Breast cancer in young women: 
challenges and opportunities
Elena Shagisultanova, MD, PhD

My disclosures
• 2016 - Pfizer ASPIRE award in breast cancer research
• 2019 - Novartis advisory board on CDK4/6 inhibitors

Objectives:
• Describe unique issues of young onset breast cancer, including challenges in diagnosis, potential genetic predisposition, and more aggressive tumor biology
• Discuss breast cancer diagnosed during pregnancy, postpartum breast cancer, and pregnancy after breast cancer
• Discuss options for fertility preservation prior to treatment
• Provide an update on treatment strategies specific for young women
• Highlight main survivorship issues faced by young patients
What is “young onset breast cancer”?

- Definition is a moving target (in US women are having kids at a later age)
- Latest definition – breast cancer in women ≤45 years old
- Challenges in diagnosis:
  - Dense breast tissue
  - Absence of screening mammography for women <40 year old
  - Controversial recommendations about the age of first mammogram

<table>
<thead>
<tr>
<th>US Preventive Task Force</th>
<th>American Society of Clinical Oncology</th>
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<tbody>
<tr>
<td>Starting from 50yo</td>
<td>Starting from 40yo</td>
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<tr>
<td>Every 2 years</td>
<td>Every year</td>
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You are seeing 35yo patient who reports a new lump in the breast. She has never had mammograms, and there is no family history of breast or ovarian cancer. You feel a vague density in the upper outer quadrant of the left breast on exam. Your best next step is:

- Reassure patient, because there is no family history
- Tell her that mammograms are not useful for patients younger then 40yo
- Order 3D screening mammogram
- Order diagnostic mammogram and US
- Order breast MRI with contrast
- Order chest CT with contrast
Young patient – what study to order?

Answer: Order diagnostic mammogram and US – best first step!

• Reassure patient, because there is no family history, and this is likely a cyst
• Tell her that mammograms are not useful for patients younger than 40yo - wrong answers, do not ignore palpable abnormalities in young patients
• Order 3D screening mammogram – only for patients with normal exam
• Order breast MRI with contrast – likely best second step
• Order chest CT with contrast – CT is suboptimal study to visualize breast tissue

Hereditary breast cancer is common in young patients

• NCCN guidelines – all breast cancer patients ≤45yo need genetic screening.
• Refer for genetic counseling, do not just order the test!

Major predisposition genes:
  ➢ Pathologic mutations lead to ≥30% lifetime probability of breast cancer
  ➢ Bilateral mastectomy may be considered
  ➢ 7 major genes: BRCA1, BRCA2, PALB2, TP53, PTEN, STK11, CDH1
  ➢ 2 other genes are commonly added – ATM and CHEK2 (risk varies depending on the type of mutation: ATM 17-52%, CHEK2 23-38%)
  ➢ Together, these genes are known as STAT9 panel

Multiple moderate predisposition genes: RAD50, RAD51, NF1, BRIP1, etc

Results: “pathologic mutation”, “negative”, “variant of undeterminate significance” (VUS)

Genetic syndromes linked to breast cancer:

BRCA1, BRCA2 and PALB2 mutations:
  ➢ These genes are involved in DNA repair
  ➢ When 1 copy is lost (germline), it is easier for a cell to lose a 2nd copy that leads to accumulation of further mutations and to cancer
  ➢ BRCA1 and BRCA2 – hereditary breast and ovarian cancer (HBOC)
  ➢ PALB2 - Partner And Localizer Of BRCA2

<table>
<thead>
<tr>
<th>Lifetime risk</th>
<th>Breast cancer</th>
<th>Ovarian cancer</th>
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<tbody>
<tr>
<td>General population</td>
<td>12%</td>
<td>1.4%</td>
</tr>
<tr>
<td>BRCA1 mutations</td>
<td>55-65%</td>
<td>39%</td>
</tr>
<tr>
<td>BRCA2 mutations</td>
<td>45%</td>
<td>11-17%</td>
</tr>
<tr>
<td>PALB2 mutation</td>
<td>35 – 58%</td>
<td>4-5%</td>
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</tbody>
</table>
Genetic syndromes linked to breast cancer:

TP53 “guardian of the genome”
“genetic key to cancer”
TP53 initiates all types of DNA damage recognition and repair

Li-Fraumeni syndrome:
Multiple cancers at a young age
- Breast cancer
- Adrenal tumors
- Sarcomas (including uterus)
- Leukemias
- Brain tumors

TP53 – molecule of the year 1993

Li-Fraumeni syndrome:
Multiple cancers at a young age
- Breast cancer
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- Leukemias
- Brain tumors

Genetic syndromes linked to breast cancer:

PTEN – Cowden syndrome
Multiple hamartomas (skin, nose, mouth, intestine)
Breast, thyroid, endometrial, colorectal cancer
Macrocephaly

STK11 – Peutz-Jeghers Syndrome
Breast, colon, pancreatic, stomach, small bowel, cervical, and endometrial cancer
Colon polyps, freckles around the mouth

Genetic syndromes linked to breast cancer:

CDH1 – hereditary breast and gastric cancer
Mutation in E-cadherin gene
Lobular carcinoma of the breast
Diffuse gastric cancer (linitis plastica)
Lifetime risk of gastric cancer 80%

E-cadherin – tight cell junctions
Is genetic referral needed?

You are a primary care provider for a 47yo women. Past surgical history is significant for right breast DCIS diagnosed 5 years ago and treated with surgery. At that time, she was not offered genetic counseling. She is confident that nobody had breast cancer on her maternal side. She does not know family history on the paternal side, because she thought it would not matter. She has read about Angelina Jolie and is asking if she is at risk for hereditary breast cancer. Your answer to her question is:

- Reassure patient because she is 47yo does not have any family history
- Reassure patient because this was DCIS and not invasive breast cancer
- Send STAT 9 test from your office
- Refer to genetic counseling
- Recommend “23 and Me” genetic panel
- Call breast surgeon to get additional details

Wrong answers:

- Reassure patient because she is 47yo does not have any family history (She was diagnosed at 42yo – age at diagnosis ≤45yo. Family history matters on both sides of the family. Patients with breast cancer ≤45yo need to be counseled regardless of family history)
- Reassure patient because this was DCIS and not invasive breast cancer (DCIS is the type of breast cancer that is diagnosed early, prior to invasion, but it is cancer)
- Send STAT 9 test from your office (Sending a genetic test without genetic counseling is suboptimal. STAT 9 is usually done when rapid results of genetic testing are needed for medical/surgical decision making)
- Recommend “23 and Me” genetic test (This is direct to consumer test that has not been validated for clinical decision making)
- Call breast surgeon to get additional details (This would not help to answer the question)

Is family history necessary to suspect hereditary breast cancer?

- It is desirable, but not obligatory
- Remember, both maternal and paternal side matter!
- If a patient is adopted, has a small family, or family members died at an early age, there may be no family history
- TP53 – frequent de novo mutations (your patient may be the first person in the family with this mutation)

Refer all patients with the age of breast cancer onset of ≤45yo for genetic counseling!
Young-onset breast cancer

Greater prevalence of aggressive subtypes
- TNBC, HER2+, luminal B subtype, poorly differentiated tumors

Emerging data that genomic profiles may differ in young women
- Upregulation of growth factor genes (MAPK, PI3K pathway)
- Downregulation of apoptotic genes
- Upregulation of mammary stem cell / immature mammary cell genes

Higher risk of
- Local recurrence (1.7 – 2.5 times)
- Systemic recurrence (1.6 times)
- Breast cancer related death (1.4 – 2.0 times)

Answer is "NO"
- Young women have greater proportion of aggressive tumor subtypes
- However, even young patients with luminal A tumors, expected to have excellent outcomes, survive worse compared to older patients.

Do aggressive breast cancer subtypes completely explain poor outcomes of young women?

Pregnancy and breast cancer – when they collide

Timing and sequence matter

Pregnancy

Breast Cancer within 5 years after birth of child

Post-partum breast cancer – area of active research
Retrospective and meta-analysis studies showed higher risk of recurrence (HR of 2.8)
Animal models showed higher risk of metastatic disease
Ongoing studies to investigate pathogenesis and improve management

Pregnancy

Breast cancer

More difficult to treat. Refer to specialized centers.
Cannot give emend, taxanes, HER2 inhibitors, neulasta or neupogen
Adriamycin and cytoxan every 3 weeks are safe in 2nd, 3rd trimester,
If appropriately treated, outcomes are the same as non-pregnant patients.

Breast cancer

As long as patients are appropriately treated, it is safe (Azim et al, Eur J Cancer 2011)
TNBC and HER2+ disease – recommend to wait 2-3 years prior to pregnancy
HR+ disease (HER2- or HER2+) – complete endocrine therapy, or POSITIVE clinical trial
POSITIVE clinical trial (NCT02308085)

Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer

- Conducted by International Breast Cancer Study Group
- 209 study locations in Europe, US and Canada
- Patients with HR+ breast cancer 18-42yo on anti-hormonal therapy, who would like to get pregnant
- Endocrine therapy interruption after having completed between ≥ 18 months and ≤ 30 months.
- Up to 2 years off therapy for conception and pregnancy
- After that time, endocrine therapy is resumed and completed to full duration

Fertility preservation in young patients:

Treatment damaging the ovaries:
- Chemotherapy

Treatment NOT damaging the ovaries:
- Anti-hormonal agents (tamoxifen, aromatase inhibitors, agents for ovarian suppression - goserelin, triptorelin, lupron)
- Targeted agents (herceptin, perjeta)

ON AVERAGE, chemotherapy has 50% chance of infertility
- depends on the regimen, women's age and baseline fertility status

Fertility preservation in young patients:

NCCN guidelines: all young patients receiving chemotherapy should be counselled on fertility preservation

- Cryopreservation of eggs or embryos (requires 2-3 weeks of time, costly; however, this is the most reliable way)
- Ovarian suppression during the time of chemotherapy
  - Goserelin, Triptorelin or Lupron (monthly or every 3 months form)
    - Start prior to chemotherapy and continue for the duration of chemotherapy
      - Meta-analysis of 5 studies presented at SABCS 2017 (Lamartini et al)
        - Premature ovarian failure: 30.9% control vs 14.1% GnRH analog recipients
        - Pregnancy: 5.5% control vs 10.3% GnRH analog recipients
        - No negative influence on disease free or overall survival
We have learned that young women breast cancer is special:
- Later diagnosis
- High load of genetic cases / hereditary breast cancer
- Greater proportion of aggressive subtypes (TNBC, HER2+, Luminal B)
- Worse outcomes, even in those with Luminal A cancer
- Different genomic profiling
- Higher risk of recurrence associated with post-partum breast cancer

Should we treat young women differently?
- Area of ongoing research
- At this point, we should treat within NCCN guidelines.
- Evidence is emerging on strategies specific for young patients

**TAILORx study – Oncotype DX**

Node-negative patients with T1-T2 N0 HR+ breast cancer

<table>
<thead>
<tr>
<th>Category of Patient</th>
<th>Very low risk</th>
<th>Low risk</th>
<th>Elevated risk</th>
<th>High risk</th>
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<tbody>
<tr>
<td>Women older than 50</td>
<td>ET only</td>
<td>ET only</td>
<td>Chemo + ET</td>
<td>Chemo + ET</td>
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<td>Very low risk</td>
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<tr>
<td>Low risk</td>
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<tr>
<td>Elevated risk</td>
<td>31</td>
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<tr>
<td>High risk</td>
<td></td>
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<tr>
<td>Women ≤50yo</td>
<td>ET only</td>
<td>ET only</td>
<td>Chemo + ET?</td>
<td>Chemo + ET</td>
<td>Chemo+ET</td>
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<tr>
<td>Low risk</td>
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**Breast Cancer Adjuvant Anti-hormonal Treatment**

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<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Category of Patient</th>
<th>Duration of Treatment</th>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>Estrogen</td>
<td>Premenopausal women</td>
<td>10 years</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td></td>
<td>Premenopausal women</td>
<td>5 years</td>
</tr>
<tr>
<td>Goserelin (used with aromatase inhibitors)</td>
<td></td>
<td>Premenopausal women</td>
<td>5 years (based on SOFT and TEXT trials)</td>
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</table>
Enrolled pre-menopausal women with early stage HR+ breast cancer
Tamoxifen x5 years vs ovarian suppression (OS) + tamoxifen x5 years vs OS + exemestane x5 years

Women of 35yo and younger: 45.7% difference in DFS

Conclusion:
- Benefits of OS + anti-hormonal therapy are significant in:
  - Higher risk disease
  - Younger patients

Pre-menopausal patients in clinical trials of metastatic disease

MONALEESA
PALBOCICLIB vs placebo
672 pre-menopausal patients with HR+/HER2- breast cancer on ovarian suppression and endocrine therapy
Significant OS benefits

PALOMA3
PALBOCICLIB vs placebo
>70% of patients had 1 line of chemotherapy
OS benefits in endocrine sensitive tumors, mostly in post-menopausal population
We are awaiting results of PALOMA2

Young survivors – cured, now what?
**Fatigue – most frequent consequence of treatment**
- Check for correctable causes (anemia – iron, B12, folate; thyroid function, vit D level)
- Responds to exercise

**Hot flashes**
- Consequence of premature menopause or ovarian suppression
- Grape seed extract
- Gabapentin
- Effexor

**Mood swings / anxiety**
- Consequence of cancer experience
- Common side effect of tamoxifen (to the lesser extend – aromatase inhibitors)
- Counseling, redirection. Some patients need anti-depressants
- Remember, most anti-depressants interact with tamoxifen (safe with tamoxifen: effexor, citalopram, escitalopram)

**Arthralgias**:
- Common side effect of aromatase inhibitors (to the lesser extend – tamoxifen)
- Exercise
- Aromatase inhibitor rotation (ex. Arimidex → Letrozole → Exemestane)
- Duloxetine
- Acupuncture

**Bone loss**:
- Common on ovarian suppression and aromatase inhibitors
- Vit D and calcium supplements (1000 – 2000 IU of vit D, 1000mg of calcium daily)
- Monitor by DEXA
- Bisphosphonates

**Vaginal dryness**:
- Replens
- Lubricants
- Low dose vaginal estrogens (Vagifem, Estring, low dose estradiol cream)

Additional: social and financial toxicities of breast cancer treatment

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Thank you! Questions?