Triple-Negative Breast Cancer: Lifestyle Changes to Reduce Risk of Recurrence

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US breast cancer statistics

• Most common diagnosed cancer in women
• Second leading cause of cancer deaths in women (first for ages 25-60)
• Estimated 230,480 new cases of invasive breast cancer in 2011
• Estimated 39,520 deaths from breast cancer in 2011
• 1 in 8 women develop breast cancer in their lifetime
Triple-Negative Breast Cancer

Only approximately 25,000-30,000 cases per year in U.S., but responsible for a disproportionate number of deaths.
Triple-Negative Breast Cancer

• Estrogen-receptor (ER), Progesterone-receptor (PR) and Human Epidermal Growth Factor receptor 2 (HER2) used for biological classification of breast cancers

• If ER-/PR-/HER2-, called Triple Negative
Patterns of Recurrence in Triple-Negative Breast Cancer

- Pattern (timing) of recurrence between TN and non-TN disease
  - Triple-negative
    - Peak recurrence at 3 yrs, declines rapidly thereafter
    - Distant recurrence: 34%
  - Non-Triple-negative
    - Constant recurrence rate over time
    - Distant recurrence: 24%

Breast Cancer Relapse is Heterogeneous

Anderson et al. Breast Cancer Res Treat 2006;100: 121-126

- Higher risk of early relapse
- Constant risk of relapse
Patterns of Relapse Sites in Triple-Negative Breast Cancer

- Lung and brain more common compared to non-triple-negative breast cancer
- Bone metastases less common

Triple-Negative Breast Cancer and Chemotherapy

• Target not known

• Chemotherapy is standard

• Many TNBCs are exquisitely sensitive to chemotherapy

• Several novel agents under investigation
What else be done to reduce risk of recurrence?
Lifestyle Modification

• Can be an empowering and effective way to boost physical and mental health in breast cancer survivors

• Data strongly suggest that lifestyle modifications may also improve breast cancer outcomes
Lifestyle modifications

- Link between obesity and breast cancer outcomes
- Physical activity and breast cancer outcomes
- Diet modification
- Role of insulin in breast cancer?
- Alcohol and breast cancer
- Coffee intake
- Vitamin D
Obesity and breast cancer

• Obesity linked to poor outcomes in women with early stage breast cancer

• Meta-analysis of 43 studies examining relationship between weight at time of diagnosis and prognosis
  – 33% increase in risk of breast cancer-related mortality and overall mortality in obese vs. non-obese women

Protani et al, Breast Cancer Res Treat 2010
Chlebowski et al, JCO 2002
• Obesity at time of diagnosis clearly associated with poorer outcomes
• Is obesity the driver or simply associated with higher risk of recurrence?
• Does reducing body weight after diagnosis improve outcome?
Lifestyle modifications

• Link between obesity and breast cancer outcomes
• Physical activity and breast cancer outcomes
Physical Activity and Survival after Breast Cancer Diagnosis

- Prospective observational study
- 2987 female registered nurses in the Nurses’ Health Study who were diagnosed with stage I, II, or III breast cancer between 1984 -1998
- Breast cancer mortality risk calculated according to physical activity category 2-5 years after diagnosis (<3, 3-8.9, 9-14.9, 15-23.9, or ≥24 metabolic equivalent task [MET] hours/ week)
  - 3 MET hrs = 1 hour average paced walking 2-2.9 mph

Holmes et al, JAMA 2005
10-yr survival rate:
<3 MET: 86%
≥9 MET: 92%
Results

• Protective benefit of physical activity similar among overweight and normal weight women

• Physical activity particularly beneficial to women with ER+ tumors (50% decrease in risk of death)
  – But #s small in ER- group so hard to draw conclusion

• Physical activity beneficial in all stages, particularly in stage III
Postulated mechanisms?

• Physical activity among overweight women is associated with decrease in levels of androgen and estrogen

• May decrease insulin levels and improve insulin resistance (more about this later)
Lifestyle modifications

• Link between obesity and breast cancer outcomes
• Physical activity and breast cancer outcomes
• **Diet modification**
Women’s Intervention Nutrition Study (WINS)

2437 women ages 48-79 yrs with resected early stage BC

**Low-fat dietary intervention:**
- target ≤ 15% calories from fat
- frequent individual counseling sessions with dietician

**Control group:**
- written info on general dietary guidelines
- dietician every 3 months

Chlebowski R T et al. JNCI J Natl Cancer Inst
2006;98:1767-1776
Results

• Intervention group successful in lowering fat intake (33.3 g/day vs. 51.3 g/day)

• 6 lb lower mean body weight in intervention group compared to controls

• 9.8% relapse rate in intervention group vs. 12.4% in control group
Chlebowski RT et al. JNCI J Natl Cancer Inst 2006;98:1767-1776

24% risk reduction at median 5 yrs follow-up
Chlebowski R T et al. JNCI J Natl Cancer Inst 2006
**Women's Healthy Eating and Living (WHEL) study**

3088 women ages 18-70 yrs with stage I, II, or IIIA breast cancer treated within previous 4 years

**Intensive intervention group**
- target 3 svgs fruit, 5 svgs vegetables, 30 g fiber, limited fat (≤ 15-20% total calories)
- telephone counseling
- cooking classes
- newsletters

**Control group**
- print materials describing "5-A-Day" dietary guidelines (5 svgs fruits and vegetables, >20 g fiber, <30 % total calorie intake from fat

Pierce et al, JAMA 2007
Results

• Intervention group did achieve and maintain increased vegetable, fruit and fiber intake and decreased fat intake.

• No difference in mean body weight between 2 groups.

• At 7-year follow-up intensive dietary intervention did not significantly decrease either breast cancer recurrence rate (17% in both groups) or mortality (10% in both groups).
Why differing results?

- Intervention group in WINS study experienced weight loss of 6 lbs compared to controls.
- No difference in weight between 2 groups in WHEL study.
- Are the improved outcomes in WINS study a result of weight loss?
Lifestyle modifications

• Link between obesity and breast cancer outcomes
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• Role of insulin in breast cancer?
Insulin

• Obesity leads to insulin resistance $\rightarrow$ compensatory elevated levels of insulin
• Insulin resistance linked to breast cancer development
• High insulin levels associated with increased risk of breast cancer recurrence
• Chronically elevated insulin $\rightarrow$ increased IGF-1 levels
  – Both growth factors that promote cell division
• Even modest weight loss can restore insulin sensitivity and affect action of IGF-1

Larsson et al, Int J Cancer 2007
Goodwin et al, JCO 2002
NCIC MA.32 clinical trial

• A Phase III Randomized Trial of Metformin vs. Placebo in Early Stage Breast Cancer
  – To compare recurrence rates in patients with early-stage breast cancer treated with metformin vs. placebo for 5 years in addition to standard adjuvant therapy
Lifestyle modifications

• Link between obesity and breast cancer outcomes
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• Diet modification
• Role of insulin in breast cancer?
• Alcohol and breast cancer
Research shows connection between regular drinking and risk of developing breast cancer

- Nurses Health Study: ~106,000 women followed from 1980-2008
  - Drinking habits recorded
  - Women who drank 3-5 drinks/wk had 15% higher risk of developing breast cancer compared to nondrinkers
  - Women who drank >30 drinks/wk had 50% higher risk
  - Amount of alcohol more closely associated than frequency of alcohol
  - Risks of cardiovascular disease lower among regular drinkers

Chen et al, JAMA Nov 2011
Million Women Study

- 1,300,000 women in UK surveyed between 1996-2001
- ~7 years follow-up
- Each additional alcoholic drink regularly consumed per day was associated with 11 additional breast cancers among 1000 women up to age 75
  - Woman who has 1 drink/d has 12% increase in relative risk compared to nondrinker
  - 2 drinks/d 25% higher risk

Allen et al, JNCI Mar 2009
LACE study

• Almost 2000 participants with early-stage breast cancer recruited from 1997-2000
• On average ~2 yrs post diagnosis
• Alcohol (wine, beer, liquor) intake at entry assessed by questionnaire
• 1 standard drink in US = 13.7 g (0.6 oz) pure ethanol
  – Non-drinkers (≤ 0.5g/d)
  – Occasional drinkers (0.6 – 5.0 g/d)
  – Regular drinkers (≥ 6 g/d)

Kwan, M. et al JCO 2010
Outcomes measured

- Recurrence
- Overall death
- Death from breast cancer
- Death from non-breast cancer
Results

- Women followed for almost 8 years
- Women who drank 3 or more drinks per week were 35% more likely to have recurrence compared to nondrinkers
- 51% more likely to die from breast cancer compared to nondrinkers
- Women who drank < 3 drinks/week had same recurrence risk as nondrinkers
Results

• Association was limited to postmenopausal women and obese women

• No difference seen between ER+ and ER- groups (but numbers small)

• Alcohol did not affect risk of death from non-breast cancer causes
So how much alcohol is safe?
Lifestyle modifications

- Link between obesity and breast cancer outcomes
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- Coffee intake
Swedish study

• Compared health histories, including coffee intake, between 2818 postmenopausal Swedish women diagnosed with breast cancer with 3,111 similar postmenopausal women without breast cancer

• Overall, coffee consumption associated with ~20% decrease in breast cancer risk

• When stratified by ER subtype, women who drank >5 cups/d were 57% less likely to be diagnosed with ER-breast cancer than women who drank ≤1 cup/d

Li et al, Breast Cancer Research 2011
German Study

• Compared health histories of 3,464 women postmenopausal women diagnosed with breast cancer with 6,657 similar postmenopausal women not diagnosed with breast cancer

• Women who drank >5 cups of coffee/d were 33% less likely to be diagnosed with ER- breast cancer (but not stat signif)

Li et al, Breast Cancer Research 2011
But data are conflicting

• Other studies have shown differing results
• Coffee is complex mixture
  – Caffeine
  – Other chemicals (eg. Phytoestrogens)
    • Carcinogenic vs protective effects?
Lifestyle modifications

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• **Vitamin D**
Vitamin D

• Normal and malignant breast cancer cells have receptors for vit D

• VDR mediates cellular growth and differentiation

• When activated influences up to 200 genes that control cell proliferation, cell survival/death, prevention of angiogenesis
Vit D and risk of developing breast cancer

- Ecologic studies have shown relationship between latitude of residence and risk of BC

- Inverse association between vit D intake and mammographic density

- Low vit D levels in healthy women have been associated with increased BC mortality
Prognostic effects of Vit D levels in early breast cancer

- 512 women with early stage breast cancer in Toronto 1989-1996

- Vit D level checked at time of diagnosis
  - Deficient, insufficient or adequate

- Low levels associated with premenopausal status, high BMI, high insulin and high tumor grade

- Women who were deficient (vs adequate) had higher rate of recurrence and lower overall survival

Goodwin, P et al. JCO 2009
Vit D levels and prognostic indicators

• Vit D levels collected from 194 early-stage breast cancer pts and 194 controls at U of Rochester 2009-2010

• Breast cancer pts had lower vit D levels than controls (32.7 ng/ml vs 37.4 ng/ml)

• Women with suboptimal levels were 3 times more likely to have triple negative BC than women with optimal levels

• Those with low levels more likely to have higher Oncotype Score as well as other worse prognostic indicators

Possible explanations?

• Vit D regulates cell growth, differentiation and invasion of breast cancer cells

• Women deficient in vit D may develop higher grade tumors

• Vit D inhibits abnormal growth of breast cells in lab and suppresses excessive proliferation

• Addition of vit D to breast cancer cell cultures can reverse certain features associated with poor prognosis in human breast cancers
Recommendations

• Studies looking at vit D supplementation and risk of developing breast cancer have yielded conflicting results

• Clinical trials of vit D supplementation in women diagnosed with breast cancer needed

• Vit D important for other health issues (eg. bone health, arthralgias)

• Women should be screened for vit D deficiency and treated accordingly
Summary

• It is clear that both the host as well as the tumor determine cancer outcome
• There is a growing body of evidence that lifestyle does matter in breast cancer prognosis
• How lifestyle changes affect breast cancer outcomes remains unclear
• Possible factors linking lifestyle behaviors with breast cancer include circulating levels of estrogen, insulin, inflammatory markers, immune function
Summary

• Maintaining a normal BMI, regular exercise and eating a diet low in fat and high in vegetables and fruit confer beneficial effects on overall health and now seem to aid in improving breast cancer outcomes
THANK YOU!

Questions?

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