2016 San Antonio Breast Cancer Symposium: Local Therapy Highlights

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Abstracts

1. Sentinel Node Dissection after Neoadjuvant Chemotherapy in Patients without Previous Axillary Node Involvement (GANEA 2 Trial): Follow-up of a Prospective Multi-institutional Cohort (S2-07)
2. Impact of Radiotherapy on Complications and Patient-Reported Outcomes after Breast Reconstruction: Findings from the Prospective Multicenter MROC Study (S3-07)
3. Radioactive Seed Localization versus Wire Guided Localization of Nonpalpable Invasive and In Situ Breast Cancer: A Danish Multicenter Randomized Control Trial (S3-08)

Abstracts

4. DCIS Biological Risk Profile Predicts Risk of Recurrence after Breast Conserving Surgery in a Kaiser Permanent NW Population (S5-01)

5. Low-fat Dietary Pattern and Breast Cancer Overall Survival in the Women [apos]s Health initiative Dietary Modification Randomized Controlled Trial (S5-04)

6. Randomized, placebo-controlled trial of Duloxetine for Aromatase Inhibitor (AI)-associated Musculoskeletal Symptoms (AIMSS) in Early Stage Breast Cancer (SWOG 1202) (S5-06)
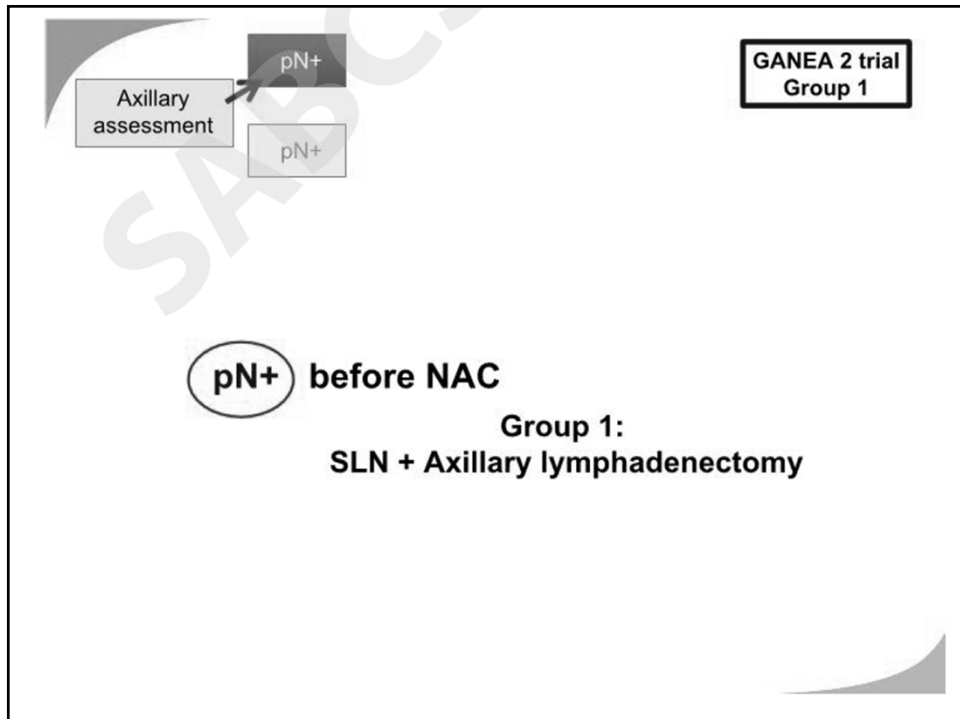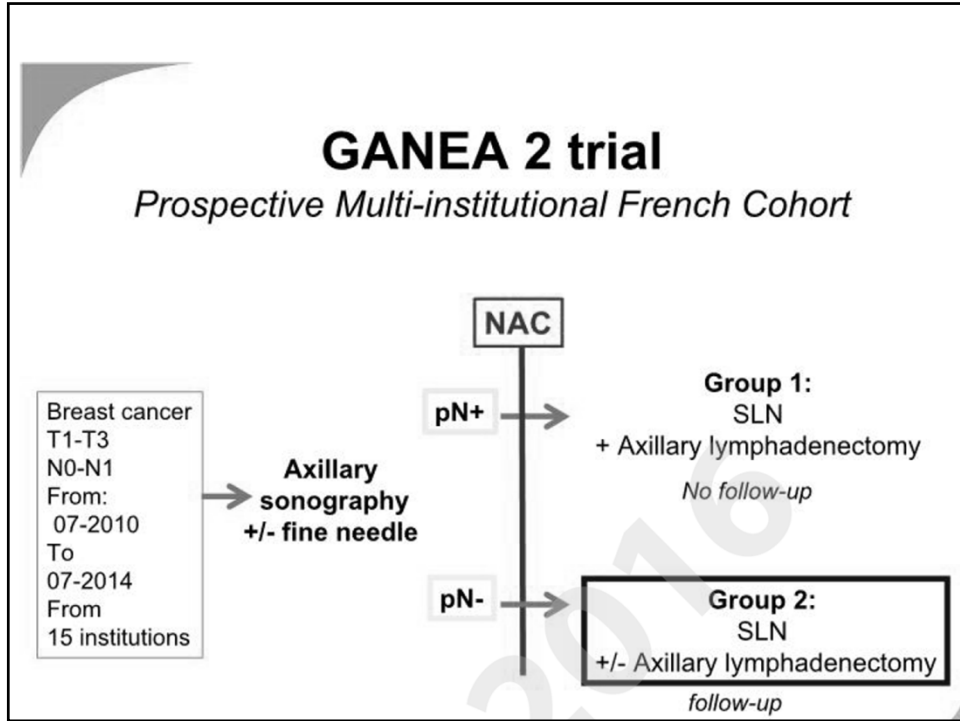

INSTITUT NATIONAL DE CANCER   Institut de Cancérologie de l'Ouest

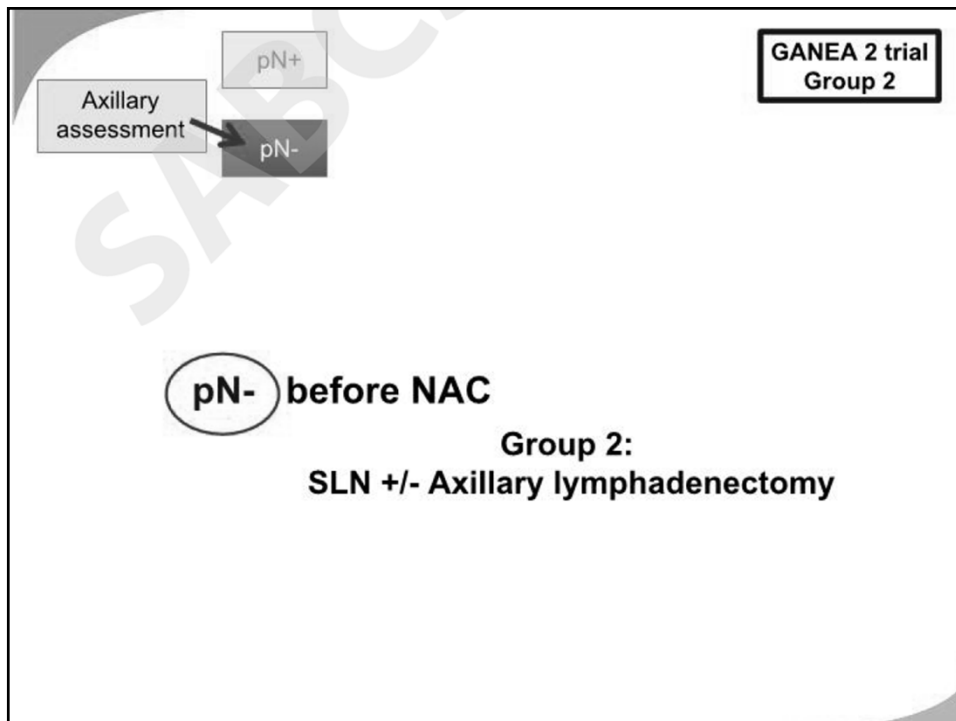## Sentinel node detection after neoadjuvant chemotherapy
(GANEA 2 trial):
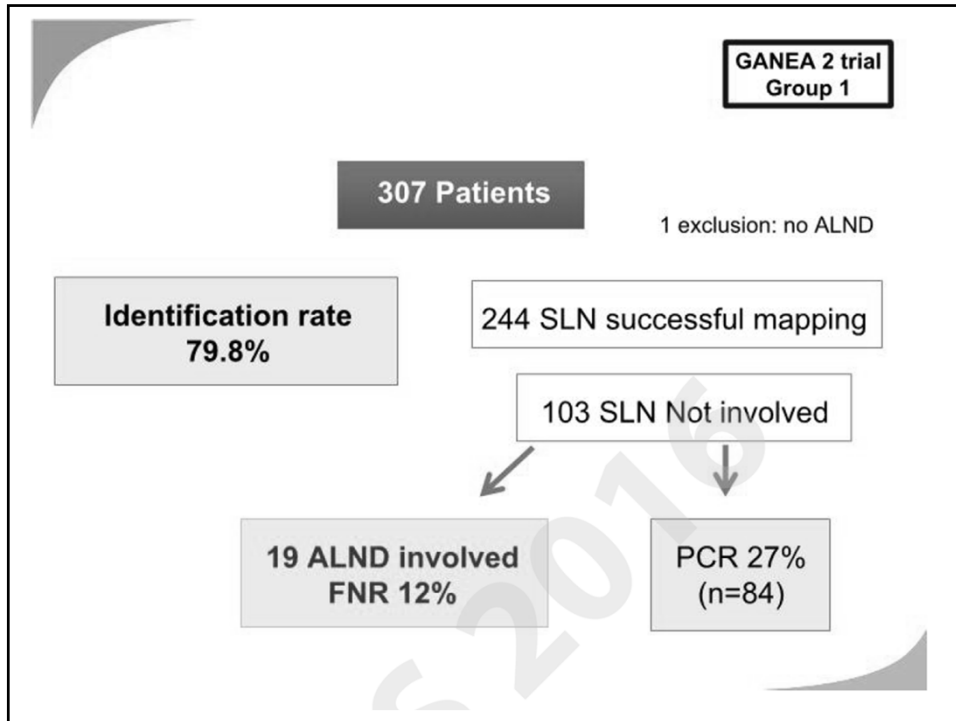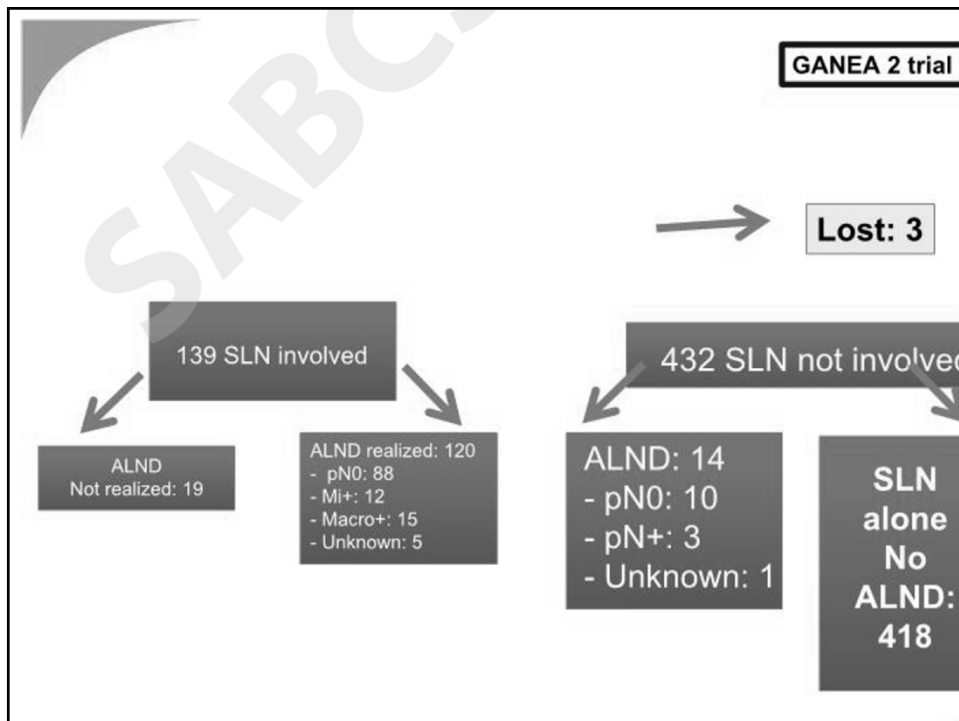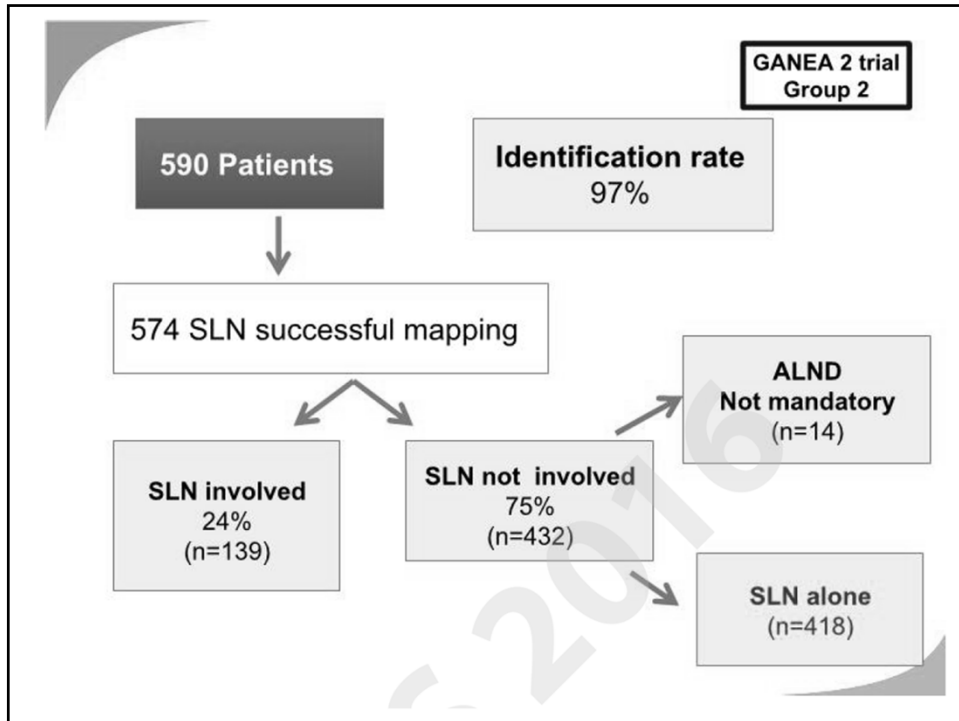Follow-up of a prospective multi-institutional cohort

Pr Jean-Marc Classe, MD, PhD

Institut de Cancérologie de l'Ouest – Centre Gauducheau – Nantes - France

GANEA 2 trial
Prospective Multi-institutional French Cohort

Breast cancer T1-T3 N0-N1 From: 07-2010 To 07-2014 From 15 institutions → Axillary sonography +/- fine needle

NAC

pN+ → Group 1: SLN + Axillary lymphadenectomy — No follow-up

pN- → Group 2: SLN +/- Axillary lymphadenectomy — follow-up

pN+
Axillary assessment
pN+

GANEA 2 trial Group 1

pN+ before NAC

Group 1:
SLN + Axillary lymphadenectomy

GANEA 2 trial
Group 2

Patients' characteristics

Patients characteristics	SLN alone n= 418	SLN pN+ (+ Lymphadenectomy) n=120	
SBR Scoring III	255 (61%)	31 (26%)	$(p<10^{-3})$
Hormonal Receptor : RO			
neg........................	212 (51%)	23 (19%)	$(p<10^{-3})$
RP neg........................	262 (62%)	32 (26%)	$(p<10^{-3})$
HERb2 3+..................	73 (17%)	10 (8%)	$(p=0.016)$

GANEA 2 trial
Group 2

Results: Breast surgery

Patients characteristics	SLN alone n= 418	SLN pN+ (+ Lymphadenectomy) n=120
Conservative surgery	379 (90%)	98 (81.5%)
mastectomy	39 (10%)	22 (18.5%)

$P=0.006$

Results: axillary nodes

Patients characteristics	SLN alone n= 418	SLN pN+ (+ Lymphadenectomy) n=120
SLN	pN-	pN+ (macro= 79/micro=41)
ALND	Not done	pN+=29 (24%) : pN-=88 (73%) (NA:3)

GANEA 2 trial
Group 2

Follow-up organization:

Clinical visit / 6 months:
Clinical breast and axillary assessment
+/- axillary sonography if necessary
AND **Mammography/ year**

3 years survival	N= 418 (SLN alone)
Overall survival	**97.8%** [94.9-99.1]
Disease free survival	**94.8%** [91.0-97.1%]

Events
418 Patients SLN alone without ALND
Median Follow-up =36 months

GANEA 2 trial
Group 2

Relapse	N=10
Metastasis	3
Breast relapse	3 homo L 3 contra L
Axillary relapse	1 (0.2%)

Take Home Message

- Axillary ultrasound with biopsy to prove nodal involvement prior to NACT is necessary to differentiate surgical approach to the axilla following NACT
- In patients without axillary nodes involved before NACT, SLNbx alone is acceptable without axillary lymph node dissection
- In patients who are initially node positive, the clinical implications of a false negative rate of 12% in SLNbx alone following NACT is unknown

Limitations

- Variety of techniques for identifying sentinel lymph node
- All patients with positive lymph node received ALND and these patients were not followed
- Did not provide data on SLN involved among Group 2 patients (all had ALND)

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Impact of Radiotherapy on Complications and Patient-Reported Outcomes after Breast Reconstruction: Findings from the Prospective Multicenter MROC Study

Reshma Jagsi, MD, DPhil,[1] Adeyiza O. Momoh, MD,[1] Ji Qi, MS,[1] Jennifer B. Hamill, MPH,[1] Jessica Billig, MD,[1] Hyungjin M. Kim, ScD,[1] Andrea L. Pusic, MD, MHS,[2] Edwin G. Wilkins, MD, MS[1]

[1]University of Michigan, Ann Arbor, MI
[2]Memorial Sloan Kettering Cancer Center, New York, New York

Integrating Post-Mastectomy Radiation and Reconstruction

- Evidence to date has been limited
  - Primarily retrospective single-institution data
  - Few multi-center studies limited
    - failure to include sufficient numbers of radiated pts
    - failure to include patients treated with different reconstruction techniques for comparison
    - failure to measure covariates
    - limitation to populations substantially different from those treated in the US

Integrating Post-Mastectomy Radiation and Reconstruction

- Practice varies widely
  - reflects historical traditions and institutional culture rather than shared decision-making informed by high-quality evidence

Approach

- Design:
  - prospective multicenter cohort study
- Study Population:
  - 553 radiated and 1461 non-radiated patients who received either implant or autologous reconstruction (at any time point before or after radiation in irradiated patients) at 11 institutions 2012-15
- Endpoints:
  - Complications, failure, and patient-reported outcomes
    - PROs measured using BREAST-Q
      - validated, condition-specific HR-QOL measure
      - specifically developed for breast reconstruction patients
      - measures multiple domains

Approach

- Mixed-effects regression models assessed impact of reconstruction type, radiotherapy, and the interaction of reconstruction and radiotherapy on outcomes after adjusting for relevant covariates
  - Covariates:
    - Reconstruction timing
    - Age
    - Extent of disease
    - Bilateral vs unilateral reconstruction
    - Chemotherapy receipt
    - Nodal management
    - BMI
    - Smoking
    - Diabetes
    - Race
    - Ethnicity
    - Education
    - Employment
    - Income
   - Marital status
    - Hospital site

Sample Characteristics

- Median age 49
- Bilateral mastectomy received by 45.6% of radiated & 53.3% of non-radiated pts (p=0.002)
- Autologous reconstruction more commonly received by radiated pts (38.3% vs 25.1%, p<0.001)
  - ~62% of radiated patients had implants and 70-80% of these implants were tissue expanders
- Immediate reconstruction less common in radiated pts (82.6% vs 95.6%, p<0.001)
  - Immediate reconstruction was most commonly implant based with tissue expander
- 70-80% of implant cohort were tissue expanders who had exchange by 1 year post-op

Complications

- By two years, at least one complication (e.g. hematoma, wound infection, etc.) occurred in 33.4% of radiated pts and 23.5% of non-radiated pts
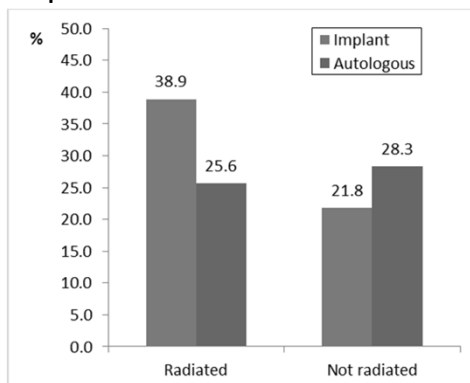
Complications

- MVA: bilateral treatment and higher BMI predictive of developing a complication, with significant interaction between RT receipt and reconstruction type
  - RT associated with 2.64 (p=<0.001) times higher odds of complication by 2 years in implant pts, while showing no significant difference in autologous pts (OR=1.12, p=0.67)
  - Among radiated patients, autologous reconstruction associated with lower 2-year risk of complications than implant-based reconstruction (OR=0.47, p=0.007)

Reconstruction Failure

- By two years, reconstructive failure occurred in 11.4% of radiated pts and 3.4% of non-radiated pts

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Results: PROs at 2 Years

Satisfaction with breast — Satisfaction with outcome

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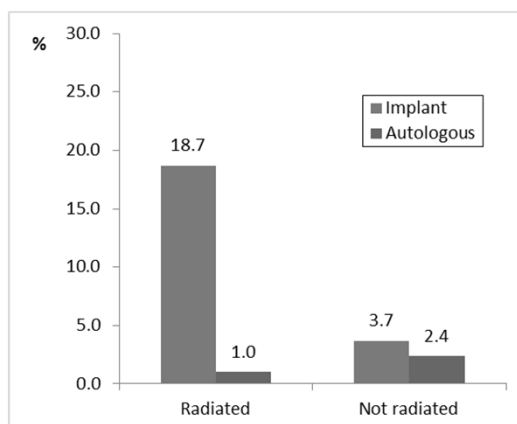San Antonio Breast Cancer Symposium – December 6-10, 2016

Results: PROs at 2 Years

Psychosocial well-being — Physical well-being

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Conclusions

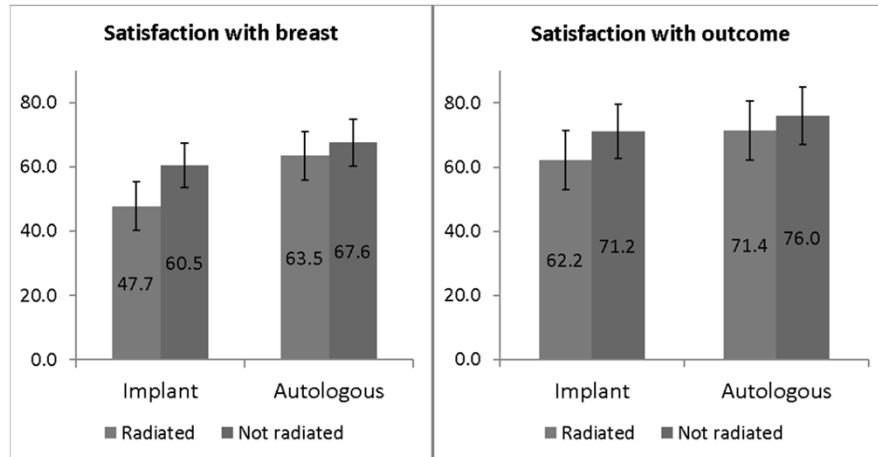- In the largest prospective multicenter study of outcomes of breast reconstruction to date, RT appears to compromise outcomes of implant reconstruction without clear impact on autologous reconstruction
- Autologous reconstruction appears to yield superior patient-reported outcomes and lower risk of complications than implant-based approaches among patients receiving PMRT
- These data are critical to inform the growing number of patients who are considering PMRT and may desire reconstruction, so that they may make informed, preference-concordant decisions

Take Home Message

- In patients who receive post mastectomy radiation, implant based (with tissue expanders) vs. autologous reconstruction is associated with more complications and worse patient reported quality of life outcomes

Limitations

- No information on cancer outcomes or how reconstruction may impact radiation technique
- Does not address optimal timing of reconstruction. 170 patients had delayed reconstruction and received radiation to the unreconstructed chestwall. They then received autologous reconstruction after radiation and were grouped in the autologous cohort. Separate analysis looking at timing of reconstruction is pending.
- 70-80% of "implant" patients had temporary tissue expanders during radiation that were replaced with permanent implant after radiation
- Vast majority of immediate reconstruction patients had tissue expander during radiation

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Radioactive Seed Localization vs. Wire-Guided Localization of Nonpalpable Invasive and In Situ Breast Cancer:
A Danish Multicenter Randomized Controlled Trial

Langhans L, Tvedskov TF, Klausen TL, Jensen MB, Talman ML, Vejborg I, Benian C, Roslind A, Hermansen J, Oturai PS, Bentzon N, Kroman N
Rigshospitalet & Herlev Hospital, University of Copenhagen, Denmark

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Mylin Torres, 12/19/2016

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Preoperative lesion localization
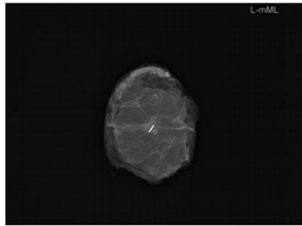
Radioactive seed localization (RSL)
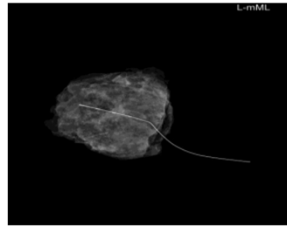
Wire-guided localization (WGL)

Study Design

Randomized controlled trial of radioactive seed localization vs. wire-guided localization of nonpalpable invasive and in situ breast cancers:

- Primary Endpoint: Positive margin rate defined as < 2.0mm for invasive or DCIS
- Secondary Endpoint:
  a) Patient's pain perception following seed placement or wire
  b) Duration of surgical procedure – time from skin incision to complete excision of specimen
  c) Weight of excised specimen

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Patients

Nonpalpable lesions

Invasive breast cancer (IBC) or ductal carcinoma in situ (DCIS)

Visible on ultrasound

Eligible for breast conserving surgery

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Trial profile

RSL   WGL

444   409/413

35

206 — 195 — 192

Allocation   Intention-to-treat   Per-protocol

207 — 195 — 186

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Results

- Inclusion period was Jan 1, 2014 to Feb 4, 2016

- Baseline characteristics were alike

- Significantly more patients with DCIS in the WGL group (p=0.006)

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Margin status

	RSL n (%)	WGL n (%)	P-value	OR (95%CI)
Intention-to-treat			0.65	1.15 (0.63-2.10)
Negative	172 (88.2%)	169 (86.7%)		
Positive	23 (11.8%)	26 (13.3%)		
Per-protocol			0.62	1.17 (0.64-2.14)
Negative	164 (88.2%)	166 (86.5%)		
Positive	22 (11.8%)	26 (13.5%)		
IBC			0.997	1.0 (0.53-1.89)
Negative	172 (88.7%)	164 (88.6%)		
Positive	22 (11.3%)	21 (11.4%)		

Secondary outcomes

	RSL	WGL	P-value
Weight total (g)	29 (18.5-43.0)	26 (18.0-40.0)	0.54
Duration (min)	10 (7-12)	10 (7-15)	0.12
Pain Perception			0.28
No	13 (7.9%)	4 (2.9%)	
Mild	88 (53.3%)	76 (55.1%)	
Moderate	48 (29.1%)	41 (29.7%)	
Severe	16 (9.7%)	17 (12.3%)	

Results

- Complication rate (p=0.89)

- Sentinel node identification rate (p=1.00)

Conclusions

No significant difference in:

- **Margin status**
- Duration of the surgical procedure
- Weight of the excised specimen
- Patients' pain perception

Perspectives

- 2 previous randomized trials with similar results on margin status

- RSL offers a major logistic advantage

- Do we have enough evidence to safely implement RSL as standard procedure?

Take Home Message

- In this randomized trial, radioactive seed placement for nonpalpable breast cancer lesions did not lead to a higher rate of positive margins, more time in the operating room, or more breast tissue removed than traditional wire guided localization procedures
- Radioactive seed placement has the potential to increase operating room throughput and convenience, as the seed may be placed several days ahead of the operating room procedure

Limitations

- Data is lacking quantifying patient perceptions of time spent having seed placed and returning for a second visit to the operating room procedure versus time and inconvenience spent in mammography suite and operating room with the wire localization procedure
- Majority of patients in this study had invasive breast cancer and very few had DCIS
- Less than 2mm margins on invasive or DCIS was considered a positive margin

Take Home Message

- DCIS biological risk signature appears to be both prognostic and predictive of benefit of radiation in DCIS patients treated with lumpectomy

Limitations

- Validation studies are ongoing
- Unclear how the clinical factors were incorporated with the biological factors and how they were weighted
- No detailed data presented on risk of invasive recurrences although presenter said it was half and half
- Unclear how the cutoff scores of 3 was determined or how biomarkers were selected

Low-Fat Dietary Pattern and Breast Cancer Mortality in the Women's Health Initiative Dietary Modification (WHI DM) Trial

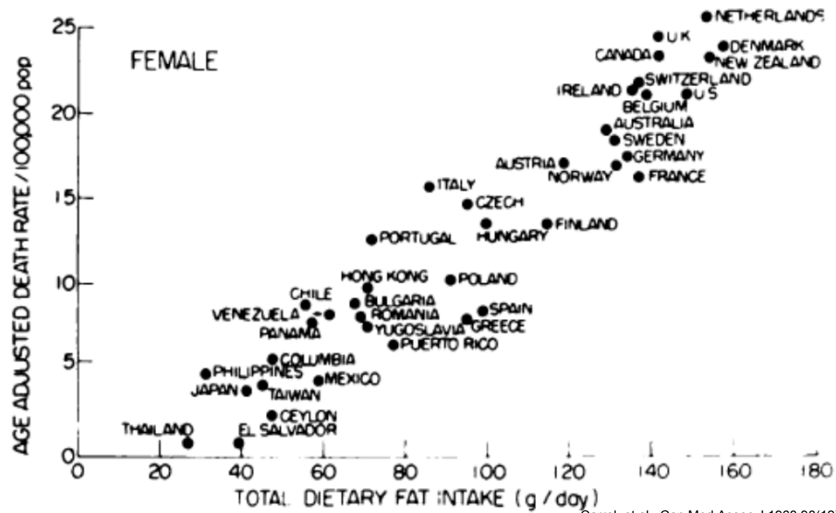Chlebowski RT, Aragaki AK, Anderson GL, Thomson CA, Manson JE, Simon MD, Howard BV, Rohan TE, Snetselar L, Lane D, Barrington W, Vitolins MZ, Womack C, Qi L, Lou L, Thomas F, Prentice RL

Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center for the Women's Health Initiative

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Country-by-Country Breast Cancer Death Rate by Estimated Dietary Fat Intake

Carrol, et al. Can Med Assoc J 1968;98(12):590-4

WHI Dietary Modification Randomized, Controlled, Primary Breast Cancer Prevention Clinical Trial Analysis Plan

Comparison
N=29,294

Postmenopausal Women
N=48,835

- Age 50-79 years
- No prior breast cancer
- Fat intake ≥ 32% calories
- Mammogram normal

- Entry: 1993-1998

Dietary Intervention
N=19,541

8.5 Years
(median)
(intervention)

16.1Years
(median)
(cumulative)

Analysis Endpoints: Deaths from breast cancer. Deaths after breast cancer
Clinical follow-up plus National Death Index queries

WHI DM: Dietary Intervention

- Dietary Intervention Goals:

  - Reduce dietary fat intake (target 20% calories from fat)

  - increase vegetables and fruit servings (target 5/day)

  - increase grains servings (target 6/day)

- Weight loss not an intervention target

- Diet Group: Year 1: 18 group sessions, then quarterly maintenance

- Control Group: received dietary guideline report only

Ritenbaugh, Patterson, Chlebowski, et al. Ann Epidemiol 2006; 13(9 suppl): S87-97 Tinker, Burrows, Henry, et al. Nutrition in Women's Health, 1996

Baseline Demographics by Randomization Group

Characteristic	Diet [N=19541] N (%)	Control [N=29294] N (%)	P-Value
Age, y			
50-59	7206 (37%)	10797 (37%)	
60-69	9086 (47%)	13626 (46%)	>.99
70-79	3249 (17%)	4871 (17%)	
Race/ethnicity			
White	15869 (81%)	23890 (82%)	
Black	2137 (11%)	3129 (11%)	
Hispanics	755 (4%)	1099 (4%)	.76
Asian/Pacific Islander	433 (2%)	674 (2%)	
Other/Unknown	362 (2%)	502 (1%)	

Baseline Demographics of WHI DM Trial Participants Did not Differ by Randomization Group

Age	Body Mass Index
Race/ethnicity	Mammogram within 2 years
Breast cancer family history	History of estrogen plus progestin use
Gail 5y breast cancer risk	History of estrogen alone use
Reproductive history	Treated diabetes

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Dietary Intake Change in the Diet Group: Types of Fat

Overall decrease in percent calories from fat of 13.9% at year 1 and 8.2% at year 5 (both P<0.001)

Howard, Manson, Stefanick et al. *JAMA* 2006;295:39-49
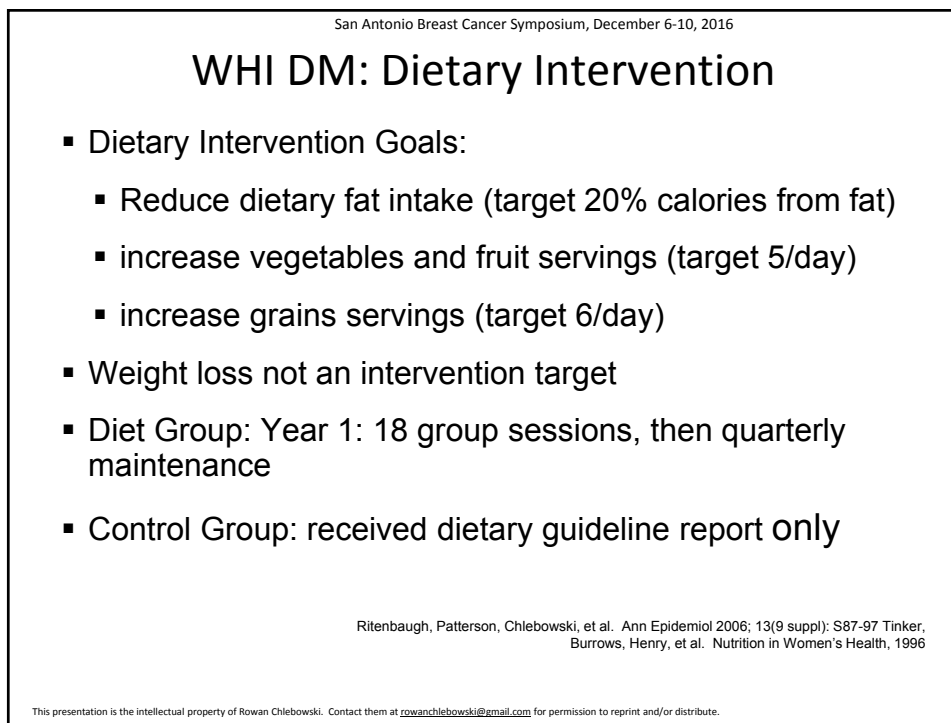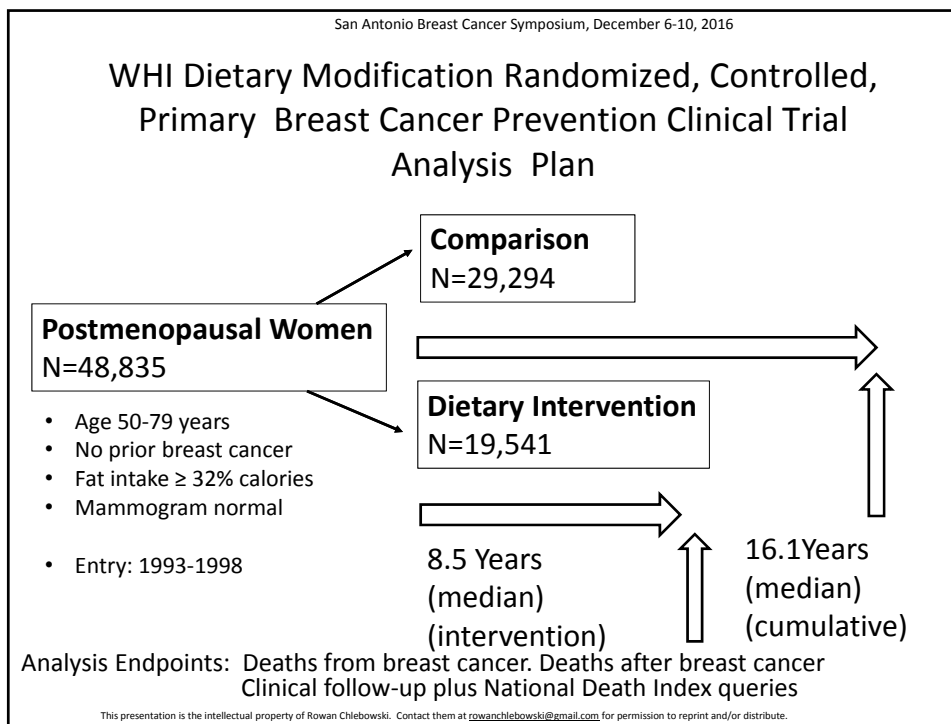Prentice RL, Caan B, Chlebowski RT et al. *JAMA* 2006;295:629-42

DietaryThis presentation is the intellectual property of Rowan Chlebowski. Contact them at rowanchlebowski@gmail.com for permission to reprint and/or distribute.

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WHI DM: Change in Body Weight by Randomization Group

Cumulative P= 0.01

P < 0.001

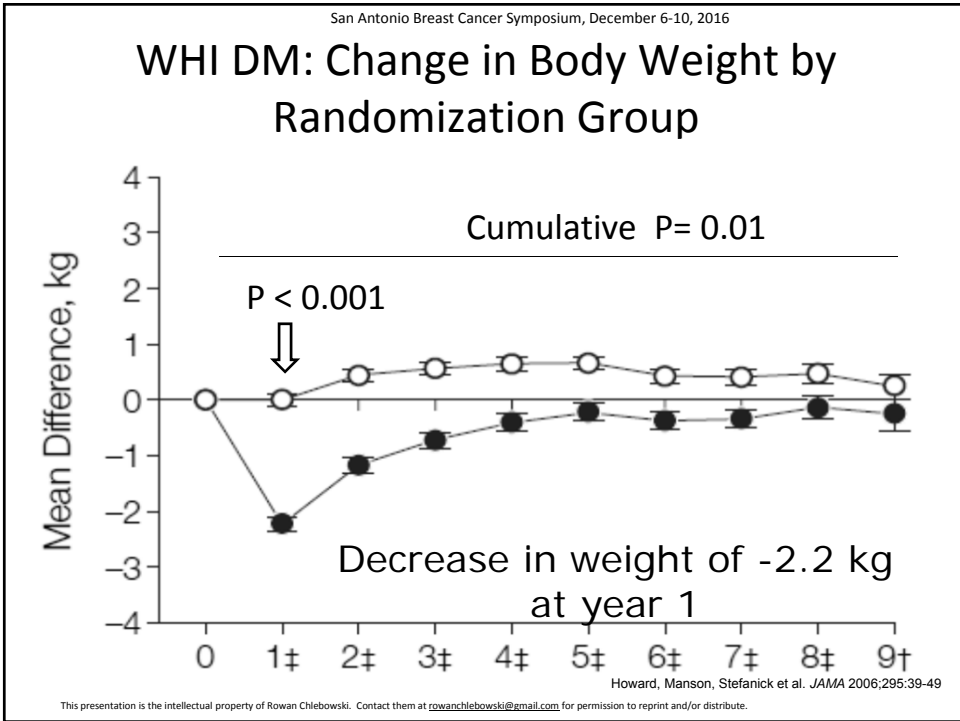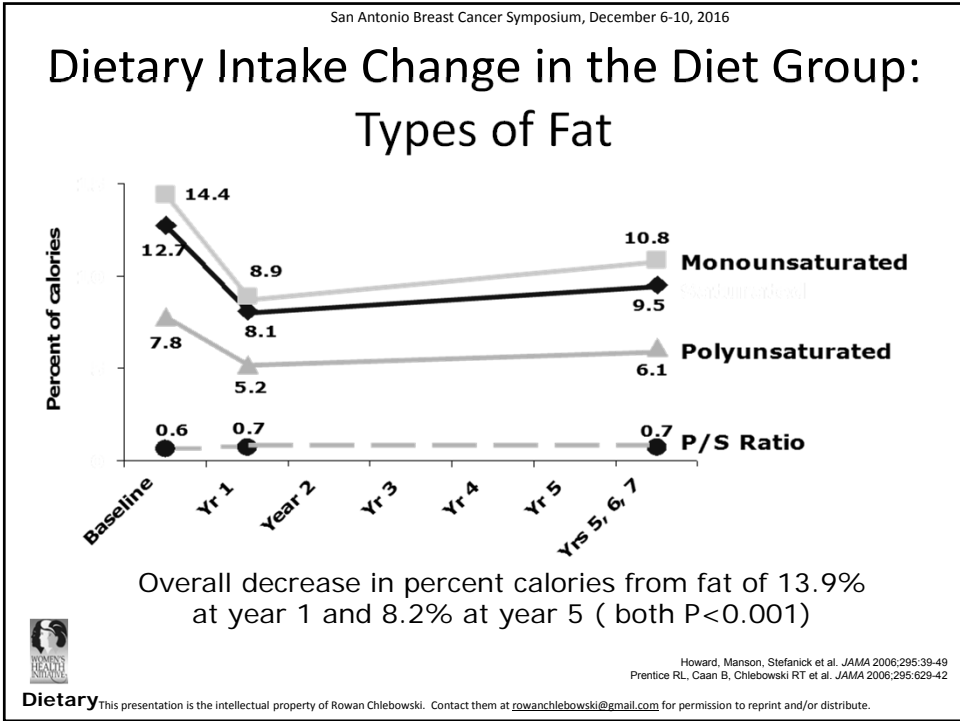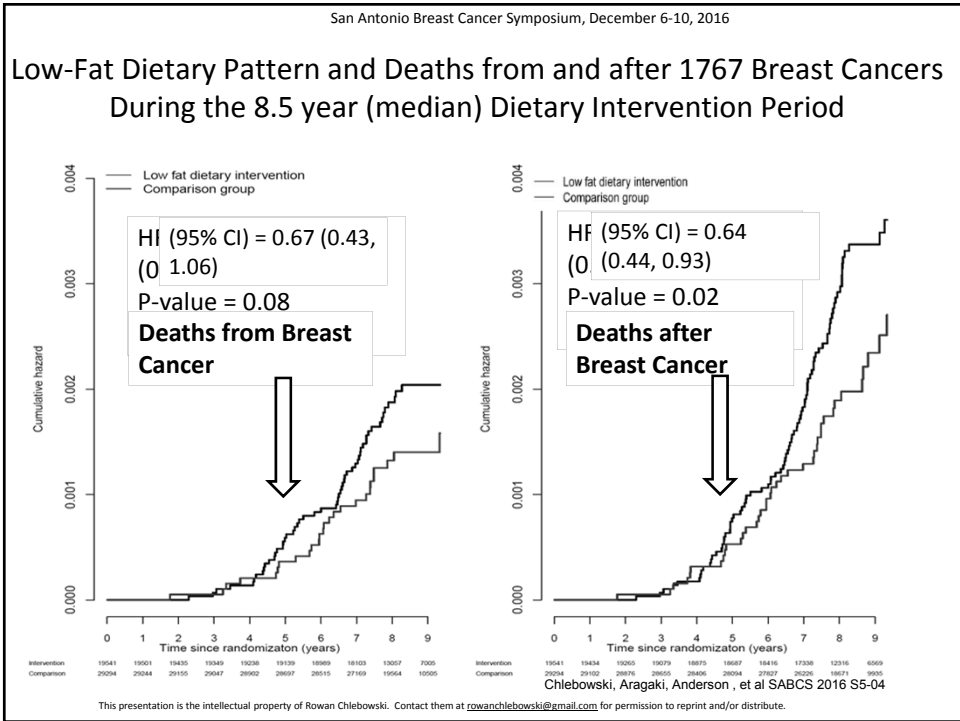Decrease in weight of -2.2 kg at year 1

Howard, Manson, Stefanick et al. *JAMA* 2006;295:39-49

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DM Trial: Breast Cancer Incidence during 8.5 year (median) Dietary Intervention Period

HR 0.91 (0.83-1.01)
1,727 breast cancers,
P =0.07
3.5% of all DM participants

For deaths from breast cancer
27 vs 53, HR 0.77 (0.48-1.22)

Prentice RL, Caan B, Chlebowski RT et al. JAMA 2006;395:629-42

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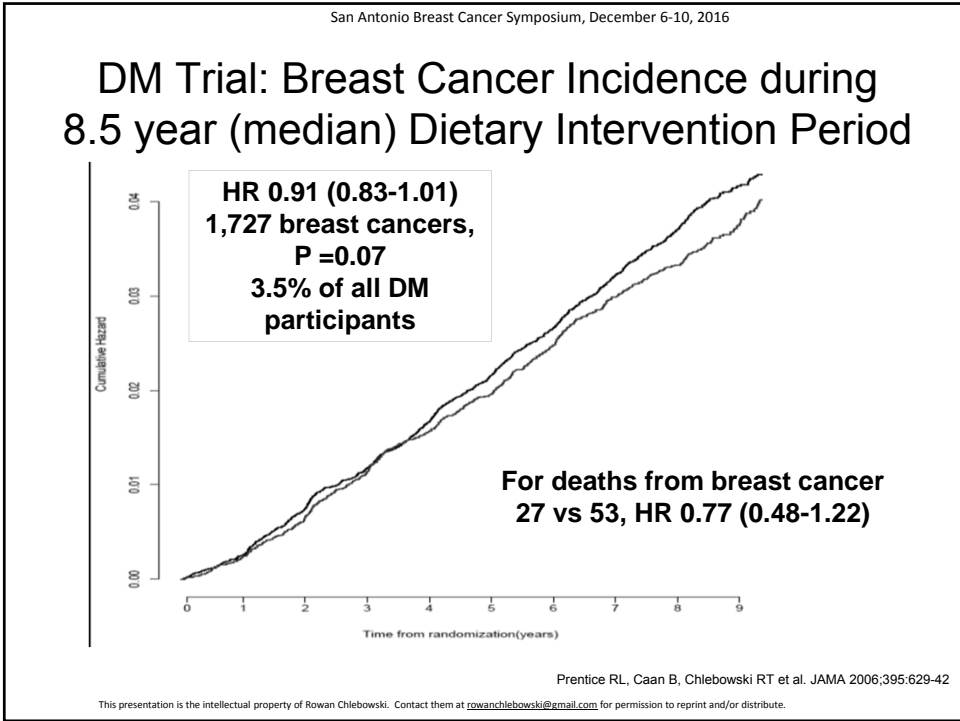

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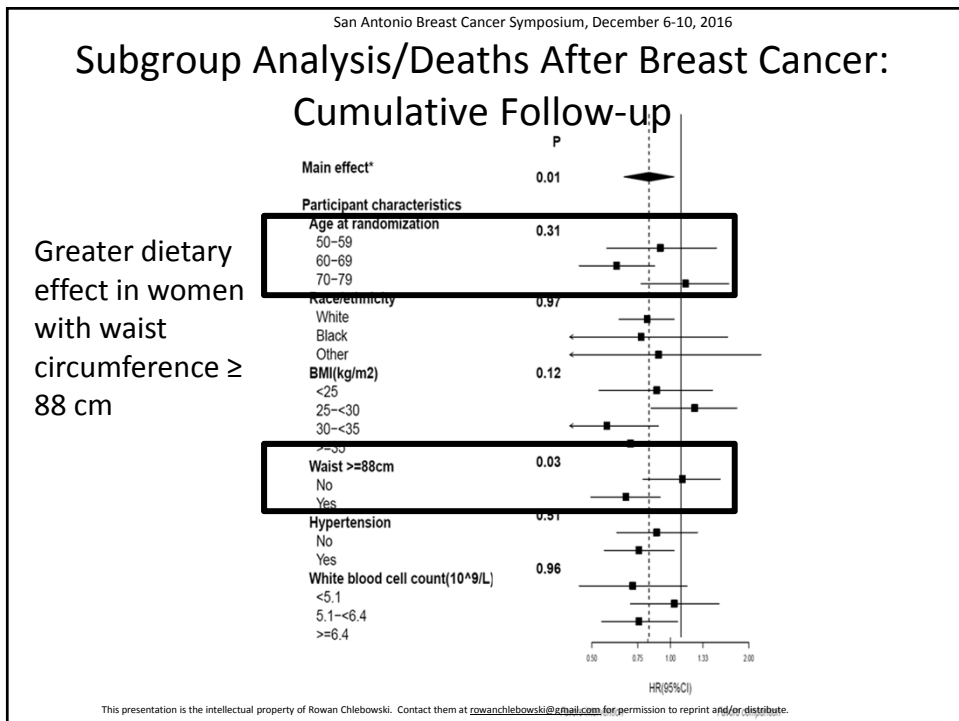**Low-Fat Dietary Pattern and Deaths from and after 1767 Breast Cancers During the 8.5 year (median) Dietary Intervention Period**

HR (95% CI) = 0.67 (0.43, 1.06)
P-value = 0.08
Deaths from Breast Cancer

HR (95% CI) = 0.64 (0.44, 0.93)
P-value = 0.02
Deaths after Breast Cancer

Chlebowski, Aragaki, Anderson , et al SABCS 2016 S5-04

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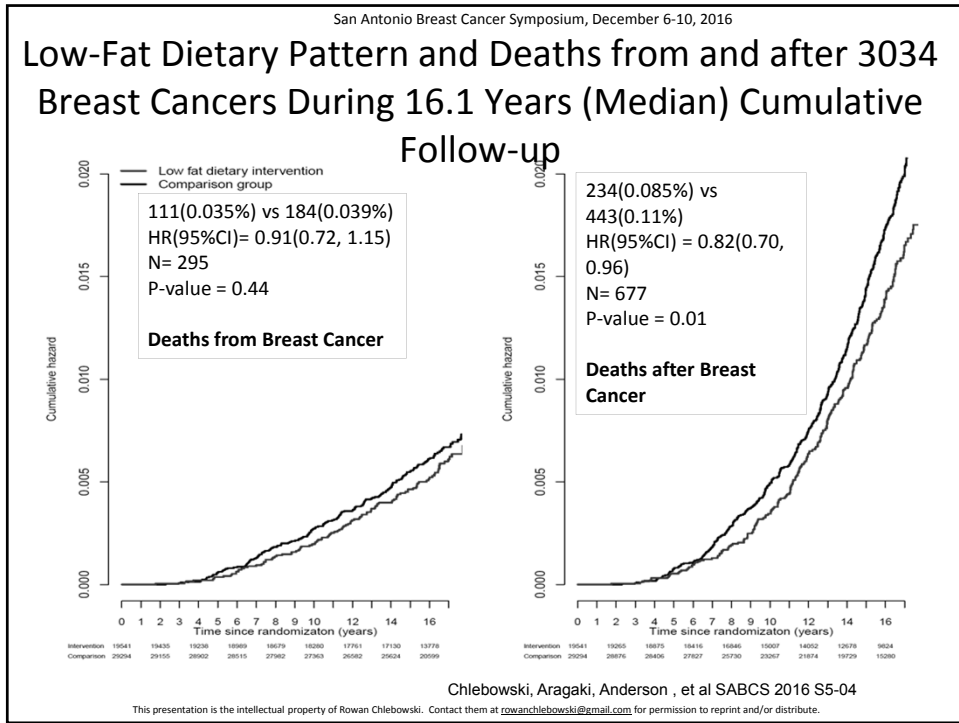San Antonio Breast Cancer Symposium, December 6-10, 2016

Low-Fat Dietary Pattern and Deaths from and after 3034 Breast Cancers During 16.1 Years (Median) Cumulative Follow-up

111(0.035%) vs 184(0.039%)
HR(95%CI)= 0.91(0.72, 1.15)
N= 295
P-value = 0.44

Deaths from Breast Cancer

234(0.085%) vs 443(0.11%)
HR(95%CI) = 0.82(0.70, 0.96)
N= 677
P-value = 0.01

Deaths after Breast Cancer

Chlebowski, Aragaki, Anderson , et al SABCS 2016 S5-04

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Subgroup Analysis/Deaths After Breast Cancer: Cumulative Follow-up

Greater dietary effect in women with waist circumference ≥ 88 cm

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Subgroup Analysis: Cases Diagnosed During Dietary Intervention, Deaths After Breast Cancer, Cumulative

Main effect	0.02
Cases-only†	0.03
Energy from fat(%)†	0.05

<27.9
27.9-<32.3
32.3-<36.8
>=36.8

Greater dietary effect in women with higher baseline dietary fat intake

0.50 0.75 1.00 1.33 2.00

HR(95%CI)

Favors intervention   *Favors comparison*

†From breast cancer cases with 4 day food records collected.

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Breast Cancer Characteristics (n=3034) of Cases Diagnosed Throughout Cumulative 16.1 year (median) Follow-up

Characteristic	Diet [N=1177] N (%)	Control [N=1857] N (%)	P-Value
STAGE			
LOCAL	871 (75.5)	1375 (75.3)	0.91
REGIONAL/DISTANT	283 (24.5)	451 (24.7)	
TUMOR SIZE			0.95
<1	307 (28.6)	504 (29.5)	
1-<2	482 (44.8)	728 (42.7)	
≥2	286 (26.6)	474 (27.8)	
POSITIVE NODES	790 (75.5)	1254 (75.9)	0.98

For breast cancer incidence HR 0.96 95% CI 0.90-1.04, p=0.33

Breast Cancer Characteristics (n=3034) of Cases Diagnosed Throughout Cumulative 16.1 yr (median) Follow-up

Characteristic	Diet [N=672] N (%)	Control [N=1095] N (%)	P-Value
ER/PR Status			
ER+PR+	793 (73.5)	1201 (70.5)	0.04
ER+PR-	141 (13.1)	282 (16.5)	
ER-PR+	145 (13.4)	221 (13.0)	
HER2 Positive	146 (15.3)	202 (13.7)	0.28
Triple negative	76 (8.1)	133 (9.1)	0.37

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Death after Breast Cancer During Cumulative Follow-up: Exploratory Analyses PR Status and Weight Change

Adjustment Variable	Death after Breast Cancer HR (95% CI)	P-value
Time-dependent variables for PR negative and unknown	0.87 (0.74-1.02)	0.08
Baseline weight and subsequent weight change	0.82 (0.70- 0.96)	0.02

PR status difference provides 27% explanation of benefit seen, weight difference does not explain the benefit seen

Chlebowski, Aragaki, Anderson , et al AACR 2016 Abst CT043

1/4/2017

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Conclusions

- Compared to a usual diet control group, women randomized to a low-fat dietary pattern had a non-significantly reduced risk of death from breast cancer and a significantly reduced risk of death after breast cancer.

- These updated results alter the interpretation of the trial.

- A dietary effect was more likely in those with either a lifestyle (≥36.8% energy from fat) or a consequence of lifestyle (≥88 waist circumference), associated with adverse breast cancer outcome.

- Future studies of other lifestyle interventions in breast cancer settings   could consider some form of a low-fat dietary pattern as a base.

Chlebowski, Aragaki, Anderson , et al SABCS 2016 S5-04

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Take Home Message

- Low fat diet was associated with fewer deaths after breast cancer but was not associated with fewer deaths due to breast cancer
- Low fat diet had the greatest positive impact in women with baseline high fat intake and large waste circumference $\geq$ 88cm
- In all likelihood, the deaths after breast cancer could be attributed to non-breast malignancies or cardiovascular disease which would have been impacted by low fat diet
- Women over the age of 70 did not benefit from low fat diet
- Low fat diet was associated with more cancers that were ER+,PR+ and fewer cancers that were ER+,PR-

Limitations

- No data presented on causes of death after breast cancer
- No data on contribution of exercise/physical activity to their findings

Randomized, placebo-controlled trial of duloxetine for aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS) in early stage breast cancer (SWOG S1202)

N. Lynn Henry, Joseph M. Unger, Anne F. Schott, Louis Fehrenbacher, Patrick J. Flynn, Debra Prow, Carl W. Sharer, Danika L. Lew, Anna Moseley, Michael J. Fisch, Carol Moinpour, Dawn L. Hershman, James L. Wade, III

Huntsman Cancer Institute; Fred Hutchinson Cancer Research Center; University of Michigan Comprehensive Cancer Center; Kaiser Permanente, Northern California; Metro Minnesota CCOP/Minnesota Oncology; William R. Bliss Cancer Center; Phoenixville Cancer Center; AIM Specialty Health; Heartland NCORP

AI-Associated Musculoskeletal Syndrome (AIMSS)

- AIMSS occurs in up to 50% of AI-treated patients, and leads to early treatment discontinuation[1].

- Premature discontinuation of AI therapy can lead to increased likelihood of breast cancer recurrence[2].

- Only exercise and acupuncture have been shown to improve symptoms in randomized controlled trials[3,4].
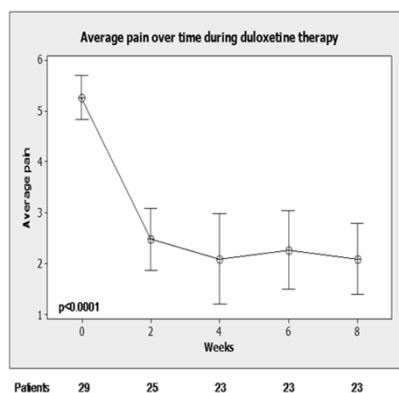
[1]Henry et al JCO 2012; [2]Chirgwin et al JCO 2016; [3]Irwin et al JCO 2015; [4]Crew et al JCO 2010

Duloxetine

- Serotonin norepinephrine reuptake inhibitor (SNRI)

- FDA-approved for treatment of multiple chronic pain disorders.

- Phase II open label trial of duloxetine for treatment of AIMSS demonstrated a 61% improvement in pain[1].

Average pain over time during duloxetine therapy

[1]Henry et al Cancer 2011

Hypothesis and Objectives

- Hypothesis: Treatment of AIMSS with duloxetine would improve average joint pain compared to placebo.

- <u>Primary objective</u>: To assess whether 12 weeks of duloxetine decreases **average joint pain**, assessed with Brief Pain Inventory, in women with AIMSS

- <u>Secondary Objectives</u>: To assess whether 12 weeks of duloxetine decreases
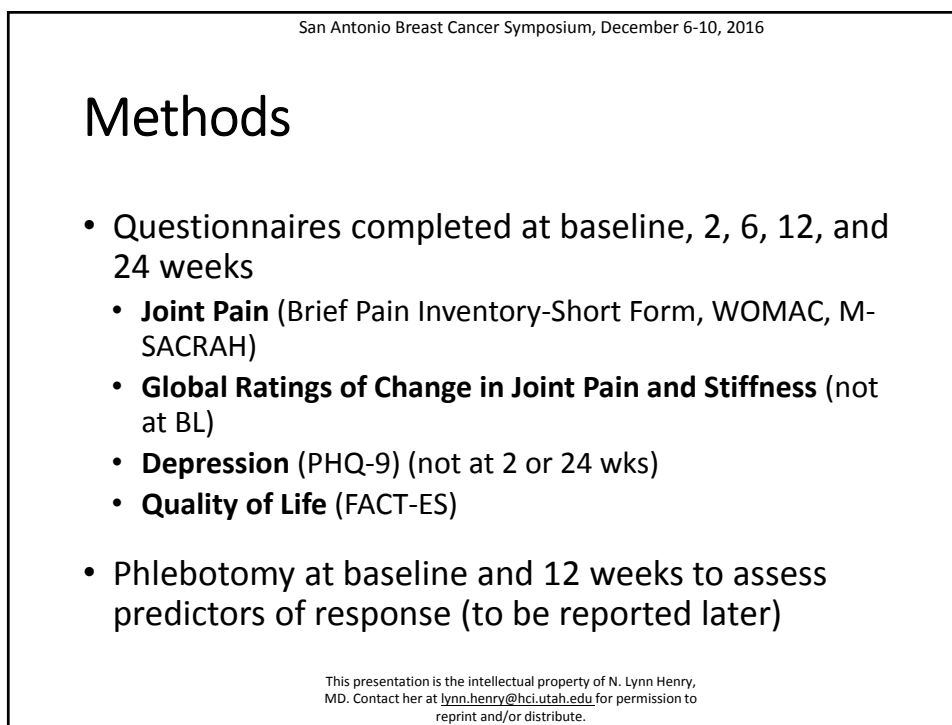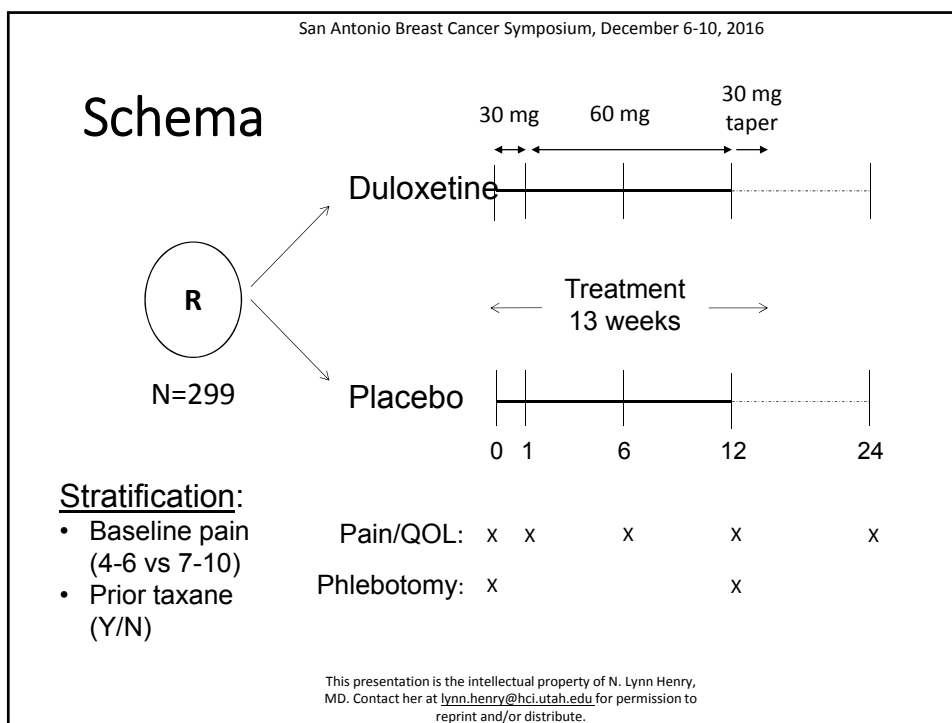 - **worst joint pain**
  - **pain interference**

Eligibility Criteria

- Postmenopausal

- Stage I-III breast cancer

- Taking AI therapy for 3 weeks - 36 months

- Average musculoskeletal pain of $\geq 4/10$ that developed or worsened since AI therapy initiation

- No contraindications to duloxetine therapy
  - No concurrent SSRI/SNRI

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Schema

30 mg   60 mg   30 mg taper

Duloxetine

R

N=299

Treatment
13 weeks

Placebo

0 1   6   12   24

Pain/QOL: x   x   x   x   x

Phlebotomy: x   x

<u>Stratification</u>:
- Baseline pain (4-6 vs 7-10)
- Prior taxane (Y/N)

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Methods

- Questionnaires completed at baseline, 2, 6, 12, and 24 weeks
  - **Joint Pain** (Brief Pain Inventory-Short Form, WOMAC, M-SACRAH)
  - **Global Ratings of Change in Joint Pain and Stiffness** (not at BL)
  - **Depression** (PHQ-9) (not at 2 or 24 wks)
  - **Quality of Life** (FACT-ES)

- Phlebotomy at baseline and 12 weeks to assess predictors of response (to be reported later)

Statistical Methods

- Assumptions:
  - 1.0 difference in pain between the groups with a 2.3 point standard deviation at 12 weeks
  - 5% non-adherence rate, 15% drop out rate at 12 weeks, and 10% contamination rate
  - Goal sample size: 270 patients
- Analysis: linear mixed models to examine average joint pain through 12 weeks by arm, adjusting for the stratification factors and assessment time

Patient Characteristics

Characteristic		Total (n=289)	Placebo (n=144)	Duloxetine (n=145)
Median Age		60 (27-83)	60 (27-82)	60 (40-83)
Race	White	248 (86%)	120 (83%)	128 (88%)
	Black	27 (9%)	17 (12%)	10 (7%)
Hispanic		11 (4%)	6 (4%)	5 (3%)
Performance status	0	196 (68%)	94 (65%)	102 (70%)
Breast cancer stage	I or II	251 (87%)	119 (83%)	132 (91%)
	III	38 (13%)	25 (17%)	13 (9%)
Baseline pain score	4-6	220 (76%)	110 (76%)	110 (76%)
	7-10	69 (24%)	34 (24%)	35 (24%)
Prior taxane use	Yes	156 (54%)	79 (55%)	77 (53%)
Prior AI duration, wk		51.3 (37.7)	50.5 (37.6)	52.4 (37.9)

*No sizeable imbalances between study arms

Grade 3/4 Adverse Events

Adverse Event	Placebo (n=141)	Duloxetine (n=138)	
Abdominal pain	0	1 (0.7%)	
Arthralgia	1 (0.7%)	1 (0.7%)	
Diarrhea	0	1 (0.7%)	
Fatigue	0	1 (0.7%)	
Headache	1 (0.7%)	0	
Hypersomnia	1 (0.7%)	0	
Insomnia	1 (0.7%)	4 (2.9%)	
Myalgia	0	1 (0.7%)	
Nausea	0	1 (0.7%)	
Pain	1 (0.7%)	0	
Pain in extremity	0	2 (1.4%)	
ROM decreased	0	1 (0.7%)	No statistically significant differences
Vomiting	0	1 (0.7%)	
Total patients	**5 (3.5%)**	**12 (8.7%)**	

Most Frequent Adverse Events (>10%)

Adverse Event	Placebo (n=141)	Duloxetine (n=138)
Arthralgia	15 (11%)	12 (9%)
Constipation	7 (5%)	17 (12%)*
Diarrhea	6 (4%)	18 (13%) *
Dizziness	4 (3%)	18 (13%) *
Dry mouth	18 (13%)	35 (25%) *
Fatigue	18 (13%)	44 (32%) *
Headache	18 (13%)	29 (21%)
Hot flashes	12 (9%)	20 (15%)
Insomnia	7 (5%)	19 (14%) *
Myalgia	10 (7%)	21 (15%) *
Nausea	9 (6%)	42 (30%) *

* p-value < 0.05 using Fisher's exact test

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Results

Linear mixed model results

Difference in average pain: 0.82 points (95% CI: 0.4 – 1.24), **p=.0002**

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Results:
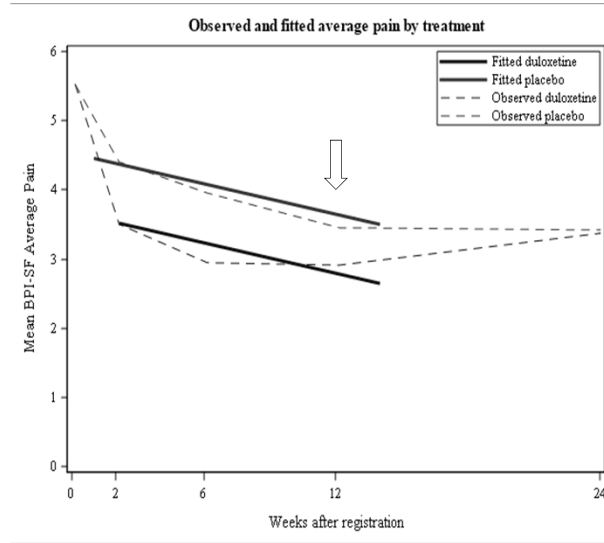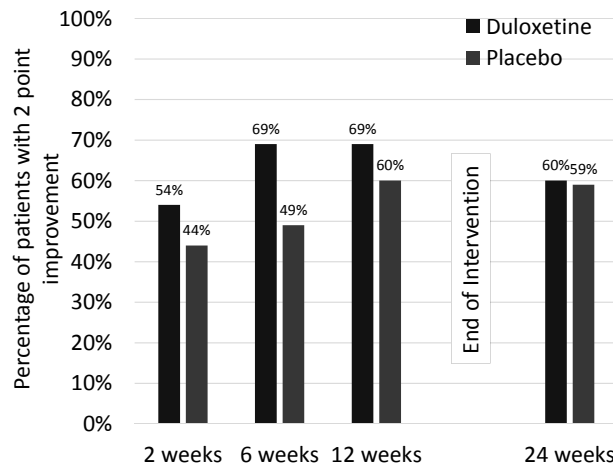## Clinically Significant (2 point) Improvement in Joint Pain

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Results of secondary objectives:
Improvement in average value between study arms

- Worst joint pain: 1.06 points (95% CI: 0.55-1.57), p<0.0001

- Pain interference: 0.95 points (95% CI: 0.55-1.35), p<0.0001

- WOMAC (knee/hip): 11.9 points (95% CI: 8-15.81), p<0.0001

- M-SACRAH (hand): 13.56 points (95% CI: 8.88-18.24), p<0.0001

Results of secondary objectives:
Improvement in average value between study arms

- FACT-ES TOI (QOL): 3.65 points (95% CI: 1.16 – 6.13), p=0.0042

- Depression (PHQ-9): 0.52 points (95% CI: -0.19-1.22), p=0.15

- Global Rating of Change Scale
  - Pain   OR 1.69 (95% CI 1.15-2.5, p=0.0085)
  - Stiffness   OR 3.8 (95% CI 1.82-7.92, p=0.0004)

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Conclusions

- Treatment with duloxetine met the primary endpoint.

- Duloxetine was superior to placebo for the treatment of AIMSS among women with early stage breast cancer.

- Improvement in joint pain was noted in both study arms.

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Conclusions

- Duloxetine was relatively well tolerated, consistent with trials of duloxetine for other indications.

- In addition to improvements in pain, duloxetine was associated with slight improvements in quality of life.

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Take Home Message

- When compared with placebo, Duloxetine improved pain symptoms in breast cancer patients who take AI. However, duloxetine is associated with insomnia, fatigue, dry mouth
- WOMAC and M-SACRAH scales have items specific for arthritis and showed larger effects of duloxetine compared with placebo

Limitations

- Did not mention which patients benefited the most from duloxetine (e.g. patients with high level of pain prior to enrollment, etc.)
- No data on whether decreasing pain level lead to higher rates of AI adherence
- Is the primary endpoint of single item rating on the BPI sensitive enough for musculoskeletal joint pain?
- Is a 1 point difference in pain at 12 weeks clinically meaningful?
- Unexpected placebo response

1/4/2017

Thank you