Impact of Body Mass Index Reduction in Primary Breast Cancer Prevention

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Presented By Jennifer Bea at 2019 ASCO Annual Meeting

Outline

- Epidemiology of obesity and breast cancer
- Effect of weight change on breast cancer risk
- BMI versus Body Composition
- Challenges and opportunities for primary prevention
- Effect of lifestyle guideline adherence

High BMI is associated with Postmenopausal Breast Cancer

- Median age diagnosis :62y; Highest Rates: 55-64y
- 1.5 to 2 times increased risk with obesity
- Every 5-unit increase in BMI = 12% increase in risk
- Strongest Associations
  - Hormone receptors positive tumors (ER+ & PR+)
  - Never users of HT
  - Advanced disease and death

BMI categories

Normal weight: <25kg/m²

Overweight: ≥25kg/m² to <30 kg/m²

Obese: ≥30kg/m²

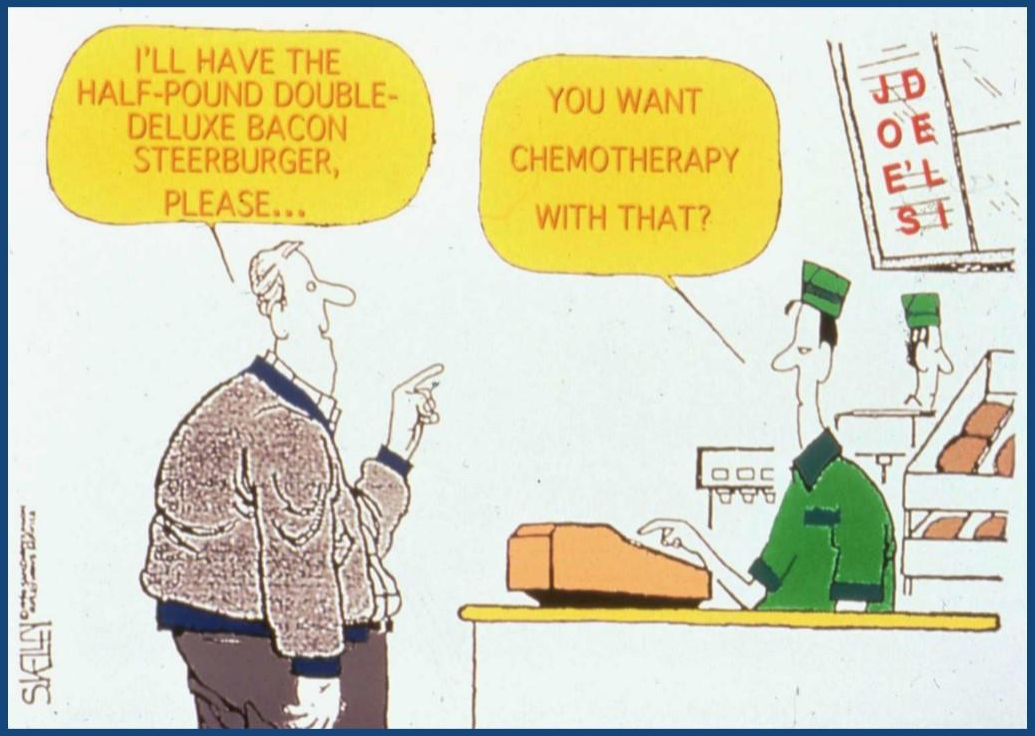
BMI and Breast Cancer continued

- High BMI is associated with breast cancer in men

- Premenopausal women
  - Null across tumor types
  - 20% decreased risk of HR+ breast tumors

Obesity Causes

- Excess food consumption
- Changes in food chemistry
- Lack of physical activity
- Labor-saving devices
- Chronic stress
- Sleep deprivation
- Environmental toxins
- Medications
- Genetics



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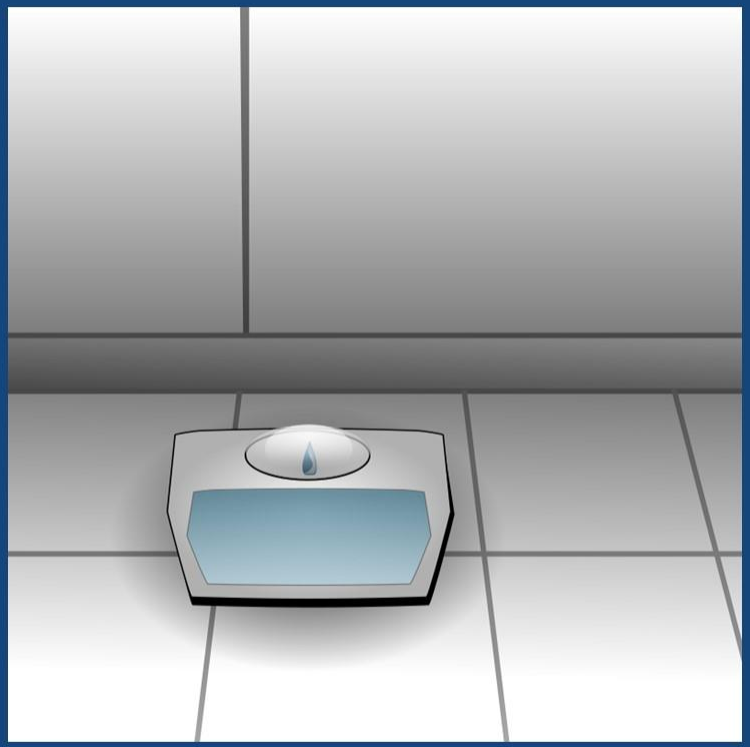
Weight gain anytime in adulthood is associated with increased postmenopausal breast cancer risk

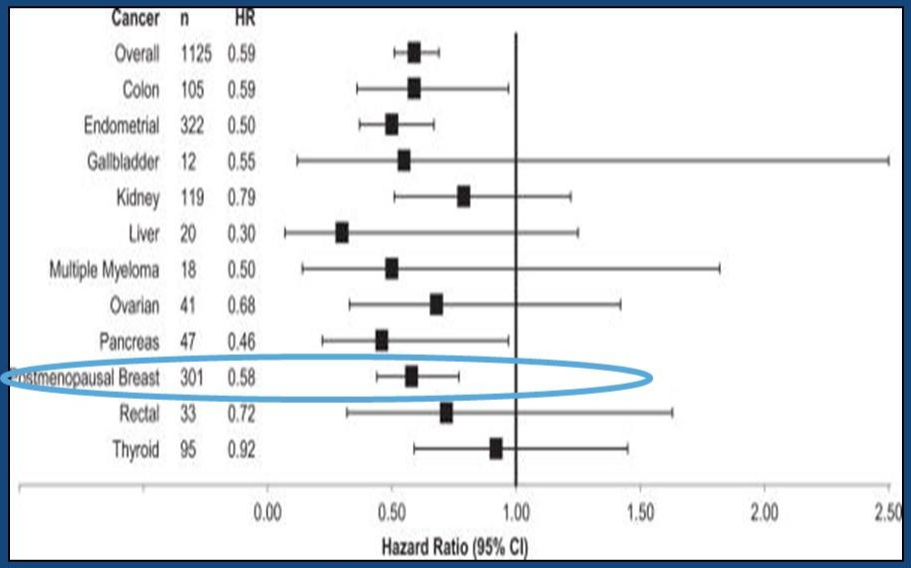
- ER+ and PR+ tumors
- Non-users of hormone therapy
- Advance disease
- Each 5kg gained = 4-8% ↑ risk
- May be racial/ethnic differences
- NS weight cycling



Stevens, *Am J Epidemiol.* 2015; Welti , *CEBP,* 2017; French SA, *Int J Obes Relat Metab Disord.* 1997; Trentham-Dietz, *Cancer Causes Control*. 2000; Eliassen AH, *JAMA,* 2006; Eng, *Am J Epidemiol*. 2005; Ahn J, Arch Int Med, 2007; Radimer, *Nutr Cancer;* 2004; Emaus, Int J Cancer, 2014; Ziegler JNCI, 1996; van den Brandt, *Cancer Causes Control*. 1997; Trentham-Dietz, *Cancer Causes Control*. 2000; Han D, Int J Cancer, 2006; Wenten M, *Ann Epidemiol*. 2002

NS=non-significant

Weight loss reduces risk of postmenopausal breast cancer



Kaiser Permanente (5 Regions)
Postmenopausal Breast: HR 0.58, 95% CI 0.44, 0.77

Favorable results across trials:

- Longitudinal & case-control
- 42% risk reduction in large multi-site US bariatric surgery trial (left)
- Behavioral equivalents needed

Schauer, Annals of Surgery. 269(1):95-101, January 2019;
Anveden; Gynecol Oncol. 2017 May; 145(2): 224–229.

WHY OUR WORK IS IMPORTANT

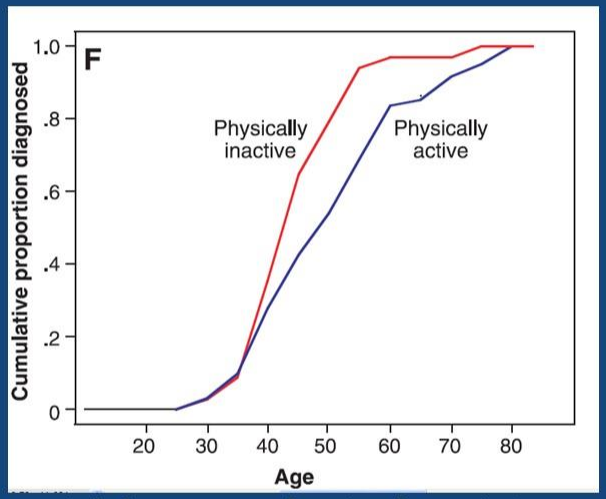
Too few Americans get the recommended amount of physical activity.

Only **1 in 5** adults and **1 in 5** high school students fully meet physical activity guidelines for aerobic and muscle-strengthening activities.

About **31 million** adults aged 50 or older are inactive, meaning they get no physical activity beyond that of daily living.

Higher levels of physical activity associated with decreased risk of breast cancers

- Effects are independent of
  - BMI
  - ER status
  - HT
  - Smoking



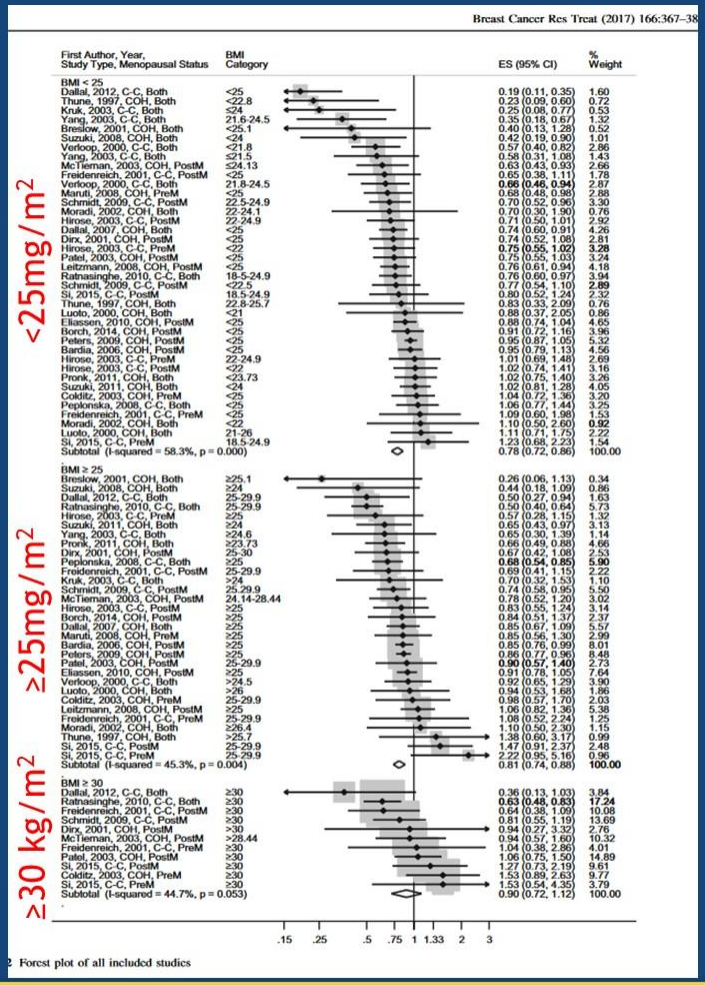
Adolescent physical activity in BRCA carriers King , Science, 2003

- Early life physical activity is also important

https://jamanetwork.com/journals/jama/fullarticle/2712935http://www.cdc.gov/obesity/data/prevalence-maps.html; PA Guidelines for Americans 2018

How much physical activity is recommended in adults?

- **Aerobic:** 150-300 min/wk moderate or 75-150 min/wk vigorous PA or combination (approx. ≥9METhrs/wk)
- **Resistance:** ≥2 days/wk
- **Balance:** Older adults
- **Stretching:** reduces injury
- **Evidence for types:** walking, household activities, vigorous activity
- **Move more & sit less!**
- **Talk Test**



Does obesity modify the relationship between physical activity and breast cancer risk?

YES!

- Meta-analysis: 29 studies
- 18 cohort; 11 case-control
- Physical activity & breast cancer risk
  - BMI<25 kg/m^2: RR 0.85, 95% CI 0.79, 0.92
  - BMI ≥25 kg/m^2: RR 0.87, 95% CI 0.81, 0.93
  - BMI ≥30 kg/m^2 : RR 0.93, 95% CI 0.76,1.13

Neil-Sztramko et al, Breast Cancer Res Treat 2017

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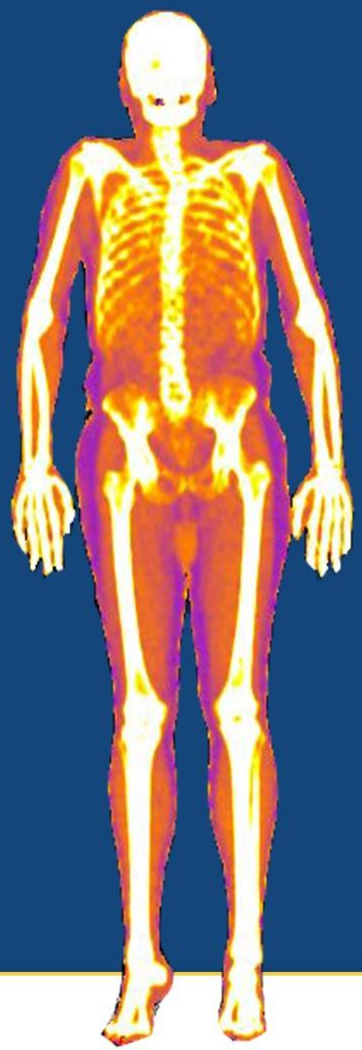
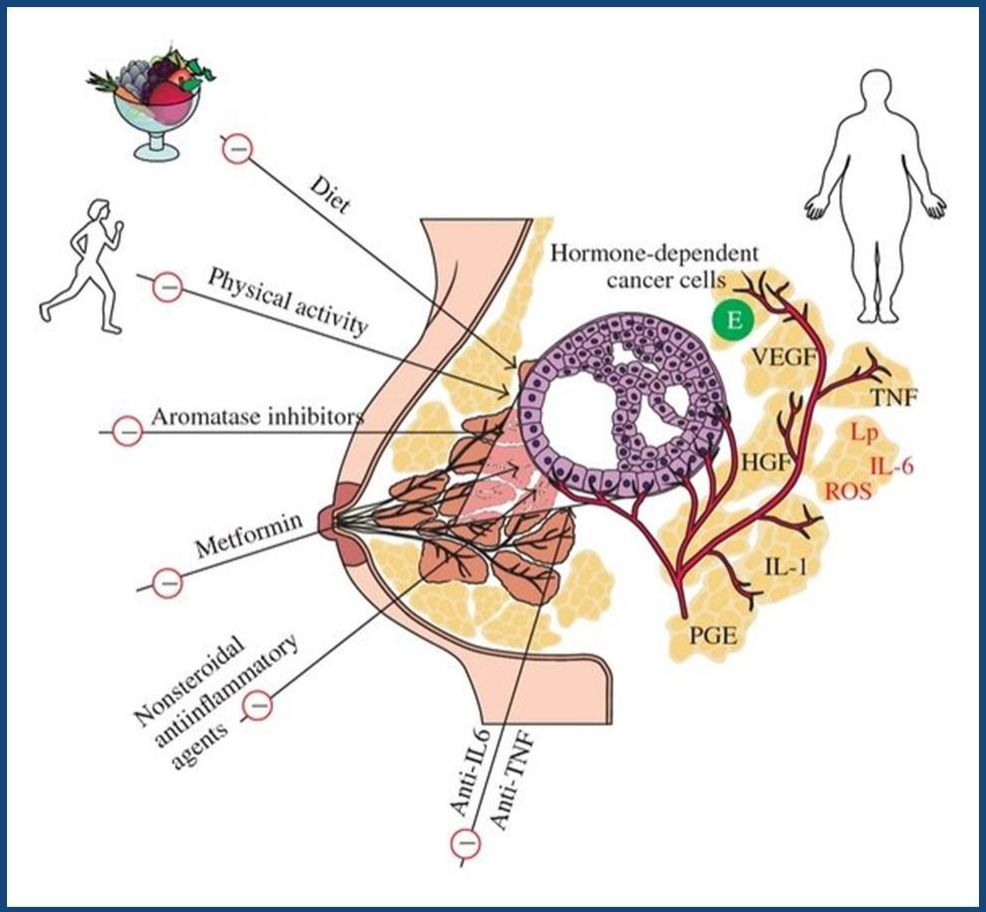
- BMI = inexpensive proxy for adiposity
- Changes in body composition and deposition patterns can be masked by stable BMI
- Divergent pre- vs postmenopausal breast cancer relation to obesity due to BMI imprecision?
- Mechanistic factors associates with adiposity, especially visceral adiposity (VAT)
  - Metabolic dysfunction
  - Inflammation
  - Estrogen
  - Leptin
- Consider more direct measures: DXA, CT, MRI





Complexity of Obesity and Breast Cancer

Adipokines-, insulin-, inflammation-, and angiogenesis-signalling pathways influence the development of hormone-dependent breast carcinoma

COX-2, cyclooxygenase-2; E, estradiol; HGF, hepatocyte growth factor; IGF, insulin growth factor; IL, interleukin; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

McTiernan, Obesity, 2006; McTiernan, CEBP, 2004; Kaaks, Proc Nutr Soc, 2001; Tworoger, J Clin Oncol, 2007; Il'yasova, et al, CEBP 2005; Antonio Macciò & Clelia Madeddu, 2011

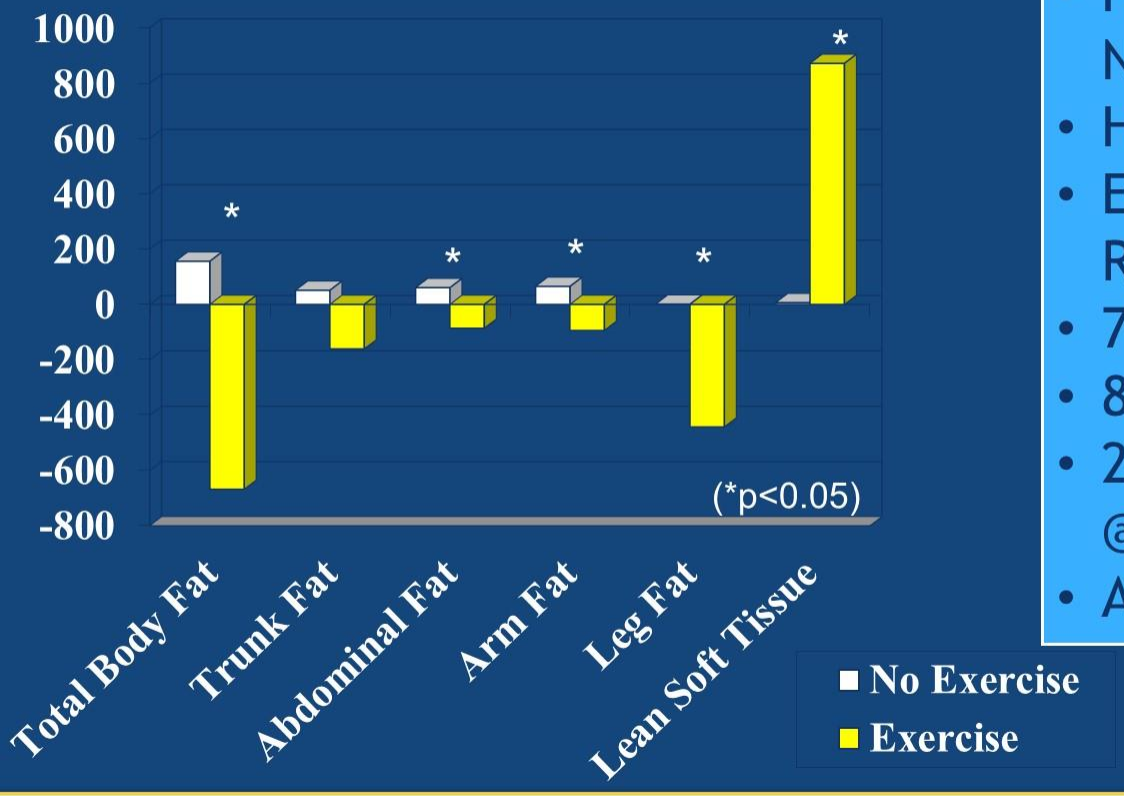
Body fat and BMI related mortality by age group

Table 4. Association Between Body Size or Body Composition and All-Cause Mortality Among Postmenopausal Women in the Women's Health Initiative, by Age Group, 1993–2013

Body Size or Composition	Age Group, years														
	<60					60–69					≥70				
	No. of Deaths	Total No. of Women	%	HR[a]	95% CI	No. of Deaths	Total No. of Women	%	HR[a]	95% CI	No. of Deaths	Total No. of Women	%	HR[a]	95% CI
BMI[b] category															
Underweight (<18.5)	0	15	0.00	N/A	N/A	6	27	22.2	1.80	0.79, 4.12	7	23	30.4	0.79	0.37, 1.69
Normal weight (18.5–24.9)	36	840	4.29	1.00	Referent	143	1,061	13.5	1.00	Referent	199	630	31.6	1.00	Referent
Overweight (25.0–29.9)	47	844	5.57	1.18	0.76, 1.84	165	1,177	14.0	0.98	0.78, 1.23	225	644	34.9	1.01	0.83, 1.23
Obese I (30.0–34.9)	35	505	6.93	1.46	0.90, 2.36	109	655	16.6	1.17	0.90, 1.52	112	334	33.5	1.02	0.80, 1.30
Obese II (35.0–39.9)	26	248	10.5	2.26	1.33, 3.83	51	267	19.1	1.40	1.00, 1.97	32	82	39.0	1.21	0.82, 1.78
Obese III (≥40.0)	20	151	13.5	2.46	1.36, 4.45	28	125	22.4	1.78	1.16, 2.71	16	39	41.0	1.41	0.83, 2.38
BMI quintile															
Q1 (≤23.3)	24	520	4.62	1.00	Referent	102	673	15.2	1.00	Referent	136	410	33.2	1.00	Referent
Q2 (23.4–25.8)	26	511	5.09	1.03	0.59, 1.81	82	652	12.6	0.80	0.60, 1.07	126	384	32.8	1.01	0.79, 1.29
Q3 (25.9–28.7)	23	459	5.01	0.96	0.54, 1.73	87	673	12.9	0.79	0.59, 1.06	119	362	32.9	0.90	0.70, 1.16
Q4 (28.8–32.6)	34	512	6.64	1.24	0.72, 2.11	108	658	16.4	1.03	0.78, 1.35	119	352	33.8	0.99	0.76, 1.27
Q5 (≥32.7)	57	601	9.48	1.68	1.01, 2.80	123	656	18.8	1.21	0.91, 1.60	91	244	37.3	1.14	0.86, 1.50
Total body fat, %															
Q1 (≤38.1)	18	570	3.16	1.00	Referent	108	654	16.5	1.00	Referent	133	376	35.4	1.00	Referent
Q2 (38.2–42.5)	38	524	7.25	2.24	1.27, 3.94	100	676	14.8	0.80	0.60, 1.05	125	379	33.0	0.92	0.72, 1.18
Q3 (42.6–46.0)	31	515	6.02	1.80	1.00, 3.25	87	655	13.3	0.71	0.53, 0.95	126	366	34.4	0.89	0.69, 1.14
Q4 (46.1–50.0)	34	484	7.02	2.01	1.12, 3.60	87	675	12.9	0.72	0.54, 0.97	126	356	35.4	0.98	0.77, 1.26
Q5 (≥50.1)	44	522	8.43	2.44	1.38, 4.34	122	671	18.2	0.99	0.75, 1.30	85	287	29.6	0.74	0.56, 0.98

Bea JW, Am J Epidemiol 2015

Bone Estrogen and Strength Training Study (BEST)



- Postmenopausal N=320, 1 yr
- HT/NHT Blocked
- EX/NEX Randomized
- 75min, 3d/wk
- 8 core lifts
- 2 sets, 6-8 reps @ 70-80% 1-RM
- All 12mo Ca^{2+}

Bea et al, 2010

Bone Estrogen and Strength Training Study (BEST) 6 year Follow-Up

- Resistance Training prevents weight and fat gain in postmenopausal women
- Potentially higher RMR via preserved lean
- Prevention of weight and fat gain is a viable strategy
- Similar results WHI

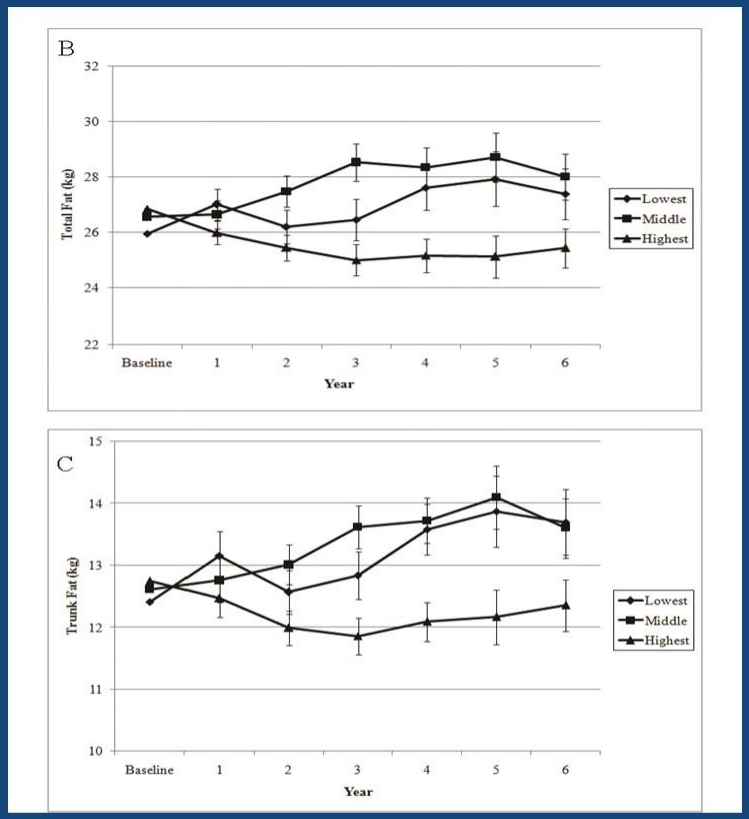


Figure 1. Annual measure of body composition by tertiles of weight lifted in the squats exercise over 6 years (n=122)

Bea, MSSE, 2010.Sims, MSSE, 2013

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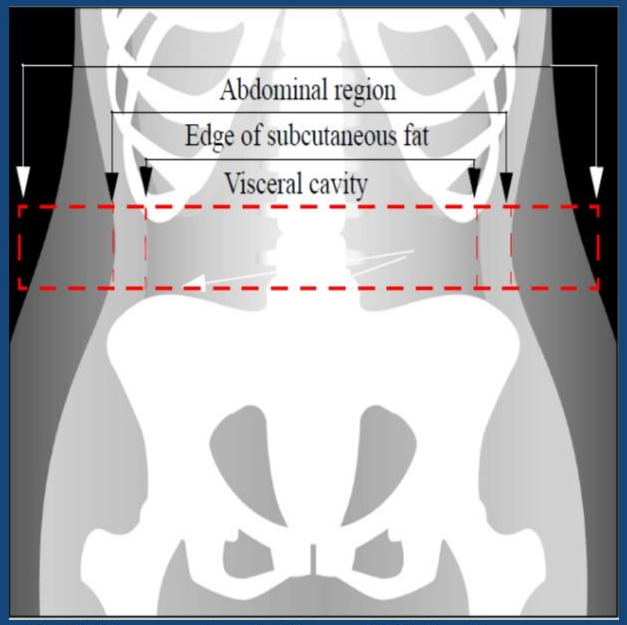
Challenges

- Better understanding of complex disease of obesity needed
  - Endogenous and exogenous hormonal influences
  - Specific fat depots
  - Practical, but precise quantification
  - Different treatments or combinations likely required
- Difficult to study effects of weight loss on breast cancer
  - Length of follow-up
  - Long-term interventions
  - Teasing apart effects of diet & physical activity from weight loss
- Competing priorities, low resources, and comorbidities in underserved communities

Practical Measure of Abdominal Adipose Tissue Depots

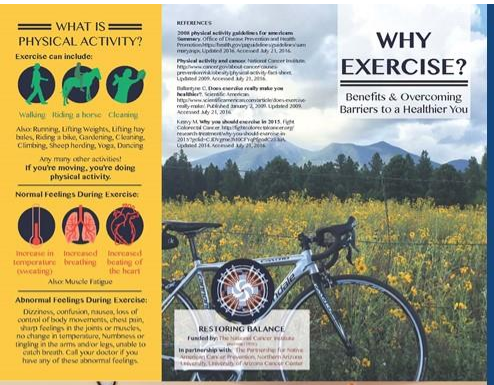
- MRI & CT validation
- Derivation of VAT and SAT in 11,020 participants in WHI
- >39,000 scans over 9y
- Trajectory VAT/SAT (in process)
- CVD outcomes (in process)
- Cancer incidence and mortality (planned)
  - VAT and SAT vs BMI and total fat
  - Common vs uderstudied cancers, such as melanoma, bladder, and hematologic cancers

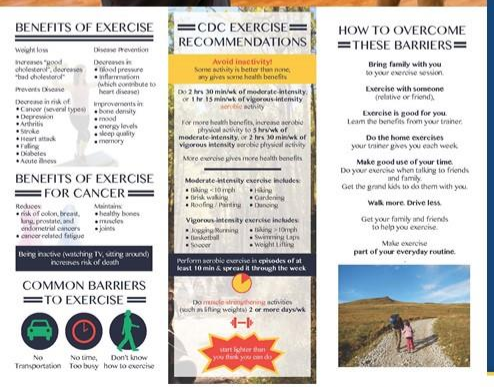


Soft tissue depiction of Hologic software ROI selection and lines of demarcation for VAT & SAT calculations

Historical DXA scan ROI placement for Hologic software VAT and SAT analysis.

PRESENTED BY: Jennifer W. Bea, PhD ; slide courtesy of Andrew Odegaard, PhD, UC Irvine





Restoring Balance in Indian Country (*NNR-14.192)*

- ACSM Cancer Exercise Guidelines
- Cultural adaptations representing 10 tribes
- Survivor + Family Members
- RCT immediate vs delayed start
- Supervised and at-home
- Outcomes at 6, 12, and 18wks
  - Body Composition
  - Metabolic Function
  - Physical Function
  - PROMIS QOL
- No diet intervention

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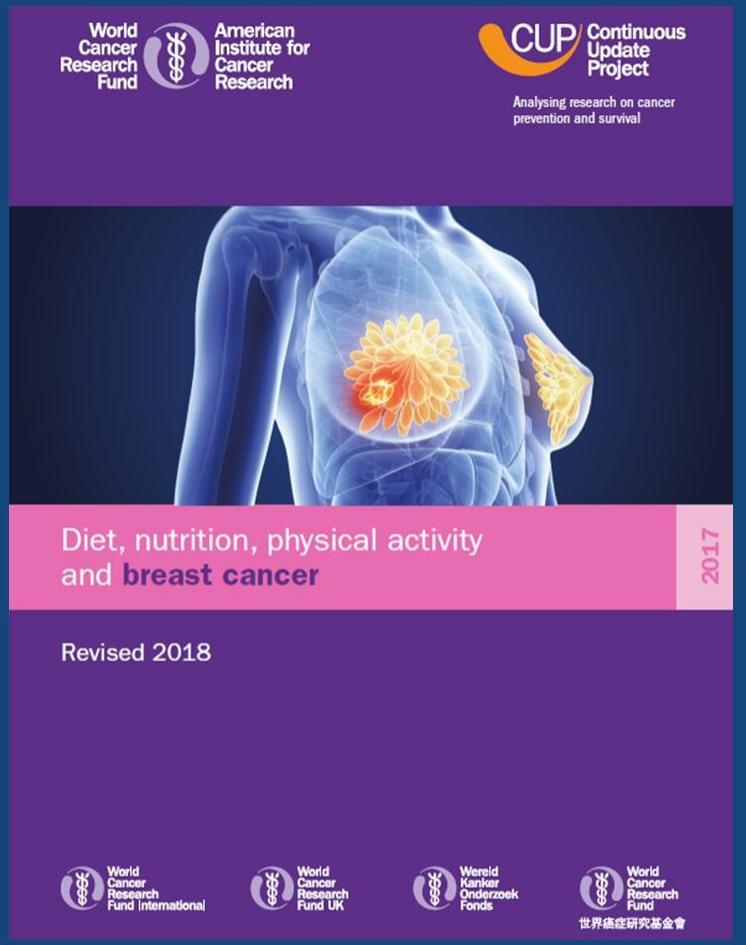
Lifestyle based cancer guidelines for individuals, WCRF/AICR (2018)

- Be a healthy weight
- Be physically active
- Eat a diet rich in whole grains
- Limit consumption of: fast foods, red and processed meat, sugar sweetened drinks, and alcohol
- Do not use supplements for cancer prevention
- For mothers: breast feed your baby, if you can
- After a cancer diagnosis try to:
  - Avoid smoking and other exposure to tobacco
  - Avoid excess sun



Guideline Adherence and Breast Cancer Risk Reduction

- Meeting ≥5 WCRF/AICR recommendations
  - 60% ↓ risk of breast cancer
  - HR: 0.40, 95% CI: 0.25-0.65
  - Each additional recommendation met =
    - Further reduction in breast cancer risk
    - HR=0.89, 95% CI: 0.84-0.95
- Systematic review aligned
  - 13-60% reduction in breast cancer risk

Hastert TA, *CEBP*, 2013;22(9):1498-1508.
Kohler LN, CEBP, 2016;25(7):1018-1028.

Take Home

- Weight management is key for reduction of risk of breast cancer & chronic conditions associated w/ increased risk & poor outcomes.
- Physical activity is associated with reduced risk of breast cancer
- Community and research programs are needed for primary prevention of breast cancer must be evaluated for both short- and long term success
- Free resources for physical activity and diet
  https://health.gov/paguidelines/moveyourway/toolkit/
  https://health.gov/dietaryguidelines/2015/resources.asp

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