Breast Cancer in Young Women

Dr Alison L Jones
LOC, London
What will we discuss?

• Incidence
• Biology
• Treatment decisions
• Late effects (physical and psychological)
• Pregnancy
Breast cancer in young women is a relatively rare disease........

(Hankey et al, JNCI 1994)
.....but breast cancer is the leading cause of cancer-related deaths in young women

<table>
<thead>
<tr>
<th>Age at diagnosis, years</th>
<th>5-year relative survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>82%</td>
</tr>
<tr>
<td>40-74</td>
<td>89%</td>
</tr>
<tr>
<td>75 and older</td>
<td>88%</td>
</tr>
</tbody>
</table>

(ACS Research, SEER 2005)
Is young age an independent prognostic indicator?

- Current studies limited
  - few women under age 35
  - little data re: tumor-host interfaces

- Future research warranted

- Age is used to direct therapy to some degree, especially when considering competing risks (i.e. tendency to give more chemotherapy to younger women for lower absolute gain)
Young women may present with more advanced disease

• Delays in diagnosis
  • Lack of reliable screening
  • Lack of awareness of risk or difficult to diagnose:
    • “Too young for breast cancer”; breast cancer during pregnancy
  • Lack of access to care

  AND

• Biology
  • ? More ER negative, high grade, LVI
  • ? More HER-2/neu positive?
Pathologic features and biomarker expression among in the young women’s breast cancer study

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<th>Clinico-pathologic Feature</th>
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<td>Poor stage (Stage 3 or 4)</td>
<td>7/33 (21%)</td>
<td>19/82 (23%)</td>
<td>37/186 (20%)</td>
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<tr>
<td>ER positive</td>
<td>20/33 (61%)</td>
<td>54/82 (66%)</td>
<td>115/186 (62%)</td>
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<td>PR positive</td>
<td>16/33 (48%)</td>
<td>49/82 (60%)</td>
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<td>HER2 positive</td>
<td>9/33 (27%)</td>
<td>35/81 (43%)</td>
<td>53/182 (29%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>67%</td>
<td>67%</td>
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</tr>
<tr>
<td>Histology ductal only</td>
<td>27/33 (82%)</td>
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<tr>
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<td>14/32 (44%)</td>
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<td>Tumor necrosis present</td>
<td>15/33 (45%)</td>
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(Collins et al., SABCS 2009)
## Pathologic Features and Biomarker Expression Among in the Young Women’s Breast Cancer Study

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(Collins et al., SABCS 2009)
Is there a molecular signature for breast cancer in young women?

• Comparison of breast tumor gene expression differences by age alone (≤ 45 vs ≥ 65) initially provocative
  • 2,154 genes differentially expressed between age-defined classes (q<0.05)
  
• Correction for additive effects of significant clinicopathologic features (including intrinsic subtype and grade), yielded only one gene difference

• Within an additional data set, 778 genes differentially expressed by age group diminished to zero gene differences

(Anders et al, JCO, 2008; Anders et al, JCO 2010)
Age was neither a prognostic nor predictive for early recurrence in the HERA Trial

STEPP Analyses According to Age

(Partridge et al., Breast Cancer Res Treat, 2010)
Quantification of gene expression by age

Select patients, only limited outcomes data in v. young

- Average recurrence score slightly higher in younger group
- Wide range observed in all groups
- Large proportion of women with low risk scores in all age groups

(Shak et al., Breast Cancer Res Treat, 2010)
Should treatments be different in young women?

- Target the tumour in consideration of the host
  - In the future, *BRCA 1* or *BRCA 2* and other genetic factors may influence adjuvant treatment more in young women

- Optimal hormonal therapy for young women
  - What is the role of suppression of ovarian function?
  - Are some young women fine/better off without chemotherapy?
Hormone Receptor
Positive Disease
Tamoxifen Effects Similar in Under and Over 50s

≈ 5 years tamoxifen vs. Not
RECURRENCE
ER+ / ER unknown, entry age < 50

10-y gain 11.2% (SE 1.6)
Logrank 2p < 0.00001

≈ 5 y Tam

0
10
20
30
40
50

Control
39.2%

Tamoxifen
Control
Rate ratio, from
(O-E) / V

Years 0 – 4
2.72 (169 / 621)
3.46 (191 / 5521)
1.73 (94 / 4067)
1.74 (72 / 4141)

Years 5 – 9
0.98 ± 0.16
-2.0 / 36.2

Years 10+
0.98 ± 0.09
-2.3 / 94.8

Recurrence rates (% / year) and logrank analyses

≈ 5 years tamoxifen vs. Not
RECURRENCE
ER+ / ER unknown, entry age 50+

10-y gain 15.0% (SE 1.1)
Logrank 2p < 0.00001

≈ 5 y Tam

0
10
20
30
40
50

Control
40.3%

Tamoxifen
Control
Rate ratio, from
(O-E) / V

Years 0 – 4
2.74 (360 / 13136)
3.72 (401 / 10788)
2.15 (236 / 10990)

Years 5 – 9
1.02 ± 0.09
-56.9 / 175.7
-2.9 / 135.2

Years 10+
0.98 ± 0.04
-258.6 / 350.9
-6.6 / 6.6

Recurrence rates (% / year) and logrank analyses
## Current Standard Options for Adjuvant Endocrine Therapy

<table>
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<tr>
<th>Menopausal Status at Diagnosis</th>
<th>Initial Therapy</th>
<th>Extended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre / peri-menopausal</td>
<td>Tamoxifen sub 5</td>
<td>Tamoxifen sub 5</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen sub 5</td>
<td>AI sub 5 (*if post-menopausal)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>AI sub 5</td>
<td>AI sub 5</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen sub 2-3</td>
<td>AI sub 2-3</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen sub 5</td>
<td>AI sub 5</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen sub 5</td>
<td>Tamoxifen sub 5</td>
</tr>
</tbody>
</table>

There are insufficient data currently to recommend AI for > 5 years.

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What about ovarian suppression? What about AI + OFS in premenopausal women?

*Adapted from ASCO Guidelines 2014. Available at: www.asco.org*
• SOFT: SUPPRESSION OF OVARIAN FUNCTION TRIAL
• TEXT: TAMOXIFEN AND EXEMESTANE TRIAL (at NYU)

Both Phase III Trials; Exemestane Plus gonadotrophin-releasing hormone (GnRH) Analogue as adjuvant therapy for premenopausal women with hormone receptor positive breast cancer

• Question: is temporary ovarian function suppression with GnRH analogues (ovarian ablation permanent with surgery or radiation) useful when combined with AI or TAM.

• Goserelin (zoladex 3.6 sc monthly), leuprorelin (lupron 3.75 im monthly), buserelin, triptorelin (3.75 im monthly)

• DFS event rate much lower than anticipated→ combined analysis (4690 patients)
TEXT & SOFT
Tamoxifen + OFS vs. Exemestane + OFS

**TEXT**
Premenopausal, HR+ BC ≤ 12 wks after surgery
N = 2672

**SOFT**
- Premenopausal HR+ BC ≤ 12 wks after surgery (if no chemo) or
- ≤ 8 mos after chemo if premen status confirmed
- N = 3066

*OFS
- **TEXT:** triptorelin 3.75 mg IM every 28 days for 6-8 weeks prior to initiation of HT or concurrently with chemotherapy.
- **SOFT:** triptorelin, bilateral oophorectomy or Ovarian irradiation

**Joint Analysis**
- Median follow up: 68 months
- 42% N+
- Neo/Adjuvant chemotherapy: 58%

Tamoxifen + OFS* (n = 1338)

Exemestane 25 mg/day + OFS* (n = 1334)

Tamoxifen 20 mg/day + OFS* (n = 1024)

Exemestane 25 mg/day + OFS* (n = 1021)

Tamoxifen 20 mg/day

Tamoxifen + OFS*
N = 2344

Exemestane + OFS*
N = 2346

SOFT/TEXT: Exemestane + OFS better DFS

Median f/u 5.7 years
### SOFT/TEXT: selected AEs

<table>
<thead>
<tr>
<th>CTCAE v3.0</th>
<th>Exemestane+OFS (N=2318)</th>
<th>Tamoxifen+OFS (N=2325)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Depression</td>
<td>50%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>89%</td>
<td>11%</td>
</tr>
<tr>
<td>Osteoporosis (% T&lt; -2.5)</td>
<td>39% (13%)</td>
<td>0.4%</td>
</tr>
<tr>
<td>Fracture</td>
<td>6.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Cardiac ischemia/infarction</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>1.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>CNS ischemia</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>0.6%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Hot flushes/flashes</td>
<td>92%</td>
<td>10%</td>
</tr>
<tr>
<td>Sweating</td>
<td>55%</td>
<td>--</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>52%</td>
<td>--</td>
</tr>
<tr>
<td>Libido decrease</td>
<td>45%</td>
<td>--</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>31%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>13%</td>
<td>0.3%</td>
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QOL not different
Early cessation of treatment 16 vs 11%
ABCSG-12: Study Design

- Key endpoints
  - Primary: DFS at 5 yrs
  - Secondary: relapse-free survival, OS, BMD, safety

1803 premenopausal pts with stage I/II BC
- 80% > 40 yrs
- N+ 30%
- OFS: Goserelin Q 28 days
- OFS started concurrently with endocrine therapy
  - Only 5% received Chemotherapy

Treatment 3 yrs (median follow-up: 62 mos)
- TAM 20 mg/day
- ANA 1 mg/day
- TAM + ZA 4 mg q6m
- ANA + ZA 4 mg q6m

Long-term monitoring for 5 yrs for recurrence and survival (DFS, OS)

3-yr BMD
5-yr BMD

ABCSG-12 (84 Months)
ET + Zometa Vs ET

DFS
88% vs 92% p=0.009

OS
95% vs 97% p=0.09

Patients at Risk, n
No ZA 903 858 833 807 758 653 521 405 191
ZA 900 862 841 822 788 674 544 419 208

ABCSG-12 (84 Months): DFS Tamoxifen vs AI

![Graph showing DFS rates for Tamoxifen and AI over 96 months.](image-url)
Conclusions

• Highly effective endocrine therapy alone offers excellent prognosis for some premenopausal women with HR+ BC
  • 95% 5 year OS in all three studies.

• Role of OFS: Await data on Tam vs Tam + OFS

• Side effects of OFS should not be underestimated.

• Are we ready to use AI + OFS in premenopausal women yet.
Musculoskeletal Events: Bone Health

• During treatment, aromatase inhibitors (AIs):
  - Reduce estrogen
  - Are associated with a decline in BMD and an increased risk of fracture
  - Exacerbate the normal progressive loss of BMD in postmenopausal women
• In contrast, tamoxifen may preserve BMD
• Osteoporosis/increased fracture risk are serious health issues for breast cancer survivors
• Patients with osteopenia/osteoporosis prior to initiation of AI therapy may be at the greatest risk

BMD=bone mineral density.
Monitoring of bone density while on an aromatase inhibitor

• Most patients should have a bone density tested within one year of starting an AI

• Recommend patients with normal BMD at baseline to take calcium, vit D, and pursue weight bearing exercise

• Patients with osteopenia should have BMD rechecked one year later to assess change

• Patients with osteoporosis at baseline or during follow up should consider bisphosphonate therapy

• Osteoporosis is not a contraindication to taking an aromatase inhibitor
Large benefit of chemotherapy in young women

(EBCTCG, Lancet, 1998)
Natural Decline of Oocytes with Age

(Lobo, NEJM 2005)
Risk of amenorrhea is related to age and treatment

Fig 1. Probability of menopause during the first year after diagnosis (from model shown in Table 3). 

(Goodwin et al., J Clin Oncol 1999)
Assessing Ovarian Function in Survivors

• FSH & Estradiol
  • Check on 3rd day of menses
  • FSH >12mIU or E2 > 75pg/ml =severely impaired fertility (or poor ovarian reserve)
  • Levels effected by tamoxifen

• Anti-Mullerian hormone (AMH)
  • Produced by early follicles, good predictor of reserve

• Antral follicle count
  • Via ultrasound on 3rd day menses, not affected by tamoxifen
  • Count # developing follicles, is proportionate to # remaining
IVF/Embryo Cryo
Breast cancer risk & infertility treatment (IVF)

Prospective cohort study using self administered questionnaires
(follow up 10 year)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Infertility treatment</th>
<th>No infertility treatment</th>
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<tr>
<td>Fertility &amp; treatment</td>
<td>92555</td>
<td>6602</td>
<td>85953</td>
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<tr>
<td>Breast cancer</td>
<td>2571</td>
<td>183 (2.7%)</td>
<td>2388 (2.7%)</td>
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RR = 0.95 (0.82 – 1.11)
Borderline significance for women with a family history of breast cancer

Gauthier et al 2004
Fertility Preservation in breast cancer patients
Ovarian stimulation: Tamoxifen vs Letrozole

<table>
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<th>60 women (age 24-43) 33 ovarian stimulation cycles</th>
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<td>Tamoxifen (60mg/day)</td>
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<tr>
<td>No follicles</td>
</tr>
<tr>
<td>Mature oocytes</td>
</tr>
<tr>
<td>Embryos</td>
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After 554 ± 31 days follow up cancer recurrence similar IVF vs control (HR = 1.5; 95% CI 0.29-74)

Oktay et al 2005
Preimplantation Genetic Diagnosis (PGD)

• Testing embryos for their genetic profile prior to embryo transfer
Oocyte Cryopreservation

- Technically difficult
- MII oocytes: extremely sensitive to temperature changes
- Crystal formation can cause cytoplasmic damage
- Cryoprotectants
  - depolymerize meiotic spindle
  - cause aneuploidy
- Hardening of zona pellucida
  - barrier to fertilization
Ovarian Sensitivity to Chemotherapy

Normal premenopausal ovary
Low level recruitment of primordial follicles

Cytotoxic chemotherapy

Oocyte toxicity

Decreased estradiol
Increased FSH

Increased follicular recruitment

More oocytes at risk
Ovarian Sensitivity to Chemotherapy

Normal premenopausal ovary
Low level recruitment of primordial follicles

Cytotoxic chemotherapy

Oocyte toxicity

Decreased estradiol
Increased FSH

GnRHa → Increased follicular recruitment

More oocytes at risk
Prevention of Early Menopause Study (POEMS)-S0230

Phase III trial of LHRH analog during chemotherapy to reduce ovarian failure in early stage, hormone receptor-negative breast cancer: an international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance)


Presented By Halle Moore at 2014 ASCO Annual Meeting
Background

- Approximately 25% of breast cancers occur in women under age 50
- Ovarian failure is a common consequence of chemotherapy treatment
- Ovarian failure rates depend on chemotherapy regimen/duration, patient age and perhaps gonadal activity at time of chemotherapy administration
POEMS/S0230 Schema

Premenopausal Stage I, II, IIIA ER-/PR- Breast Cancer
Under Age 50

Stratified by age and chemotherapy regimen
Randomization

Standard cyclophosphamide containing (neo)adjuvant chemotherapy

Standard cyclophosphamide containing (neo)adjuvant chemotherapy + goserelin

Presented By Halle Moore at 2014 ASCO Annual Meeting
POEMS/S0230 Schema

Premenopausal Stage I, II, IIIA ER-/PR-Breast Cancer Under Age 50

Stratified by age and chemotherapy regimen

Randomization

- Standard cyclophosphamide containing (neo)adjuvant chemotherapy
- Standard cyclophosphamide containing (neo)adjuvant chemotherapy + goserelin

Presented By Halle Moore at 2014 ASCO Annual Meeting
Results

• Ovarian failure at 2 years
  • Standard chemotherapy: 15/69 - 22%
  • Standard chemotherapy + Goserelin: 5/66 - 8%

• More women attempted and achieved successful pregnancies in the goserelin arm compared to the chemotherapy alone arm
  • 12/113 (12%) vs 22/105: (21%)

• Total number of babies: 12 vs 18

• Increased menopausal symptoms during treatment

• No negative impact on cancer outcomes
Take Home Message

• Fertility preservation is an important issue for young patients

• Current Options:
  - Ovarian Stimulation and embryo cryopreservation
  - Oocyte cryopreservation
  - Ovarian tissue cryopreservation (Experimental)
  - GnRH agonist during chemotherapy?
Other Options for Preserving Fertility for Women with Cancer

• Ovarian suppression (LHRH agonists) during treatment
• Cryopreservation of embryos
• Cryopreservation of ovarian tissue
• Cryopreservation of oocytes
• Pharmaceutical protection with anti-apoptotic agents (eg. Sphingosine-1-phosphate)
• Oocyte donation and gestational surrogacy
Pregnancy after Breast Cancer

• Survivors who become pregnant do not appear to suffer worse outcomes than those who do not

• Meta-analyses
  • Azim et al
    • 14 studies with 1244 cases and 18,145 controls
    • For overall survival, pooled relative risk was 0.59 (95% CI: 0.50-0.70), favoring survivors with subsequent pregnancy
  • Valachis et al
    • 9 studies
    • Pooled hazard ratio of death was 0.51 (95% CI: 0.42-0.62), favoring survivors with subsequent pregnancy

• Similar findings for women with estrogen-receptor positive tumors

• Limitations of the data
Gaps in Care

• Even experts have hard time keeping up on information and nuances of care for young women

• Attention to supportive care and survivorship issues have been repeatedly found deficient in young patients:
  • Fertility
  • Menopausal concerns
  • Body image
  • Sexual functioning
  • Genetic risk
  • Psychosocial issues
The Definition of a Cancer Survivor
(National Coalition for Cancer Survivorship\textsuperscript{1})

“A ‘Cancer Survivor’ is defined by the National Coalition for Cancer Survivorship as anyone with a history of cancer, from the time of diagnosis and for the remainder of life, whether that is days or decades.”\textsuperscript{2}

Essential Components of Survivorship Care

- Prevention: Treating the consequences of cancer and its treatments
- Surveillance: Recurrence, second cancers, and assessing medical and psychosocial late effects
- Intervention: Recurrence, new cancers, late effects
- Coordination: Interdisciplinary coordination between PCPs and specialists

Spectrum of Potential Side Effects

- Hot flashes/night sweats
- Arthralgia/joint symptoms
- Sexual dysfunction
- Cognitive dysfunction
- Depression
- Weight gain
- Cardiovascular effects
- Chronic fatigue
- Genitourinary symptoms
- Other 2nd-malignancy (ie, endometrial cancer)
- Early breast cancer treatments including:
  - Radiation therapy
  - Chemotherapy
  - Monoclonal antibody
  - Hormonal therapy
- Osteoporosis/bone fractures
- Arthralgia/joint symptoms

Hot Flash Severity

Change from baseline in hot flash severity

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<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>-8</td>
<td>-10</td>
<td>-12</td>
</tr>
<tr>
<td>Gabapentin 900 mg</td>
<td>-10</td>
<td>-10</td>
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Estrogen Deprivation: Sexual Dysfunction Symptoms

• 40% to 100% of cancer survivors report some form of sexual dysfunction (ie, vaginal dryness, painful intercourse)\(^1\)

• Multiple dimensions\(^2\):
  • Psychological/body image
  • Hormonal treatment effects

• After primary treatment with mastectomy and chemotherapy\(^3\):
  • 34% of women lacked sexual interest
  • ~25% of women report difficulty with arousal, orgasm, or lubrication

Vaginal Dryness

• Non-estrogenic vaginal lubricants

• Vaginal estrogens (Cream or ESTRING)

• Pilocarpine

• Vaginal Testosterone Cream
“Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors”

• Serum estradiol, FSH, and LH levels were followed in 7 postmenopausal women using vaginal estrogen preparations while on Al for breast cancer
  • Serum was analysed for estradiol, FSH and LH at baseline then 2, 4, 7-10 and 12 weeks since commencement of vaginal estradiol
  • Estradiol was measured on an assay specifically developed for measuring low levels in postmenopausal women

• Serum estradiol levels rose from baseline levels < or = 5 pmol/l consistent with Al therapy to a mean 72 pmol/l at 2 weeks

• By 4 weeks this had decreased to < 35 pmol/l in the majority (median 16 pmol/l) although significant further rises were seen in two women

• Vagifem significantly raised estradiol levels, at least in the short term

“This reverses the estradiol suppression achieved by aromatase inhibitors in women with breast cancer and is contraindicated”

Kendall et al, Annals Oncol 2006
Effect of obesity in premenopausal ER+ early breast cancer:

• EBCTCG data on 80,000 patients in 70 trials
• Independent prognostic factor (regardless of surgery type, tumor size, grade, LN status, chemo, hormonal therapy)
• Dose response: increasing BMI → increasing BC mortality

Pre-menopausal ER+ disease: 20,000 women
Obese (BMI ≥ 30) vs normal weight (BMI 20-25 kg/m²)

RR=1.34 (2p<0.00001, 95% CI 1.22-1.47)
10-year difference 5% (CI 3.0-6.8)

21.5% Obese
16.6% Normal

Pan et al. PASCO2014 abst # 503
Obesity confers worse outcomes in premenopausal ER+ BC

**Pre-menopausal ER+ disease:** 20,000 women
Breast cancer mortality by 5 BMI groups

**Post-menopausal ER+ disease:** 40,000 women
Breast cancer mortality by 5 BMI groups

**Pre/post-menopausal ER- disease:** 20,000 women
Breast cancer mortality by 5 BMI groups

Pan et. al. PASCO2014 abst # 503
Summary: Optimal Care of Young Women with Breast Cancer

• Young age may not be an independent predictor of outcome

• Targeting the tumor in consideration of the host (including psychosocial concerns) is most prudent

• Tamoxifen is beneficial with or without chemotherapy

• Ovarian suppression (OS) is beneficial without chemotherapy, though the benefit in addition to chemotherapy and/or tamoxifen remains uncertain