostatectomy. Patient/tumor characteristics were as follows: range of body mass index (BMI) 21.0-40.5 (9 subjects BMI <25 (lean), 12 subjects BMI 25-30 (overweight), and 9 subjects BMI>30 (obese)); Gleason pattern: 52.5% (3+3), 35% (3+4), and 12.5% (4+3); 12.8% had extracapsular extension (ECE) which signifies aggressive PCa.
MR Spectroscopy: PRESS localized proton MR spectra were acquired from 1µL voxels in the adipose specimens on a 14.1T Bruker Avance imaging spectrometer without water suppression using TR 40s, TE 7.5ms, spectral width 8000Hz and 16k complex points. FIDs were Fourier transformed after applying 2.5Hz exponential multiplication filter.
Data Analysis: Peak integrals of FA functional groups, corrected for T_2 relaxation time, were measured from the spectra. The fractions of saturated (f_S), mono-unsaturated (f_M), poly-unsaturated (f_P), and total unsaturated (f_U) FA were calculated as described in literature [2]. The following FA ratios were compared between PPA and SQA: mono-unsaturated to saturated FA (f_M/f_S), poly-unsaturated to saturated FA (f_P/f_S), and total unsaturated to saturated FA (f_U/f_S). The corresponding receiver operating characteristic (ROC) curves were compared against pathologically determined ECE by using the area under the curve (AROC) and computing the 95% confidence intervals (CI) based on percentile boot straps (1000 bootstrap samples).

Results: In patients with BMI<25 (lean) and BMI 25-30 (overweight), the FA profiles of PPA and SQA were statistically similar (Table 1). However, in patients with BMI>30 (obese), f_M/f_S and f_U/f_S were significantly elevated in the PPA relative to their SQA. f_P/f_S was also higher in obese PPA, but not significantly. In a separate study of mouse models of PCa, we found that PPA tissues in *ob/ob* mice also had elevated mono-unsaturated FA compared to PPA in lean wildtype (WT) mice (f_M/f_S 1.98±0.36 vs 1.16±0.19; p<0.002; n=4). *Ob/ob* mice develop prostatic hyperplasia and lean WT mice do not.

Table 1. Fatty acid profile of PPA and SQA tissues in prostate cancer patients

	f_M/f_S			f_P/f_S			f_U/f_S		
BMI Gr.	*PPA*	*SQA*	*p-value*	*PPA*	*SQA*	*p-value*	*PPA*	*SQA*	*p-value*
<25	1.26±0.12	1.34±0.09	0.65	0.90±0.07	0.95±0.06	0.57	2.16±0.16	2.29±0.13	0.56
25-30	1.39±0.13	1.46±0.16	0.74	0.94±0.08	0.94±0.07	0.99	2.33±0.24	2.40±0.22	0.81
>30	1.60±0.16	1.17±0.07	**0.03**	1.30±0.26	0.81±0.06	0.09	2.93±0.28	1.99±0.12	**0.05**

ROC analysis of data from all PCa patients revealed that several differential MRS measures of FA composition (Δ) between PPA and SQA have potential for predicting pathologically determined ECE, a marker for aggressive PCa, as shown by their AROC and 95% CI (given in parentheses): $\Delta f_M/f_S$ 0.83 [0.66 – 0.98], Δf_M 0.92 [0.81 – 0.99], Δf_U 0.84 [0.68 – 0.98] and Δf_S 0.16 [0.02 – 0.32]. Values of AROC closer to 1 or 0 indicate high predictive potential.

Discussion: Bioenergetic demands and increased membrane synthesis in PCa progression might be responsible for the altered FA profile in the PPA. Elevated f_M/f_S seen in obese patient PPA is consistent with increased activity of fatty acid desaturases, such as stearoyl-CoA desaturase-1, which moderates signaling processes related to cell proliferation, survival and malignant transformation to cancer [3]. Our ROC analysis suggests that alterations in FA composition of the PPA relative to SQA might be useful in developing a marker for aggressive PCa. Men within an active surveillance program currently require repeated biopsies for evaluation of their cancer. A non-invasively measured MRS marker for aggressive PCa has the potential to improve the accuracy of differentiating indolent from aggressive PCa and thereby eliminate unnecessary biopsies that cause trauma to the patient.

Conclusions: Lipid metabolism is altered in the vicinity of the tumor in PCa. FA profile of the PPA in obese PCa patients might represent a unique metabolic microenvironment permissive to cancer progression. Our results suggest that *in vivo* MRS may have potential for developing noninvasive biomarkers for aggressive PCa which will benefit men participating in active surveillance programs.

References:
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