Health Issues in Breast Cancer Survivors

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Cancer Survivors 2009 (U.S.)

Trends in 5-Year Relative Survival Rates by Year of Diagnosis, All Cancers, United States

Jemal et al. CA Cancer J Clin 2009; 59:225
High Rates of Long-term Survival Among Breast Cancer Survivors

There are an estimated 2.5 million breast cancer survivors in the United States

Patients Alive (%)

Years After Diagnosis

US Cancer Prevalence: 10 Million+

Approximately one-fourth are breast cancer survivors

Three Seasons of Survivorship

Acute
- Diagnosis
- Selection of treatment
- Fear and anxiety
- Confrontation with mortality

Extended
- Disease stabilization
- Surveillance
- Consolidation of therapies
- Recurrence anxiety
- Thoughts of returning to normal

Permanent
- Revulsion
- Late side effects of therapy
- Long-term risks

Survivorship Issues

- What is the impact on health of being a long-term cancer survivor?
- What is the cost of being a survivor—physically, emotionally, spiritually and financially?
- Is our healthcare system prepared to handle the growing number of people diagnosed with cancer, and the treatment and follow up needed for quality of life?

Differences in cancer follow up care - A world perspective

- In many countries, access to subspecialists is limited
- Primary care physicians and other "physician extenders" play a bigger role in health care in general

GREAT BRITAIN

- In a randomized trial of 296 women with a history of breast cancer, transfer of routine oncology follow-up care to a family physician did not result in an increase in the time to diagnosis of recurrence
  - Patient satisfaction was greater
  - Health service costs were less
  - Anxiety and health related quality of life were unaffected

CANADA

- 968 early-stage breast cancer patients who had completed adjuvant treatment were randomized to follow up in a cancer center or with their own family physician
  - No differences in number of recurrences, deaths, recurrence related serious clinical events
  - No difference in patient reported health-related quality of life


2005 Institutes of Medicine Guidelines on Survivorship

Key Recommendations:
1. All cancer stakeholders should work to raise awareness of cancer survivorship and to establish this as a distinct phase of cancer treatment
2. Each patient should be given a Survivorship Care Plan reimbursed by insurers
3. Plan components should be developed and refined using evidence-based clinical practice guidelines and assessment tools


Optimizing Care: Practice Considerations and Barriers in the Community

1. Fragmented system of care
2. Lack of training
3. Absence of agreed-upon standards of care
4. Reimbursement
5. Communication

Essential Components of Survivorship Care

Prevention

- Recurrence, new cancers, late effects

Intervention

- Treating the consequences of cancer and its treatments

Surveillance

- Recurrence, second cancers, and assessing medical and psychosocial late effects

Coordination

- Interdisciplinary coordination between PCPs and specialists

- 56 year old postmenopausal woman is diagnosed with a Stage I invasive ductal carcinoma
  - 1.5 cm grade 2 IDC
  - ER positive, PR positive, HER2 negative
  - She is treated with a lumpectomy, SLND, and radiation to the breast
  - She has recently started on an aromatase inhibitor

She comes to see her primary care MD for routine health care and is extremely worried about breast cancer recurrence. She wants to have lab tests and scans to "make sure her cancer hasn't come back".

What are the chances that this patient will die of breast cancer in the next 10 years?

1. < 5%
2. 5-10%
3. 10-20%

Should you order any lab tests or scans to follow up on her cancer?
Breast Cancer Follow Up: 
What to do and What NOT to do

  - Routine labs, CT scans, bone scans are not necessary or indicated

- American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast (JCO Nov 20 2007: 5287-5312)
  - TUMOR MARKERS ARE NOT RECOMMENDED

Breast Imaging Recommendations

- NCCN, ACSO, and ACS guidelines recommend follow up mammograms every 6-12 months for affected breast in the setting of breast conserving surgery

- Breast MRI only indicated for the following:
  - Pts with equivocal mammographic and/or US at primary diagnosis
  - Pts presenting with malignant axillary adenopathy and unknown site of primary tumor
  - Patient with extensive or locally advanced cancer undergoing chemotherapy
  - Screening of women at increased (20% to 25%) lifetime risk
    - Known BRCA1 or BRCA2 gene mutation carrier
    - Pt with first-degree relative with a BRCA1 or BRCA2 gene mutation who has not had genetic testing themselves
    - Radiation therapy to the chest between the ages of 10-30 yo
    - Genetic disease such as Li-Fraumeni or Cowden syndrome or one of these syndromes in first-degree relatives

Critical Issues in Breast Cancer Survivorship

- Cancer survivors are at risk for a range of late physical effects and emotional and practical issues due to their primary treatment

  Physical Effects
  - Fatigue
  - Chronic pain or neuropathy
  - Organ damage
  - Cognitive dysfunction
  - Sexual dysfunction
  - Premature menopause or infertility
  - Osteoporosis
  - Lymphedema

  Emotional Issues
  - Increased concerns about the future and health
  - Sadness, depression, and sense of loss
  - Coping with stopping treatment

  Practical Issues
  - Financial issues and insurance coverage
  - Employment workplace discrimination
  - Obtaining future medical or life insurance

Orel S, JCO Feb 2008

Persistent Peripheral Neuropathy in Breast Cancer Survivors Treated With Taxane Chemotherapy

- 20%-30% of patients receiving taxanes develop peripheral neuropathy; little is known about long-term effects of this dose-limiting toxicity.
- Study design:
  - 35 patients receiving adjuvant paclitaxel for breast cancer were followed for a median of 14 months following taxane therapy.
  - Quantitative sensory testing was performed, FACT-Tax and Neuropathic Pain Scale assessments were completed, and serum levels of nerve growth factor were evaluated.
- Results:
  - Highest grade of neuropathy during treatment was strongly associated with delayed moderate-severe symptoms (P = .03).
  - Overall, significant peripheral neuropathy (> 60%) was seen a year or more after taxane therapy completion.

<table>
<thead>
<tr>
<th>Patients With Neuropathy (%)</th>
<th>Patients With Moderate to Severe Neuropathy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness in Hands</td>
<td>62%</td>
</tr>
<tr>
<td>Numbness in Feet</td>
<td>95%</td>
</tr>
<tr>
<td>Pain in Hands</td>
<td>69%</td>
</tr>
<tr>
<td>Pain in Feet</td>
<td>97%</td>
</tr>
</tbody>
</table>

Crew, SABCS 2007, Abstract 6089
What medications breast cancer patients might be taking

And what to worry about with these medications…

Acute effects of tamoxifen and AIs on menopausal symptoms in breast cancer patients

• Prospective study of 181 consecutive postmenopausal women starting hormonal therapy
• Both first line tamoxifen and AIs increased occurrence and severity of hot flashes
• Musculoskeletal pain and dyspareunia significantly increased with AIs
• Sexual interest decreased significantly with tamoxifen
• Younger age was associated with more hot flashes and vaginal dryness

Morales et al, Anti-Cancer Drugs 2004

Changes in menopausal symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>AI (Baseline)</th>
<th>AI (3 mo)</th>
<th>TAM (Baseline)</th>
<th>TAM (3 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td>54/46/0</td>
<td>23/69/8</td>
<td>52/44/4</td>
<td>13/64/23</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>36/57/7</td>
<td>18/46/36</td>
<td>56/40/4</td>
<td>40/53/6</td>
</tr>
<tr>
<td>Vaginal Dryness</td>
<td>67/32/0</td>
<td>50/46/4</td>
<td>65/27/8</td>
<td>53/32/15</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>68/21/11</td>
<td>37/37/25</td>
<td>74/19/8</td>
<td>50/38/12</td>
</tr>
<tr>
<td>Decreased sexual interest</td>
<td>63/21/16</td>
<td>31/37/31</td>
<td>53/37/10</td>
<td>21/32/47</td>
</tr>
<tr>
<td>Emotional disturbance</td>
<td>45/50/5</td>
<td>53/47/6</td>
<td>35/56/8</td>
<td>27/64/9</td>
</tr>
</tbody>
</table>

(no symptom or mild/mod-severe/intolerable)
Tamoxifen

- Tamoxifen has been shown to decrease disease recurrence and increase overall survival
- Remains the standard of care for pre-menopausal breast cancer patients
- CYP2D6 pharmacogenetics varies and results in different levels of therapeutic efficacy
  - Certain antidepressants should be avoided in patients on tamoxifen
- Tamoxifen use has been associated with endometrial cancer and thromboembolism


Thrombotic Effects of Tamoxifen

- Tamoxifen increases the risk of thromboembolic events and cerebrovascular disease by approximately threefold\(^1,2\)
  - Patients under the age of 50 do not appear to have a statistically significant increase in risk based on data from the NSABP P-1 trial
- A meta-analysis indicated a 29% increase in risk of stroke in women randomized to tamoxifen vs placebo or other therapies\(^3\)
  - During a mean follow-up period of 4.9 years, the frequency of ischemic stroke was 0.71% with tamoxifen vs 0.39% for controls (absolute increased risk, 0.32%; number needed to harm [NNH], 313)
- Concurrent combination of chemotherapy and tamoxifen has been associated with a further increased risk of thromboembolism\(^4\)


Aromatase Inhibitors

- Alcs have been shown to decrease disease recurrence compared with tamoxifen
- Several regimens have been shown to be more effective than 5 yrs of tamoxifen alone
  - 5 yrs of adjuvant AI therapy
  - 2 to 3 yrs of tamoxifen, followed by 2 to 3 yrs of an AI
  - 5 yrs of tamoxifen, followed by 5 yrs of AI

Your breast cancer patient comes in to see you three months later and is complaining of pain in her right hip and also stiffness in her hands. She says she has tried acetominophen without relief. What should you do?

1. Reassure patient that joint pains are a common side effect of the aromatase inhibitors.
2. Order plain films of her hands and/or hip
3. Order a bone scan
4. Suggest she try NSAIDS and exercise

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

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
Aromatase Inhibitors and Bone Loss

IV bisphosphonates may decrease AI-associated bone loss

Z-FAST study evaluated 36-month safety and efficacy of upfront vs delayed IV ZA in decreasing AI-associated bone loss in postmenopausal women with early breast cancer


Musculoskeletal Events: Joint Symptoms

- AIs are associated with significantly higher rates of joint symptoms/arthralgias vs tamoxifen
  - Typical onset within 2 months of treatment initiation
  - Symptoms may resolve over time
  - The true etiology and the optimal treatment is not known


ATAC Substudy: Joint Symptoms With Anastrozole vs Tamoxifen

- Joint problems secondary to estrogen depletion is well documented after menopause and known adverse effect of AI use
- Joint symptoms* analyzed in 2799 and 2795 patients on anastrozole and tamoxifen from ATAC trial at 5 years
  - Occurred in 1128 (36.5%) vs 957 (30.9%) patients (OR: 1.28 [95% CI: 1.15-1.43; P < .001])
  - Most joint symptoms mild to moderate
  - Occurred soon after treatment initiation
- Symptoms abated in both arms with ↑ time on treatment

*Joint symptoms (occurring during treatment or within 14 days of cessation) defined as arthralgias, arthritis, arthrosis, or other joint disorder.

ATAC Substudy: Risk Factors for Developing Joint Symptoms

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Joint Symptoms, n (%)</th>
<th>Multivariate OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole</td>
<td>1040 (37.2)</td>
<td>1.31 (1.16-1.47)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Previous HRT</td>
<td>840 (42.3)</td>
<td>1.52 (1.35-1.72)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>485 (38.9)</td>
<td>1.20 (1.04-1.36)</td>
<td>.01</td>
</tr>
<tr>
<td>HR negative</td>
<td>130 (27.7)</td>
<td>0.76 (0.61-0.95)</td>
<td>.02</td>
</tr>
<tr>
<td>Region of origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• UK</td>
<td>563 (30.2)</td>
<td>1.19 (1.01-1.37)</td>
<td>.04</td>
</tr>
<tr>
<td>• North America</td>
<td>803 (47.7)</td>
<td>2.1 (1.81-2.43)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m² (vs &lt; 25)</td>
<td>555 (38.3)</td>
<td>1.36 (1.17-1.57)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

* Use of previous HRT led to greater difference in joint symptoms between patients on anastrozole vs tamoxifen

Estrogen Deprivation: Vasomotor Symptoms

- Chemotherapy can induce ovarian failure
- Hormone therapy can exacerbate vasomotor symptoms
- Hot flashes and sleep disturbances are common
- May lead to additional physical and psychosocial symptoms including mood lability


Management of hot flashes in breast cancer

- Placebo effect
  - Several placebo controlled studies have shown that placebo can decrease hot flashes by 25% over 3-4 week period
  - 10% of women may >75% reduction
  - 10% will have a 50-75% reduction

Loprinzi et al, Lancet Oncol 2001
Phyto-estrogens

- NCCTG found no evidence of efficacy or toxicity from soy phyto-estrogen equivalent of 3 glasses of soy milk
- Small placebo controlled randomized trial found 50 mg of soy isoflavone equivalent to reduce hot flashes by 45% (c/w 25% in control arm)
- Larger randomized trial of soy preparation found statistically significant decrease in hot flashes at 6 weeks (p=0.03) but not at 12 wks

Quella et al, JCO 2000; Scambia et al, Menopause 2000; Upmalis et al, Menopause 2000

Progestational Agents

- Megestrol acetate (Megace) tested in placebo controlled, double-blinded, randomized crossover trial in men and women
  - Megace reduced hot flashes by 75-80% c/w 20% with placebo
  - Women on tamoxifen had transient increase in hot flashes, resolving in 2-3 wks
  - Well tolerated but many pts d/c’d treatment due to perceived side effects (weight gain)
- Attractive option in metastatic breast cancer pts due to anti-cancer effects of Megace


Other “Safe” Options

- Vitamin E
  - Double blind placebo controlled trial in breast cancer survivors
    - 800 IU/day was slightly more effective than placebo, decreased hot flash frequency by one per day
- Black Cohash
  - Herb, Cimicifuga racemosa, approved in Germany for menopausal symptoms
  - Ongoing trials in US and Europe with mixed results
- Bellergal
  - Several small studies showed decrease in hot flash frequency (at 2 wks only) and severity (retrospective)
Placebo (n=420)
Soy (n=78)
Clonidine (n=75)
Megestrol (n=74)
Fluoxetine (n=36)
Venlafaxine (n=48)
Vitamin E (n=53)
Black Cohosh (n=50)
Loprinzi et al, Lancet 2000

Venlafaxine Study Results

Hot flash score (percent of baseline)

Weeks

Loprinzi et al, Lancet 2000

Fluoxetine Study Results

Hot flash score (percent of baseline)

Weeks

Loprinzi et al, JCO 2002
Paroxetine Study Results

Stearns et al, JCO 2005

Estrogen Deprivation:
Sexual Dysfunction Symptoms

- 40% to 100% of cancer survivors report some form of sexual dysfunction (e.g., 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 estrogens compared to Replens for vaginal dryness**

- Open-label study comparing effects of Replens to a local estrogen therapy in the treatment of vaginal dryness symptoms
- 15 women evaluated in each treatment group during a 12-week period
- Replens was safe and effective alternative to estrogen vaginal cream
- Both therapies exhibited statistically significant increases in vaginal moisture, vaginal fluid volume, and vaginal elasticity with a return of the premenopausal pH state

Nachtigall LE, Fert Steril 1994

Loprinzi et al JCO 15, 969-973; 1997
Are vaginal estrogens safe in breast cancer patients?

The jury is still out…

**Vagifem - Controversial**

- Prospectively measured the serum E levels in 6 women on adjuvant AI therapy for early breast cancer using Vagifem
- All were prescribed Vagifem 25 mcg tablets administered qd for 2 weeks then twice weekly
- Serum was analyzed for E, FSH and LH at baseline then 2, 4, 7–10 and 12 weeks since commencement of vaginal estradiol
- Serum E levels rose from baseline levels ≤5 pmol/l consistent with AI 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


**Efficacy and Safety of Vaginal Testosterone for Atrophic Vaginitis in Breast Cancer Patients on AIs: a Pilot Study**

- Objectives: To determine the efficacy and safety of topical testosterone in pts with AI associated atrophic vaginitis
- Results
  - 6 pts with vaginal atrophic symptoms on AIs for early breast cancer were given topical testosterone 300ug daily for 28 days
  - Estradiol levels remained low
  - Testosterone level changes were small
  - Self report symptom scores (0=none, 3=severe) improved in 5/6 women
    - Vaginal dryness: 2.5 pretreatment to 0.5 post-treatment
    - Dyspareunia: 2.2 pretreatment to 0.83 post-treatment
    - Itching/irritation: 1.0 pretreatment to 0.83 post-treatment
  - 1 pt experienced vaginal rash, 1 pt with HA and pruritis

Withey, SABCS 2007, Abstr 6086
Transdermal Testosterone in Female Cancer Survivors with Decreased Libido – NCCTG N02C3

- 4 weeks Testosterone* 10 mg/day
- 4 weeks Placebo**
- R
- Placebo** 4 weeks
- Testosterone* 10 mg/day

* In Vanicream
** Vanicream

JCO 24:469S, 2006 ASCO abstract #8507

Libido Change from Baseline

- P=0.58
- P=0.71

Mean Change from baseline:
Free testosterone concentrations

- (Norms: 0.3-1.9 ng/dl)
- P<.0001
Efficacy and Safety of Vaginal Testosterone for Atrophic Vaginitis in Breast Cancer Patients on AIs: a Pilot Study

**Objective:** Determine the efficacy and safety of topical testosterone in this patient population in patients with AI-related atrophic vaginitis.

**Results:**
- Six postmenopausal patients taking AIs for early breast cancer who had symptoms of atrophic vaginitis were given vaginal testosterone 300 µg daily for 28 days.
- Estradiol levels remained low, and testosterone level changes were small after treatment.
- Self-reported symptom scores (0 = none, 3 = severe) improved for 5 women:
  - Vaginal dryness (2.5 pretreatment to 0.5 posttreatment)
  - Dyspareunia (2.2 pretreatment to 0.83 posttreatment)
  - Itching/irritation (1.0 pretreatment to 0.83 posttreatment)
- Safety: 1 patient with vaginal rash and 1 patient with headache and pruritus

*Witherby, SABCS 2007, Abstract 6086*

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UCSF Trial - A Phase II Study of Vaginal Testosterone Cream vs. the ESTRING for Vaginal Dryness or Decreased Libido in Early Breast Cancer Patients Treated with AIs

**Objectives:**
- To evaluate the safety, based on serial estradiol levels, of intravaginal testosterone cream or the ESTRING administered for relief of vaginal dryness and/or decreased libido related to AI therapy in early breast cancer patients
- To document the systemic estradiol and testosterone levels in early breast cancer patients on AIs being treated with intravaginal testosterone cream or the ESTRING

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**TREATMENT / EVALUATION**

Patients are randomized to a 12 week course of either:
- Testosterone Cream 1% micronized in velvachol - 0.5 gm of cream vaginally 3 times a week for total of 12 weeks of treatment
  - OR
- Estring 2mg ring inserted vaginally once every 12 weeks
- Serum estradiol at baseline, week 4 and week 12
- Serum testosterone at baseline, week 4 and week 12 in testosterone cream arm
- Repeat estradiol at week 6-8 if week 4 estradiol is elevated outside post-menopausal range or >10pg/ml above baseline
What other long term health and QOL issues may be in store for your breast cancer patient?

- Weight gain
- Unfavorable lipid profiles?
- Persistent cognitive complaints?
- Chronic fatigue?

What Are the Most Essential Aspects Required to Optimize Survivorship Care?

a) Monitoring for recurrence
b) Managing treatment-related side effects
c) Adherence to therapy
d) Overall wellness promotion
e) Emotional health
f) Coordination of care
g) Monitoring late effects of treatment
h) Patient/caregiver counseling/education about recurrence risk
i) Referrals
j) Other

Potential Impact of Lifestyle Factors on Survivorship

<table>
<thead>
<tr>
<th>Diet and Weight</th>
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</thead>
</table>
| - Weight and weight gain may be associated with higher rates of breast cancer recurrence and mortality, especially in 
  - Those who have never smoked
  - Premenopausal women
  - Women who were normal weight at diagnosis
  - Women with early stage cancers
  - Some studies have shown that a diet high in fat may be associated with an increased risk of recurrence |

<table>
<thead>
<tr>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Regular moderate exercise may improve survival, particularly in women with hormone receptor-positive tumors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Limited alcohol consumption is recommended by the NCCN to promote a healthy lifestyle</td>
</tr>
</tbody>
</table>

3. Holmes MD et al. JAMA. 2009;293:2479-2486
Takeaway Messages for HCPs of Breast Cancer Survivors

- Cancer patients face many long term complications and symptoms from their treatment
- Many cancer patients will be cured of their disease
  - Not every symptom is a recurrence of cancer!!
  - Before you order a scan or test, consider contacting patient’s treating oncologist to discuss what test would be best and what the implications will be