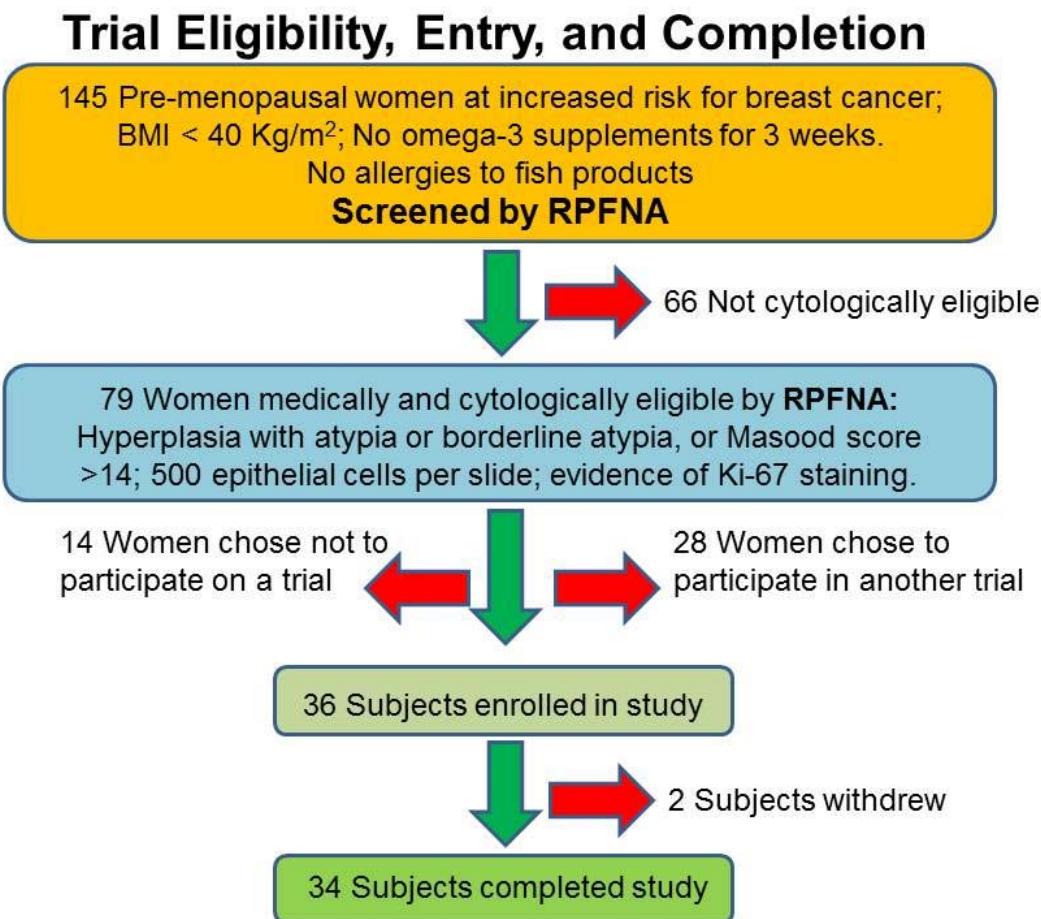


Supplemental Figure 1: CONSORT diagram for flow of potential and actual subjects enrolled on study



Supplementary Table 1. Demographic and risk information at baseline for 36 enrolled subjects.

Variable	median	mean \pm SD	range
Age, years	44.5	42.9 \pm 6.1	32 - 52
Height (cm)	168	167 \pm 6	155 - 182
Weight (Kg)	69.3	71.8 \pm 11.6	50.4 – 95.8
BMI (kg/m^2)	25.0	26.0 \pm 4.7	17.0 – 34.7
5-Year Gail Risk, % [N=27] (9 could not be calculated because of prior DCIS, LCIS, IC)	1.9	2.0 \pm 1.1	0.6 – 4.5
Variable	Number	Frequency	
Risk Conditions for Entry on Study			
Elevated projected risk (Gail or other)	21	58%	
Family History	30	83%	
Breast pre-cancer (AH, LCIS, DCIS) or prior treated invasive cancer	9	25%	
RPFNA evidence of atypia within 3 years	29	81%	
Systemic Hormone Replacement Therapy			
Mammographic density >50%	17	47%	
BMI > 30 kg/m^2			
Highest Education -			
High School Grad	6	17%	
College Graduate	13	36%	
Post Graduate Degree	17	47%	

Race: 35 White; 1 Black

Ethnicity: 36 Non-Hispanic

Supplementary Table 2. Change in fatty acid content in all five compartments for the 34 subjects who completed the trial. PLs=Phospholipids; TAGs=Triacylglycerides

Tissue /Lipid Compartment Fatty Acid Component	Median Values Percent of total fatty acid content (Percent change relative to Baseline)			P-Value (Wilcoxon) for Baseline to FNA2
	Baseline N=34]	6 mo ^a [N=34]	6.5 mo (FNA2) ^b [N=32]	
AA				
RBC PLs	12.8	10.7 (-18%)	10.8 (-16%)	<0.001
Plasma PLs	9.9	8.2 (-19%)	8.6 (-11%)	<0.001
Plasma TAGs	1.58	1.44 (-5%)	1.50 (-10%)	0.30
Breast PLs	0.65		0.57 (3%)	0.54
Breast TAGs	0.32		0.34 (7%)	0.47
EPA				
RBC PLs	0.4	2.24 (399%)	1.27 (235%)	<0.001
Plasma PLs	0.54	2.80 (344%)	0.64 (31%)	0.0013 {<0.001}
Plasma TAGs	0.18	1.02 (368%)	0.24 (28%)	0.017 {<0.001}
Breast PLs	0.051		0.049 (21%)	0.30
Breast TAGs	0.033		0.096 (165%)	<0.001
DHA				
RBC PLs	2.95	5.46 (74%)	4.71 (64%)	<0.001
Plasma PLs	2.5	4.50 (76%)	3.35 (37%)	<0.001
Plasma TAGs	0.47	1.94 (302%)	0.67 (61%)	<0.001
Breast PLs	0.13		0.15 (18%)	0.16
Breast TAGs	0.073		0.147 (42%)	<0.001
EPA+DHA:AA Ratio				
RBC PLs	0.27	0.76 (178%)	0.56 (117%)	<0.001
Plasma PLs	0.3	0.91 (185%)	0.45 (44%)	<0.001
Plasma TAGs	0.38	1.97 (310%)	0.73 (49%)	<0.001

Breast PLs	0.23		0.32 (35%)	0.044
Breast TAGs	0.29		0.51 (96%)	<0.001
Total n3				
RBC PIs	5.38	10.57 (89%)	8.48 (61%)	<0.001
Plasma PLs	4.18	9.12 (111%)	4.88 (34%)	<0.001
Plasma TAGs	2.05	5.59 (113%)	2.56 (23%)	0.0014 {<0.001}
Breast PLs	0.78		0.62 (15%)	0.77
Breast TAGs	1.32		1.51 (18%)	0.032
Total n6				
RBC PIs	28.7	22.7 (-18%)	24.2 (-14%)	<0.001
Plasma PLs	32.9	27.9 -14%)	32.9 (-2%)	0.042 {<0.001}
Plasma TAGs	22.5	23.7 (4%)	23.3 (3%)	0.78
Breast PLs	3.15		2.85 (-4%)	0.48
Breast TAGs	18.1		17.3 (-3%)	0.10
Total n3:n6 ratio				
RBC PIs	0.19	0.47 (141%)	0.34 (87%)	<0.001
Plasma PLs	0.13	0.34 (145%)	0.15 (30%)	<0.001
Plasma TAGs	0.1	0.24 (102%)	0.13 (25%)	<0.001
Breast PLs	0.11		0.12 (13%)	0.60
Breast TAGs	0.07		0.085 (18%)	0.0026

a) Blood collected within 24 hours of scheduled discontinuation of drug, after a nominal 6 months of intervention.

b) Second blood specimen collected on the day of the second aspiration, a median of 21 days after scheduled drug discontinuation.

{} denotes comparison of baseline to 6 month levels.

Supplementary Table 3. Change in anthropomorphic variables.

Variable	Median Pre-Study	Median Post-Study	Median Absolute Change	Median Relative Change	P-Value (Wilcoxon)
Weight, Kg	69.3	69.9	0.2	0.3%	0.64
BMI, Kg/m ²	25.0	25.2	0.0	0.3%	0.68
Percent body fat	39.7	39.1	0.8	2%	0.36
Percent android fat	43.3	41.6	-0.2	-0.4%	0.87
Waist circumference, cm	85	81	-2	-2%	0.0091
Hip circumference, cm	103	105	1	1%	0.58
WHR	0.81	0.77	-0.03	-3%	0.014

Supplementary Table 4: Changes in levels of cytokines and adipokines in 25 sets of paired, non-bloody, RPFNA specimens, assessed by Luminex technology and expressed as relative to the amount of protein in each specimen. Eight paired specimens where either was visibly contaminated with blood were excluded from analysis

Biomarker	Median Pre-Study	Median Post-Study	Median Absolute Change	Median Relative Change	P-Value (Wilcoxon)
Adiponectin, pg/µg prot.	105	114	-6	3%	0.37
Leptin, pg/µg protein	0.12	0.17	0.02	20%	0.20
Adipo:Leptin Ratio	809	924	66	9%	0.97
HGF, ng/µg protein	244	261	13	4%	0.95
Insulin, pg/µg protein	3.8	3.2	-0.4	-23%	0.60
MCP-1, pg/µg protein	23.4	16.2	1.0	11%	0.15
NGF, pg/µg protein	0.050	0.050	0.000	4%	0.83
PAI-1, ng/µg protein	102	82	-18	-20%	0.12
Resistin, ng/µg protein	1.3	1.1	-0.0	-3%	0.64
TNF- α , pg/µg protein	0.035	0.070	0.020	61%	0.015

Supplementary Table 5: Changes in levels of mRNA in RPFNA specimens, assessed by RT-qPCR technology and expressed as relative to three reference transcripts: HPRT1 (hypoxanthine phosphoribosyl-transferase 1), PPIA (peptidylprolyl Isomerase A, Cyclophilin A), PPIG (peptidylprolyl isomerase G, cyclophilin G).

Transcript (protein encoded)	Number where values decrease	Number where values increase	P-Value (Wilcoxon 2-sided)
ADIPOQ (Adiponectin)	11	14	0.42
LEP (Leptin)	10	15	0.15
Adiponectin:Leptin Ratio	12	13	0.60
ALOX15 (Arachidonate 15-lipoxygenase)	6	7	0.86
ALOX15B (Arachidonate 15-lipoxygenase, type B)	11	8	0.26
ALOX5 (Arachidonate 5-lipoxygenase)	9	15	0.39
ALOX5AP (Arachidonate 5-lipoxygenase-activating protein)	11	14	0.60
CD44 (CD44 antigen)	12	13	0.86
COX-2 (Prostaglandin-endoperoxide synthase 2)	15	10	0.99
Cyclin B1	10	13	0.93
Cyclin D1	11	14	0.35
ERP44 (Endoplasmic reticulum protein 44)	12	12	0.70
ER α (Estrogen Receptor alpha)	14	11	0.64
GLUT-4 (Glucose transporter type 4)	12	13	0.43
GREB1a (Growth regulation by estrogen In breast cancer 1a)	10	15	0.54
HGF (Hepatocyte growth factor)	14	11	0.84
HPGD (Hydroxyprostaglandin dehydrogease 15-(NAD)) Assay 1	15	10	0.43
HPGD Hydroxyprostaglandin dehydrogease 15-(NAD)) Assay 2	14	11	0.30
ICAM1 (Intercellular adhesion molecule 1)	15	10	0.56
IGFBP2 (Insulin-like growth factor binding protein -2)	16	9	0.14
KISS1 (Kisspeptin)	8	8	0.72

LTA4H (Leukotriene A4 hydrolase)	12	13	0.70
LKB1 (Liver kinase B1)	10	15	0.28
MCM2 (Mini-chromosome maintenance 2)	15	10	0.22
MCP1 (Monocyte chemotactic protein 1)	11	13	0.81
PPAR γ (Peroxisome proliferator-activated receptor gamma)	11	14	0.33
PGR (Progesterone Receptor)	10	15	0.41
pS2 (Trefoil factor 1)	12	12	0.71
SDF-1a (Stromal cell-derived factor 1a)	9	15	0.92
SDF-1b (Stromal cell-derived factor 1b)	12	13	0.53
SDC1 (Syndecan 1)	14	11	0.37
TXNIP (Thioredoxin interacting protein)	11	10	0.82
VEGF (Vascular endothelial growth factor)	11	14	0.32
XIAP (X-linked inhibitor of apoptosis)	10	15	0.88
Additional transcripts (failed reference transcripts)			
β -actin (Beta-Actin)	11	10	0.72
GUS β (Beta-glucuronidase)	18	7	0.12
B2M (Beta-2-microglobulin)	10	11	0.61

If only 2-fold relative changes are considered meaningful (ratio <0.5 or >2.0), the results are not altered, i.e., no transcripts are identified as being statistically significantly affected.

Supplementary Table 6: Changes in levels of all peptides and specific phosphopeptides as assessed in RPFNA specimens by Reverse Phase Protein Array. Change over course of trial was analyzed by Wilcoxon signed ranks test (2-tailed), without correction for multiple comparisons.

Peptide Fragment Identifier		Excludes Bloody Specimens			
Antibody Name ^a	Gene Name	Number where values decrease	Number where values increase	P-value (Wilcoxon 2-sided)	P-Values (includes bloody specimens ^b)
14-3-3_beta	V YWHAB	9	7	0.26	0.61
14-3-3_epsilon	YWHAE	5	11	0.30	0.033
14-3-3_zeta	V YWHAZ	6	10	0.18	0.69
4E-BP1	V EIF4EBP1	9	7	0.76	0.15
4E-BP1_pS65	V EIF4EBP1_pS65	5	11	0.049	0.036
4E-BP1_pT37_T46	V EIF4EBP1_pT37	4	12	0.0045	0.068
53BP1	TP53BP1	8	8	0.61	0.69
ACC_pS79	V ACC_pS79	6	10	0.47	0.86
ACC1	ACC1	4	12	0.18	0.36
ACVRL1	ACVRL1	6	10	0.47	0.43
Akt	V AKT	8	8	0.33	0.83
Akt_pS473	V AKT_pS473	3	13	0.039	0.036
Akt_pT308	V AKT_pT308	7	9	0.23	0.41
AMPK_alpha	AMPK_alpha	6	10	0.57	0.65
AMPK_pT172	V AMPK_pT172	7	9	0.96	0.43
Annexin_VII	V ANXA7	11	5	0.28	0.78
AR	V AR	5	11	0.47	0.37
B-Raf	BRAF	9	7	0.61	0.43
Bad_pS112	V BAD	6	10	0.30	0.14
Bak	BAK1	9	7	0.23	0.39
Bax	V BAX	8	8	0.96	0.39
Bcl-2	V BCL2	13	3	0.0072	0.0081
Bcl-xL	V BCLxL	10	6	0.47	0.21
Beclin	BECN1	10	6	0.15	0.63
beta-Catenin	V CTNNB1	5	11	0.18	0.26
Bid	BID	8	8	0.92	0.83
Bim	V BIM	9	7	0.72	0.86
BRCA2	BRCA2	8	8	0.92	0.86
c-Jun_pS73	V JUN	6	10	0.20	0.36
c-Kit	V KIT	6	10	0.30	0.86
c-Met_pY1235	V MET	10	6	0.57	0.13

Peptide Fragment Identifier		Excludes Bloody Specimens			
Antibody Name ^a	Gene Name	Number where values decrease	Number where values increase	P-value (Wilcoxon 2-sided)	P-Values (includes bloody specimens ^b)
c-Myc	MYC	9	7	0.92	0.63
C-Raf	V CRAF	13	3	0.049	0.17
C-Raf_pS338	CRAF_pS338	12	4	0.030	0.016
Caspase-7_cleavedD198	CASP7	11	5	0.079	0.029
Caveolin-1	V CAV1	9	7	0.96	0.69
CD31	V PECAM1	7	9	0.64	0.58
CD49b	V ITGA2	9	7	0.96	0.36
CDK1	V CDC2	11	5	0.30	0.14
Chk1	CHEK1	9	7	0.35	0.93
Chk1_pS345	CHEK1_pS345	4	12	0.049	0.083
Chk2-M-E	CHEK2	9	7	0.28	0.45
Chk2_pT68	CHEK2_pT68	8	8	0.92	0.67
Claudin-7	V CLDN7	11	5	0.079	0.95
Collagen_VI	V COL6A1	9	7	0.44	0.58
Cyclin_B1	V CCNB1	11	5	0.13	0.58
Cyclin_D1	V CCND1	11	5	0.044	0.055
Cyclin_E1	V CCNE1	6	10	0.44	0.45
DJ-1	PARK7	7	9	0.88	0.78
Dvl3	V DVL3	9	7	0.44	0.045
E-Cadherin	V CDH1	6	10	0.61	0.88
eEF2	EEF2	2	14	0.0011	0.0013
eEF2K	V EEF2K	4	12	0.011	0.015
EGFR	V EGFR	7	9	0.88	0.48
EGFR_pY1068	EGFR_pY1068	5	11	0.11	0.021
EGFR_pY1173	V EGFR_pY1173	8	8	0.44	0.95
elf4E	V EIF4E	14	2	0.0016	0.012
elf4G	EIF4G1	8	8	0.30	0.38
ER-alpha	V ESR1	9	7	0.61	0.65
ER-alpha_pS118	V ESR1_pS118	11	5	0.33	0.72
FASN	V FASN	7	9	0.76	1.00
Fibronectin	V FN1	13	3	0.0052	0.023
FOXO3a	FOXO3	10	6	0.35	0.86
FoxM1	V FOXM1	6	10	0.53	0.52
G6PD	V G6PD	7	9	0.96	0.094
Gab2	V GAB2	6	10	0.38	0.69

Peptide Fragment Identifier		Excludes Bloody Specimens			
Antibody Name ^a	Gene Name	Number where values decrease	Number where values increase	P-value (Wilcoxon 2-sided)	P-Values (includes bloody specimens ^b)
GAPDH	GAPDH	9	7	0.33	0.52
GATA3	V GATA3	13	3	0.023	0.023
GSK3-alpha-beta	V GSK3aB	11	5	0.088	0.12
GSK3-alpha-beta_pS21_S9	V GSK3aB_pS21	11	5	0.68	0.25
GSK3_pS9	V GSK3aB_pS69	5	11	0.18	0.13
HER2	V HER2	9	7	0.098	0.45
HER2_pY1248	HER2_pY1248	8	8	0.92	0.35
HER3	V HER3	13	3	0.011	0.16
HER3_pY1298	HER3_pY1298	10	6	0.21	0.036
Heregulin	V NRG1	9	7	0.68	0.95
IGFBP2	V IGFBP2	4	12	0.18	0.74
INPP4B	INPP4B	8	8	0.72	0.45
IRS1	V IRS1	6	10	0.26	0.47
JNK_pT183_pT185	V MAPK8	9	7	0.92	0.90
JNK2	MAPK9	5	11	0.098	0.14
Lck	V LCK	4	12	0.079	0.089
MAPK_pT202_Y204	V MAPK_pT202	5	11	0.38	0.35
MEK1	V MEK1	8	8	0.92	0.22
MEK1_pS217_S221	V MEK1_pS217	9	7	0.76	0.41
MIG-6	V ERRFI1	11	5	0.38	0.74
mTOR	V mTOR	8	8	0.50	0.36
mTOR_pS2448	mTOR_pS2448	7	9	0.35	0.69
MYH11	V MYH11	7	9	0.53	0.83
Myosin Ila pS1943	V MYH9	12	4	0.011	0.0014
N-Cadherin	V CDH2	12	4	0.088	0.023
N-Ras	V NRAS	10	6	0.13	0.36
NDRG1_pT346	V NDRG1	6	10	0.38	0.56
NF-kB-p65_pS536	NFKB1	4	12	0.088	0.023
NF2	NF2	13	3	0.010	0.0013
Notch1	V NOTCH1	8	8	0.50	0.43
p27	V p27	6	10	0.28	0.74
p27_pT157	p27_pT157	13	3	0.16	0.50
p27_pT198	V p27_pT198	6	10	0.18	0.014
p38_MAPK	V p38_MAPK	9	7	0.50	0.059
p38_pT180_Y182	V p38_pT180	6	10	0.18	0.039

Peptide Fragment Identifier		Excludes Bloody Specimens			
Antibody Name ^a	Gene Name	Number where values decrease	Number where values increase	P-value (Wilcoxon 2-sided)	P-Values (includes bloody specimens ^b)
p53	TP53	5	11	0.61	0.064
p70S6K	V p70S6K	10	6	0.18	0.14
p70S6K_pT389	V p70S6K_pT389	8	8	0.92	0.39
p90RSK	p90RSK	11	5	0.10	0.11
p90RSK_pT359_S363	p90RSK_pT359	11	5	0.16	0.61
Paxillin	PXN	5	11	0.26	1.00
PCNA	PCNA	5	11	0.044	0.0039
PDCD4	PDCD4	7	9	0.41	0.90
PDK1	V PDK1	10	6	0.64	0.90
PDK1_pS241	V PDK1_pS241	4	12	0.049	0.045
PEA15	V PEA15	6	10	0.28	0.88
PEA15_pS116	V PEA15_pS116	12	4	0.023	0.023
PI3K-p110-alpha	PIK3CA	6	10	0.088	0.22
PI3K-p85	V PIK3R1	8	8	1.00	0.24
PKC-alpha	V PRKCA	2	14	0.0038	<0.001
PKC-alpha_pS657	PRKCA_pS664	10	6	0.64	0.69
PKC-delta_pS664	V PRKCD	12	4	0.070	0.41
PKC-pan_Betall_pS660	V PKC	11	5	0.84	0.98
PR	V PGR	12	4	0.0027	0.0026
PRAS40_pT246	V AKT1S1	13	3	0.0027	0.0013
PTEN	V PTEN	6	10	0.35	0.78
Rab11	RAB11	7	9	0.80	0.26
Rad50	V RAD50	8	8	1.00	0.36
Rad51-M-E	RAD51	7	9	0.21	0.078
Raptor	V RPTOR	13	3	0.0052	<0.001
Rb_pS807_S811	V RB1	5	11	0.044	0.0068
RBM15	V RBM15	8	8	0.76	0.11
Rictor	RICTOR	8	8	0.57	0.14
Rictor_pT1135	V RICTOR_pR1135	11	5	0.13	0.29
S6_ps235_S236	V S6_ps235	8	8	0.64	0.72
S6_ps240_S244	V S6_ps240	12	4	0.21	0.39
SCD	V SCD	13	3	0.0045	0.024
SF2	V SFRS1	10	6	0.30	0.30
Smad1	V SMAD1	12	4	0.056	0.0039
Smad3	V SMAD3	14	2	0.0023	<0.001
Smad4	V SMAD4	10	6	0.18	0.39

Peptide Fragment Identifier		Excludes Bloody Specimens			
Antibody Name ^a	Gene Name	Number where values decrease	Number where values increase	P-value (Wilcoxon 2-sided)	P-Values (includes bloody specimens ^b)
Src	V SRC	11	5	0.30	0.72
Src_pY416	SRC_pY416	7	9	0.50	0.47
Src_pY527	V SRC_pY627	3	13	0.017	0.015
STAT3_pY705	V STAT3	10	6	0.57	0.52
STAT5-alpha	V STAT5A	11	5	0.044	0.0039
Stathmin	V STMN1	9	7	0.96	0.56
Syk	V SYK	14	2	0.013	0.013
TAZ	V WWTR1	8	8	0.96	0.98
TFRC	V TRFC	5	11	0.88	0.81
TIGAR	V C12ORF5	7	9	0.38	0.17
Transglutaminase	V TGM2	11	5	0.044	0.35
TSC1	TSC1	10	6	0.30	0.073
TTF1	V TTF1	9	7	0.80	0.74
Tuberin	TSC2	7	9	0.76	0.27
Tuberin_pT1462	V TSC2_pT1462	4	12	0.0061	0.0017
VEGFR2	V KDR	7	9	0.92	0.52
VHL	VHL	11	5	0.070	0.019
XRCC1	XRCC1	11	5	0.088	0.56
YAP	YAP1	6	10	0.26	1.00
YAP_pS127	YAP1_pS127	4	12	0.049	0.61
YB-1	V YBX1	8	8	0.64	0.38
YB-1_pS102	V YBX1_pS102	9	7	0.53	0.29

a) V indicates validated antibody; p21 and rab25 were omitted because of quality control concerns.

b) Seven additional paired specimens