Breast cancer in young women and girls

Fedro Peccatori
Fertility and Procreation Unit
Gynecologic Oncology Division
European Institute of Oncology
European School of Oncology
Milan, Italy

ESMO PRECEPTORSHIP PROGRAMME
ADOLESCENT & YOUNG ADULT MALIGNANCIES
Lugano, 11-12 May 2018
Breast Cancer in Young Women and Girls

✓ INCIDENCE

✓ PROGNOSIS & BIOLOGY

✓ ANYTHING DIFFERENT IN YOUNG GIRLS?

✓ HIGHLIGHTS FROM BCY3
INCIDENCE
Incidence of Breast Cancer in Young Women

US - Europe

~ 6% of BC in AYA

LMIC

~ 20-25% of BC in AYA

Incidence of Breast Cancer in Young Women

US - Europe

~ 6% of BC in AYA

LMIC

~ 20-25% of BC in AYA

## Incidence of Breast Cancer in Young Women

**Incidence Rate:** 6 /100,000

**Estimated New Cases Yearly:** 146,660

<table>
<thead>
<tr>
<th>Country</th>
<th>ASR</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>13.2</td>
<td>0.6</td>
</tr>
<tr>
<td>France</td>
<td>12.8</td>
<td>0.59</td>
</tr>
<tr>
<td>UK</td>
<td>11</td>
<td>0.5</td>
</tr>
<tr>
<td>Israel</td>
<td>9.9</td>
<td>0.45</td>
</tr>
<tr>
<td>US</td>
<td>9.8</td>
<td>0.45</td>
</tr>
<tr>
<td>Argentina</td>
<td>9</td>
<td>0.41</td>
</tr>
<tr>
<td>Nigeria</td>
<td>8.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Japan</td>
<td>7.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Egypt</td>
<td>7</td>
<td>0.32</td>
</tr>
<tr>
<td>Brazil</td>
<td>6.3</td>
<td>0.29</td>
</tr>
<tr>
<td>Turkey</td>
<td>5.8</td>
<td>0.26</td>
</tr>
<tr>
<td>Russia</td>
<td>5.3</td>
<td>0.24</td>
</tr>
<tr>
<td>China</td>
<td>4.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 1: ASR and CR of breast cancer in various countries

ASR: Age-standardized rate per 100,000 per year; CR: Cumulative risk
### Breast Cancer Statistics, 2011

Carol DeSantis, MPH\(^1\); Rebecca Siegel, MPH\(^2\); Priti Bandi, MS\(^3\); Ahmedin Jemal, DVM, PhD\(^4\)

<table>
<thead>
<tr>
<th>Age</th>
<th>In Situ Cases</th>
<th>Invasive Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 40</td>
<td>1,780</td>
<td>11,330</td>
</tr>
<tr>
<td>Under 50</td>
<td>14,240</td>
<td>50,430</td>
</tr>
<tr>
<td>50-64</td>
<td>23,360</td>
<td>81,970</td>
</tr>
<tr>
<td>65+</td>
<td>20,050</td>
<td>98,080</td>
</tr>
<tr>
<td>All ages</td>
<td>57,650</td>
<td>230,480</td>
</tr>
</tbody>
</table>

Testicular cancer ≈ 8,000/y  
Hodgkin lymphoma ≈ 9,000/y  
Laryngeal cancer ≈ 12,000/y
Breast cancer in AYA


* includes testicular cancer
** includes breast, cervical, colon, and other less prevalent cancers
*** includes malignant bone tumors and other less prevalent cancers
…with increasing incidence in some countries.
Incidence

✅ Possible absolute increase, at least in some countries

✅ Possible relative increase in countries with high percentage of young women

✅ Causal factors related to increasing incidence not known (genetic, environmental, reproductive??)
Prospective Observational Study of Breast Cancer Treatment Outcomes for UK Women Aged 18–40 Years at Diagnosis: The POSH Study

Ellen Copson, Bryony Eccles, Tom Maishman, Sue Gerty, Louise Stanton, Ramsey I. Cutress, Douglas G. Altman, Lorraine Durcan, Peter Simmonds, Gill Lawrence, Louise Jones, Judith Bliss, Diana Eccles; POSH Study Steering Group

N=2,956 (Year 2000 – 2008)

68.2% and 67.6% of patients are free of distant relapse and alive at 8 years, respectively.
BC in the young associated with poor(er) prognosis

Whole population (n=2901)

**Log-Rank: p<0.0001**
**Log-Rank test for trend: p=0.0003**

**HR=1.65 (1.30-2.10)**
**Log-Rank P=0.0001**

More advanced tumors (no screening)

Gnerlich JL et al; J Am Coll Surg 2009

<table>
<thead>
<tr>
<th></th>
<th>&lt; 40 (n=15,548)</th>
<th>&gt; 40 (n=227,464)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T &gt; 2cm</td>
<td>61.4%</td>
<td>48.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive nodes</td>
<td>45.4%</td>
<td>33.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ER-negative</td>
<td>28%</td>
<td>14.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PgR-negative</td>
<td>30.1%</td>
<td>20.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>42.6%</td>
<td>25.9%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

More HER2+, Lum B and TN at young age!

(Keegan et al, BCR, 2012)
Breast Carcinomas Arising at a Young Age: Unique Biology or a Surrogate for Aggressive Intrinsic Subtypes?
Age-Specific Differences in Oncogenic Pathway Deregulation Seen in Human Breast Tumors

Carey K. Anders¹, Chaitanya R. Acharya², David S. Hsu¹,²,³, Gloria Broadwater³, Katherine Garman², John A. Foekens⁴, Yi Zhang⁵, Yixin Wang⁵, Kelly Marcom¹, Jeffrey R. Marks², Sayan Mukherjee², Joseph R. Nevins⁵, Kimberly L. Blackwell¹, Anil Potti¹,²,⁵
Genomic aberrations in young and elderly breast cancer patients

Hatem A. Azim Jr1, Bastien Nguyen1, Sylvain Brohée1, Gabriele Zoppoli2 and Christos Sotiriou1

Different Pattern of Somatic mutations in Young women

≤ 45 y

TP53 27.9%
GATA3 15.2%
PIK3CA 28.8%
TNN 13.5%
Others, each <10%

46 – 69 y

TP53 33.4%
CDH1 13.1%
TTN 15.1%
Others, each <10%
PIK3CA 32.7%

≥ 70 y

TP53 23.2%
CDH1 14.8%
TTN 29%
Others, each <10%
PIK3CA 41.9%
GATA3 mutations ..

- Affect ER binding
- Modulate response to BC cells to estrogen signaling
- Promote tumor growth
- Associated with endocrine resistance
Young breast cancer patients have worse prognosis particularly if their tumors are ER+.
Young women are less compliant to endocrine treatment

EDITORIAL

New Insights Into Nonadherence With Adjuvant Endocrine Therapy Among Young Women With Breast Cancer

Shoshana M. Rosenberg, Ann H. Partridge

Affiliation of authors: Dana-Farber Cancer Institute, Boston, MA (SMR, AHF).

Correspondence to: Ann H. Partridge, MD, MPH, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215 (e-mail: ann_partridge@dfci.harvard.edu).

Despite the well-established survival benefit associated with adjuvant endocrine treatment (ET), ensuring that breast cancer survivors adhere to the prescribed duration of therapy remains challenging. Studies have found young age to be a risk factor for nonadherence and nonpersistence to ET (1). However, little is known about the reasons why young women are less likely to take ET as prescribed, including noninitiation and early discontinuation. In this issue of the Journal, Llarena et al. focus on the potential predictors and reasons for nonadherence in this particularly high-risk population. Their findings not only shed new light on the role of side effects and concern about side effects on nonadherence in young women, but also draw attention to the impact of fertility concerns on adjuvant ET decision-making (2).

While patients of all ages may contend with myriad decisions surrounding their treatment, the youngest women with early-stage hormone receptor–positive breast cancer who are interested in having biological children after treatment face et al. who did not take tamoxifen or who stopped treatment early, most indicated that they had been adequately informed about fertility preservation, with only 9% reporting that they had not (2). However, the generalizability of these findings is limited by the very nature of how this study was conducted, using the information provided after an electronic medical record prompt flagged providers to ask young patients about interest in future fertility.

Regarding the impact and safety of an interruption of ET in order to attempt a pregnancy, the Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine-Responsive Breast Cancer (POSITIVE) Trial will prospectively address the important question of whether temporarily stopping ET for up to two years after 18 to 30 months of initial ET in young women who desire a pregnancy affects disease, fertility, and psychosocial outcomes. Findings from a recent survey that assessed potential patient willingness to participate in
Ovarian suppression may be suboptimal in young women with breast cancer

Twelve-Month Estrogen Levels in Premenopausal Women With Hormone Receptor–Positive Breast Cancer Receiving Adjuvant Triptorelin Plus Exemestane or Tamoxifen in the Suppression of Ovarian Function Trial (SOFT): The SOFT-EST Substudy

Ovarian suppression may be suboptimal in young women with breast cancer.

At each time point, at least 17% of pts had estradiol levels >2.72 pg/mL.
Prognosis, biology and endocrine issues

- Prognosis remains worse in very young women with breast cancer, compared to their older counterpart.
- No screening, more advanced cases.
- Higher percentage of HER2+, Luminal B and triple negative (race/ethnicity).
- Intrinsic genomic differences (genetics, hormones, other?).
- Non adherence to endocrine treatment and suboptimal suppression causative for worse prognosis in ER+ tumors?
ANYTHING DIFFERENT IN YOUNG GIRLS?
Breast cancer in adolescents (15-20 years)

✓ Very rare occurrence (less than 0.1% of all breast cancer)

✓ Secretory carcinoma mostly reported (ETV6-NTRK3)

✓ In the pediatric population, breast metastasis are more frequent than primary tumors
HIGHLIGHTS FROM BCY3
Original article

ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3)

Shani Paluch-Shimon a,1, Olivia Pagani b,1, Ann H. Partridge c, Omalkhair Abulkhair d, Maria-Joao Cardoso e, Rebecca Alexandra Dent f, Karen Gelmon g, Oreste Gentilini h, Nadia Harbeck i, Anita Margulies j, Dror Meirov k, Giancarlo Pruneri l, Elzbieta Senkus m, Tanja Spanic n, Medha Sutija o, Luzia Travado p, Fedro Peccatori q,1, Fatima Cardoso r,2,*

* Sheba Medical Center, Ramat Gan, Israel
b Oncology Institute of Southern Switzerland, Breast Unit of Southern Switzerland, Bellinzona, Switzerland
c Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
d King Abdullah Medical City for National Guard, Riyadh, Saudi Arabia
e Breast Unit Champalimaud Clinical Center, Lisbon, Portugal
f National Cancer Centre Singapore, Singapore, Singapore
g British Columbia Cancer Agency, Vancouver, Canada
h Breast Surgery Unit, San Raffaele Hospital, Milan, Italy
i Breast Center, Dept. Oncology, University of Munich (LMU), Munich, Germany
j Clinical Oncology Home, KGH Executive Board, Zurich, CH, Switzerland
k European Institute of Oncology, European School of Oncology, Milan, Italy
l University of Milan, Istituto European di Oncologia, Milan, Italy
m Medical University of Lodz, Lodz, Poland
n European Institute of Oncology, Milan, Italy
o Young Survival Coalition, NY, USA

ARTICLE INFO

Article history:
Received 24 July 2017
Accepted 24 July 2017
Available online 17 August 2017

Keywords:
Guidelines

ABSTRACT

The 3rd International Consensus Conference for Breast Cancer in Young Women (BCY3) took place in November 2016, in Lugano, Switzerland organized by the European School of Oncology (ESO) and the European Society of Medical Oncologists (ESMO). Consensus recommendations for the management of breast cancer in young women were updated from BCY2 with incorporation of new evidence to inform the guidelines, and areas of research priorities were identified. This manuscript summarizes the ESO-ESMO international consensus recommendations, which are also endorsed by the European Society of Breast Specialists (EUSOMA).

© 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Breast cancer in young women (≤40 years) is an uncommon disease with a 0.40–0.45% cumulative risk by 40 years of age [1], representing less than 7% of all women diagnosed with breast cancer in developed countries [2]. Breast cancer in young women has greater morbidity than in older women and a greater case-fatality rate with increased risk of both local and systemic disease recurrence and death [3]. Young women who are diagnosed with more advanced disease, have a greater proportion of triple negative and HER2/neu positive disease and have less favourable outcome than older women especially amongst endocrine-responsive tumours [4–9]. The consequences of treatments including premature menopause and impaired fertility have far reaching impact for these women both medically and psycho-socially, thus, specific multimodality care is paramount. Most of what we know about breast cancer is based upon studies in older women, and young women are under-represented in more contemporary research evaluating risk-stratification models and molecular tools [10][11].

Many young women may be at risk of being over-treated based solely on age considerations.
General recommendations

The care of all young patients with breast cancer (either early stage, EBC, or advanced disease, ABC) should be discussed within a multidisciplinary team before any treatment decision-making, and provided in specialized breast clinics.
General recommendations

In view of the many specific aspects related to young age, personalized psychosocial support, counseling on genetic predisposition, fertility, sexual health, & socio-economic impact are highly recommended as part of the individual treatment planning.

Patients’ and support groups should be developed and promoted. Open discussion and shared-decision making should be promoted in a clear, culturally appropriate form, encouraging patients to be proactive in their cancer care.

(LoE: Expert opinion)

1. I agree 17 100,0 %
2. I don’t agree 0 0,0%
3. I abstain 0 0,0%
Young age by itself should **not be the reason to prescribe more aggressive therapy** than in other age groups. Factors influencing choice of treatment should include but not be limited to the complete biological characteristics of the tumor (ER/PR, HER-2, proliferation markers (e.g. Ki-67), histological grade), tumor stage, hormonal milieu, genetic status (if available) and patient's co-morbidities and preferences.
Adjuvant systemic endocrine treatment

All patients with ER positive disease should receive adjuvant ET. Tamoxifen alone for 5 years is indicated for low risk patients. Switching to an AI, after 5 years of tamoxifen, should be considered for women who have become definitively post-menopausal. Tamoxifen for 10 years should be considered in high-risk patients, if tolerated.

The addition of a GnRH agonist to tamoxifen or aromatase inhibitors is indicated in patients at higher risk who remain premenopausal after chemotherapy.
Adjuvant systemic chemotherapy treatment

Standard duration of chemotherapy (minimum of 4 and maximum of 8 cycles) should be prescribed.
Sequential regimens have at least equal or superior efficacy over combinations and are better tolerated.
Young age by itself should not be an indication to prescribe a more intense combination of cytotoxic agents.
Adjuvant systemic treatment

In view of the long potential life expectancy, particular attention should be paid to possible long-term toxicities of adjuvant treatments (e.g. secondary cancers, cardiovascular toxicity, irreversible ovarian failure, weight gain, cognitive function, bone health).

Clinics dedicated to the assessment and management of early and late treatment side effects, adherence to treatment and follow-up guidelines should be developed.
Young patients should be strongly encouraged to adopt the following healthy lifestyle changes:
- maintain BMI ≤25
- perform regular aerobic exercise
- not to smoke
- to limit daily alcohol intake

Supportive and follow-up care