



FONO: Endocrine Therapy in Breast Cancer  
& Naturopathic Co-management  
Dr Jen Green ND, FABNO  
[www.knowoncology.org](http://www.knowoncology.org)



## Disclosures

- This presentation is based on current best evidence as of August 2023. The research will definitely change with time...
- Dedicated to all of the people living with cancer who participated in the trials included in this talk. We all benefit so much from their participation
- I have no commercial affiliations



## Webinar One: Breast Cancer Endocrine Therapy

- Thinking critically about cancer research
- Overview of breast cancer subtypes
- Health disparities
- Facilitating Informed Choice Discussion with Predictive Tools
- Comparing the 5 common Estrogen Blockers; Tamoxifen, anastrozole/Arimidex, letrozole/Femara, exemestane/Aromasin and fulvestrant/ Faslodex
- Harm reduction: Splitting 5 years between different estrogen blockers
- Extended Endocrine Therapy/ET from 5 to 10 yrs
- Ovarian suppression in younger survivors: pro's and cons
- Questions



## Webinar Two: MANAGING SIDE EFFECTS

- Tamoxifen support
- Hot flashes
- AIMSS (AI Induced Musculoskeletal Syndrome)
- Genitourinary syndrome of Menopause
- Sexual dysfunction
- Cardiac late effects
- Cognitive Changes
- Fatigue

(Note: Bone density support is included in webinar 3)



## **Webinar 3: Metastatic Breast Cancer – Endocrine Therapy, CDK4/6 Inhibitors & Bone Supports**

- Endocrine Therapy for metastatic breast cancer
- Overview of CDK4/6 Inhibitors
- CDK4/6 Inhibitor Side effect management;
  - Neutropenia
  - Diarrhea
  - Nausea
  - Fatigue
  - Urinary Tract Infections
- Use of Denosumab in women with bone metastasis
- Naturopathic bone density support
- Naturopathic supports for bone pain

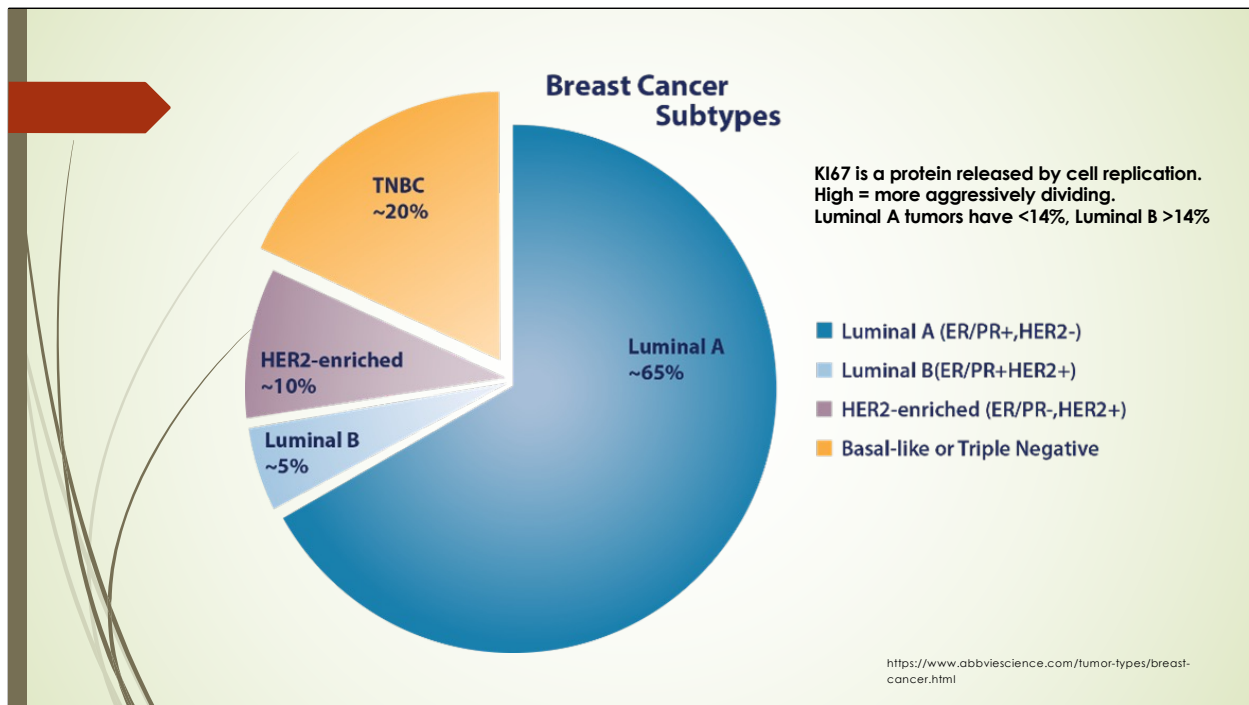
### Breast Cancer Staging

pT		pN		pTNM-Stage	
<b>Tis</b>	DCIS LCIS Paget nipple	<b>pN1mi</b>	Micrometastasis > 0,2 mm to 2 mm	<b>0</b>	DCIS
<b>T1 mic</b>	≤ 0,1 cm	<b>pN1a</b>	1-3 axillary nodes	<b>IA</b>	T1No
<b>T1a</b>	≤ 0,5 cm	<b>pN1b</b>	Internal mammary nodes with microscopic/macrosopic metastasis by sentinel node biopsy but not clinically detected	<b>IB</b>	To-1N1mi
<b>T1b</b>	> 0,5 - 1 cm			<b>IIA</b>	To-1N1 T2No
<b>T1c</b>	> 1 cm - 2 cm			<b>IIIB</b>	T2N1 T3No
<b>T2</b>	> 2 cm - 5 cm	<b>pN1c</b>	1-3 axillary nodes and internal mammary nodes and internal mammary nodes with microscopic/macrosopic metastasis by sentinel node biopsy but not clinically detected	<b>IIIA</b>	To-2N2 T3N1-2
<b>T3</b>	> 5 cm			<b>IIIA</b>	T4No-2 T3N1-2
<b>T4a</b>	Extension to chest wall (does not include pectoralis muscle invasion only)	<b>pN2a</b>	4-9 axillary nodes	<b>IIIC</b>	anyT N3
		<b>pN2b</b>	Internal mammary nodes, clinically detected, without axillary nodes		
<b>T4b</b>	Ulceration, ipsilateral satellite skin nodules, or skin oedema - including peau d'orange.	<b>pN3a</b>	≥ 10 axillary nodes or infraclavicular	<b>IV</b>	systemic
		<b>pN3b</b>	Internal mammary nodes, clinically detected, with axillary node(s) or > 3 axillary nodes and internal axillary mammary nodes with microscopic metastasis by sentinel node biopsy but not clinically detected		
<b>T4c</b>	a+b	<b>pN3c</b>	Supra-clavicular		
<b>T4d</b>	Inflammatory ca				

<https://radiologyassistant.nl/breast/breast-cancer/staging-and-treatment-of-breast-cancer>

### Pathological vs clinical staging

Clinical staging often occurs neoadjuvantly, and after neoadjuvant hope for big difference between the two



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7460595/>

Survival differences by subtype: eg. Five-year survival rates were 84% for LA, 83% LB, 84% HER2 and 77% in TN

Ki67 protein from cell replication, when high means more aggressively dividing, Less than 10% is considered low, 20% or higher is considered high

**Luminal A Tumors:** ER+, PR+, HER2 negative, Ki-67 index less than 14%

**Luminal B Tumors:** ER+ and/or PR +, HER2 negative, Ki-67 index greater than 14% or, are ER+ and/or PR+, HER2 positive, and have any Ki-67 index

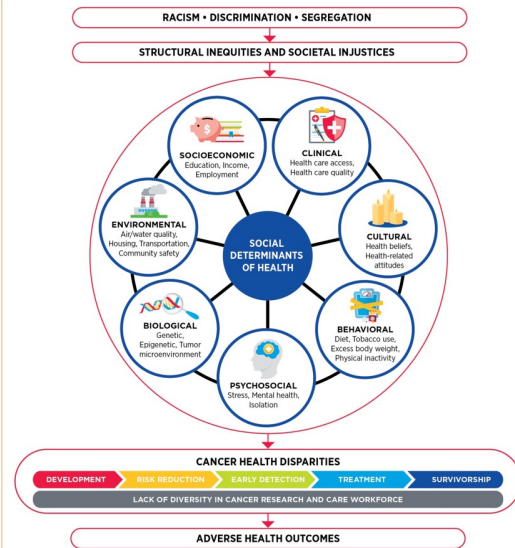
**HER2 enriched**

**Triple negative/basal-like**

Lobular more unpredictable than ductal carcinomas

## Racial & Ethnic Disparities in BC

FIGURE 5 Why Do U.S. Cancer Health Disparities Exist?



- Geography a major driver (central states in US poorer outcomes than periphery)
- Intersecting factors in breast cancer; advanced stage at diagnosis, limited access to high-quality care (language/financial barriers), more aggressive subtypes of breast cancer, lower socioeconomic status, mental health burdens, higher type 2 diabetes, higher insulin, obesity, higher parity in the absence of breast feeding, exposure to hazardous air pollutants, traffic emissions and radon, lower treatment adherence (4-6)

<https://cancerprogressreport.aacr.org/disparities/cdpr22-contents/cdpr22-the-state-of-cancer-health-disparities-in-2022/>

Lower treatment adherence blames the victim  
 Undertreatment and overtreatment both concerning  
 Second opinions and our job to refer

1. <https://pubmed.ncbi.nlm.nih.gov/32824813/>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9086889/>
3. <https://cancerprogressreport.aacr.org/disparities/cdpr22-contents/cdpr22-the-state-of-cancer-health-disparities-in-2022/>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9086889/>
5. Understanding/Addressing Health Disparities to improve Breast Cancer Care. Otis Webb Brawley MD. NCCN 2021 Virtual Congress: Breast Cancer with updates from San Antonio Breast Cancer Symposium
6. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7852513/>



## Racial & Ethnic Disparities in BC

- Incidence: Age-adjusted breast cancer incidence highest in Whites (131.3/100,000), followed by Blacks (124.8), Asians and Pacific Islanders (102.9), Hispanics/Latinos (99.1) and American Indians & Alaska Natives/AI/AN (79.5) (5)
- Mortality: Blacks, AI/AN and Hispanic/Latinos have a higher risk of breast cancer-specific mortality relative to non-Hispanic White women. eg. Breast cancer mortality is 1.1- to 2x higher in Black women (2) and 1.7x higher in Hispanic women (4)
- Breast Cancer Subtypes:
  - Blacks and Hispanics more likely to be diagnosed with ER-tumor phenotypes (5) eg. Black women twice as likely as White women to have triple negative disease (3)
  - Hispanics and Asian women at increased risk of HER2+ disease (5)

1. <https://pubmed.ncbi.nlm.nih.gov/32824813/>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9086889/>
3. Understanding/Addressing Health Disparities to improve Breast Cancer Care. Otis Webb Brawley MD. NCCN 2021 Virtual Congress: Breast Cancer with updates from San Antonio Breast Cancer Symposium
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6002943/>
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7852513/>



## Racial & Ethnic Disparities in BC

- ▶ Guideline based treatment:
  - ▶ Several studies demonstrate underserved populations such as Hispanic or Black women less likely to receive guideline-based treatments
  - ▶ Women who did not receive indicated endocrine therapy or radiotherapy had 2.0- to 2.3 x risk of breast cancer mortality, independent of other risk factors (4)
- ▶ Genetic differences:
  - ▶ SNP at 6q25 among Hispanics/Latinas associated with a lower risk of breast cancer, especially HR<sup>-</sup> subtypes
  - ▶ *BRCA* mutations more frequent in Hispanics and Ashkenazi Jews
  - ▶ Blacks & Asians higher rates of variants of unknown significance (5)

1. <https://pubmed.ncbi.nlm.nih.gov/32824813/>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9086889/>
3. Understanding/Addressing Health Disparities to improve Breast Cancer Care. Otis Webb Brawley MD. NCCN 2021 Virtual Congress: Breast Cancer with updates from San Antonio Breast Cancer Symposium
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## Breast Cancer Recurrence Risk

- Recurrence can be local (breast), regional (chest wall) or distal (most commonly regional lymph nodes, bones, liver, lungs)
- Early vs Late recurrence: According to the International Breast Cancer Study Group, annualized hazard of recurrence highest in first 5 years (10.4%) with a **peak between years 1 and 2** (15.2%) (4)
- ER+ has a lower annualized hazard than ER- (9.9% v 11.5%), but **after 5 yrs, ER+ has higher risk than ER-** (4)
- For ER+, annualized hazards of recurrence remain elevated and stable beyond 10 years; 2% yr 10-15, 2.1% yr 15-20 and 1.1% yr 20 to 25 (4)
- **Molecular subtype matters!** Distal recurrence highest in triple negative (27.4%), lowest in Luminal A (6.4%). Local recurrence risk highest in Triple Negative (12%), lowest in Luminal A (2%)(3)

Note distal recurrence>local

1. <https://academic.oup.com/jnci/article/114/3/391/6423212>
2. <https://www.breastcancer.org/treatment/planning/risk-of-recurrence> accessed 6/28/23
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5222631/>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933127/>
5. <https://pubmed.ncbi.nlm.nih.gov/36988749/>
6. <https://cancerchoices.org/handbook/breast-cancer/reducing-your-risk-of-breast-cancer/>
7. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6002943/>

## Relapse Risk by Histological subtype

Slide courtesy of Dr Lise Alschuler ND, FABNO

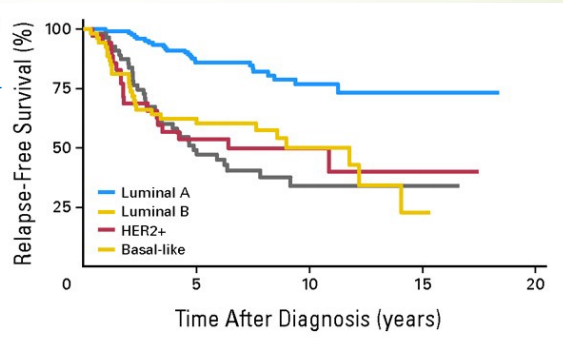
**Luminal A:** (characterized by hormone receptors (ER)-positive tumor cells and low Ki-67 expression; human epithelial growth factor receptor 2 (HER2)-negative status)

**Luminal B:** (ER-positive cells and high Ki-67 expression; HER2-negative status)

**Luminal/HER2** (ER-positive cells and HER2-positive status)

**HER2 enriched** (ER-negative and HER2-positive status)

**Basal-like** (HR-negative and HER2-negative status)



Jatoi I, Anderson WF, Jeong J-H, Redmond CK *Journal of Clinical Oncology* 2011, **29**(17):2301-2304



## Breast Cancer Recurrence Risk

- ▶ Risk of recurrence unique to each person; cancer stage, cancer size >5cm, number of positive lymph nodes, hormone receptor status, HER2 status, age at diagnosis (2), guideline-based treatment (7)
- ▶ Recall modifiable risk factors that Naturopathic Medicine excels at; being physically active, avoiding alcohol, managing stress, managing weight, eating a Mediterranean Diet, regular sleep, vitamin D status, minimizing exposure to residential pesticides, PAH, phthalates, parabens (6)

Note distal recurrence>local

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4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933127/>
5. <https://pubmed.ncbi.nlm.nih.gov/36988749/>
6. <https://cancerchoices.org/handbook/breast-cancer/reducing-your-risk-of-breast-cancer/>
7. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6002943/>

## Evaluating Benefits of Endocrine Therapy

- ▶ <https://breast.predict.nhs.uk/tool>
- ▶ <http://www.lifemath.net/cancer/breastcancer/therapy/index.php>
- Enter stats (age, cancer type, ER +/-, PR +/-, her2 +/-, KI 67 +/-, size in mm, grade, node status, select treatment options ie. Hormone Therapy)
- Results for 5,10 and 15 year survival rates and absolute benefit
- Recall the difference between **Relative Risk vs Absolute Risk**, hormone therapies roughly half relative risk
- Usually ET reduces cancer mortality more than chemotherapy
- BUT, keep in mind completion of ET is far lower than chemotherapy

Know your local docs and who to send for second opinions, not just med onc general approach, way the conversation would happen, US vs Canada, delay tactic sometimes Informed choice discussions sometimes fall to us but this is a heavy responsibility

KI67 protein from cell replication, when high means more aggressively dividing, Less than 10% is considered low, 20% or higher is considered high

**Luminal A Tumors:** ER+, PR+, HER2 negative, Ki-67 index less than 14%

**Luminal B Tumors:** ER+ and/or PR +, HER2 negative, Ki-67 index greater than 14% or, are ER+ and/or PR+, HER2 positive, and have any Ki-67 index



## Individualizing care

**Example 1:** a 44 yr old neighbor with an ER+, HER2-, 23mm grade 2 tumor, with 2 lymph nodes involved. Predict analysis;

- 10 yr absolute survival benefit from hormone therapy of 6.1% & chemotherapy benefit of 3%
- 15 yr absolute survival benefit from hormone therapy of 8.5% & chemotherapy benefit 4.3%
- Overall survival: At 15 yrs, a 64% OS with surgery alone, 73% OS with hormone therapy added and 77% with chemotherapy added (keeping in mind that without breast cancer 5% of people that age die from other causes within 15 years)
- Considerations: 15 yr survival especially relevant for younger survivors. Compliance with hormone therapy much lower than chemotherapy



## Individualizing care

**Example 2:** a 71 yr old with an ER+, HER2-, 23 mm grade 2 tumor with 0 lymph nodes involved

- 10 absolute yr survival benefit from hormone therapy of 2.4% and chemotherapy benefit 1.5%
- 15 yr absolute survival benefit from hormone therapy of 3% and chemotherapy benefit 1.4%
- Overall survival: At 10 yrs, a 70% OS with surgery alone, 73% OS with hormone therapy added and 74% with chemotherapy added (keeping in mind that without breast cancer, 22% would die of other causes).
- At 15 yrs, 52% survive with surgery alone and 55% with hormone therapy added with 38% dying of other causes





## Thinking Critically about Cancer Research

- Cancer research heavily biased by pharmaceutical industry
- Cancer trial outcomes are often presented with drug benefits as a Relative Risk and drug side effects as Absolute Risk (which creates bias towards treatment)
- Many new trials of established drugs will report “No new safety signals” instead of properly reporting adverse events
- **Progression free survival/PFS or Recurrence free survival/RFS does not equal overall survival/OS.** PFS is a poor surrogate for OS when survival post-progression is long (like is often the case in breast cancer) (5).
- PFS is simply a measure of a cancer drug's effect on tumor growth while it is administered and is not a surrogate for OS (6)

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4650202/>
2. <https://catalogofbias.org/biases/reporting-biases/>
3. <https://www.bmj.com/content/349/bmj.g6501>
4. <https://bmjopen.bmj.com/content/4/9/e005253>
5. <https://pubmed.ncbi.nlm.nih.gov/22115991/>
6. <https://pubmed.ncbi.nlm.nih.gov/19826357/>

## Thinking Critically about Cancer Research

- Reporting bias common (withholding of study data or the active attempt by manufacturers to suppress the publication of findings) (2)
- In a Cochrane cohort review, **86% of studies** did not report data on the main harm outcome of interest. Outcome reporting bias was suspected in nearly **2/3** of clinical studies (3)
- In a systematic review, discrepancies between prespecified and reported outcomes occurred in **1/3** of the studies (1)
- The Cochrane risk of bias tool (which we use in KNOW!) is not as accurate as thought bec of reporting bias. In a sample assessment of 14 oseltamivir trials, over half (55%, 34/62) of the previous assessed 'low' risk of bias studies were reclassified as 'high' (4)

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4650202/>
2. <https://catalogofbias.org/biases/reporting-biases/>
3. <https://www.bmj.com/content/349/bmj.g6501>
4. <https://bmjopen.bmj.com/content/4/9/e005253>
5. <https://pubmed.ncbi.nlm.nih.gov/22115991/>
6. <https://pubmed.ncbi.nlm.nih.gov/19826357/>
7. <https://www.bmj.com/content/360/bmj.k668>
8. <https://jamanetwork.com/journals/jamaoncology/fullarticle/2546172>



## NCCN Guidelines

- NCCN Guidelines are open access documents that provide standards of care in oncology and are searchable by tumor type: [https://www.nccn.org/guidelines/category\\_1](https://www.nccn.org/guidelines/category_1)
- “NCCN Guidelines® are the recognized standard for clinical direction and policy in cancer care and are the most thorough and frequently updated clinical practice guidelines available in any area of medicine.”
- A practical tour of NCCN Guidelines is available here by Dr Katherine Neubauer, ND, FABNO: <https://oncanp.org/learn-classical-to-play-better-jazz-a-practical-tour-of-the-nccn-guidelines/>

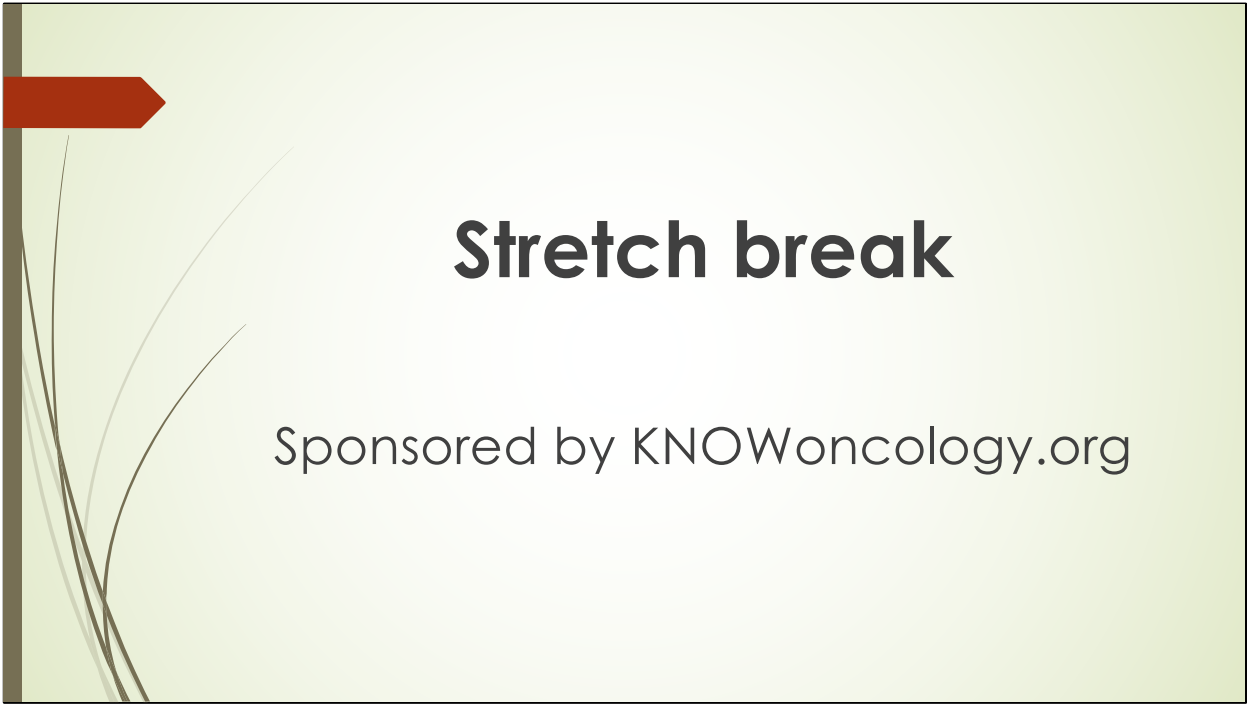
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7. <https://www.bmj.com/content/360/bmj.k668>
8. <https://jamanetwork.com/journals/jamaoncology/fullarticle/2546172>
9. <https://www.nccn.org/guidelines/guidelines-process/about-nccn-clinical-practice-guidelines> accessed 7/1/23

## NCCN Guidelines

- In a BMJ review, 47 drugs were authorized for 69 FDA approved indications, whereas NCCN recommended these drugs for 113 indications. Only 23% (n=10) of the additional NCCN recommendations were based on evidence from RCT's, and only 16% (n=7) of these were based on evidence from phase III studies (7)
- “NCCN frequently recommends beyond the FDA approved indications even for newer, branded drugs. The strength of the evidence cited by the NCCN supporting such recommendations is weak. Our findings raise concern that the NCCN justifies the coverage of costly, toxic cancer drugs based on weak evidence.” (7)
- In a cross-sectional analysis of 125 NCCN Guideline authors, 86% had financial conflicts of interest/COI. 6% had financial COI in excess of the \$50 000 net and/or \$20 000 single-company maximums stipulated by NCCN (8)

On other hand, drugs often put in to fill gaps in care

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4650202/>
2. <https://catalogofbias.org/biases/reporting-biases/>
3. <https://www.bmj.com/content/349/bmj.g6501>
4. <https://bmjopen.bmj.com/content/4/9/e005253>
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7. <https://www.bmj.com/content/360/bmj.k668>
8. <https://jamanetwork.com/journals/jamaoncology/fullarticle/2546172>
9. <https://www.nccn.org/guidelines/guidelines-process/about-nccn-clinical-practice-guidelines> accessed 7/1/23



# Stretch break

Sponsored by [KNOWoncology.org](http://KNOWoncology.org)



## KNOWoncology.org

- ▶ Integrative oncology database that systematically searches and summarizes human studies on nutrition, natural agents and cancer care
- ▶ Clinical and research tool **made by and for ND's** to access current best evidence
- ▶ Searchable by Tumor Type, Side Effect, Conventional Therapy, Natural Therapy
- ▶ Results by level of evidence, drops down arrow shows study details in curated abstract
- ▶ Can export references to patient recommendations, letters to care teams and presentations like this one
- ▶ Free for oncANP members – ND member and Allied healthcare professionals
- ▶ Now available for licensing to libraries, cancer care teams, integrative cancer research groups



## Types & Uses of Endocrine Therapies

SERMs: Selective Estrogen Receptor Modulator, competitively blocks estrogen receptors

- Doesn't block estrogen everywhere. Antiestrogen in breast while estrogenic in bone and uterus
- Lowers circulating IGF-1
- Tamoxifen/Nolvadex, raloxifene/Evista. Oral daily dose (20mg standard Tam, 5mg baby Tam) with or without food
- Approved for for primary prevention (eg. atypical ductal hyperplasia, DCIS), preventing recurrence in premenopausal BC and in post menopausal women who don't tolerate an AI

`DCIS precancer/stage 0

1. <https://jamanetwork.com/journals/jamaoncology/article-abstract/2783593>



## Types & Uses of Endocrine Therapies

- Aromatase Inhibitors/AI's
  - Suppresses synthesis of estrogen by inhibiting aromatase, the enzyme that converts peripheral androgens to estrogens
  - Inactive in women with intact ovarian function so must combine with ovarian suppression in premenopausal women
  - letrozole/Femara 2.5mg, anastrozole/Arimidex 1mg, exemestane/Aromasin 25mg. Oral daily dose with or without food
  - Approved for preventing recurrence in post menopausal BC, treating metastatic BC alone or with a CDK4/6 inhibitor, can be used neoadjuvantly to facilitate breast-conserving surgery

1. <https://jamanetwork.com/journals/jamaoncology/article-abstract/2783593>





## Types of Endocrine Therapies

- SERDs: Selective Estrogen Receptor Down-regulator
  - degrades/down regulates estrogen receptors
  - fulvestrant/Faslodex, elacestrant/Orserdu. Fulvestrant 250mg or 500 mg IM injection on days 1, 15, 29, then once monthly. Elacestrant 400mg orally
  - Best option for OS in metastatic BC
- LHRH agonists (luteinizing hormone-releasing hormone)
  - suppresses ovaries from making estrogen
  - goserelin/Zoladex subcutaneous injection with a pre-filled 10.8mg syringe usually monthly or leuprolide/Lupron either subQ 3.75mg injection monthly or intramuscular 11.25 mg every 3 (sometimes 4 or 6) months
  - Approved for preserving fertility during chemotherapy. Sometimes combined with Tam or AI for premenopausal breast cancer

## Comparing & Contrasting Endocrine Therapies

	<u>Tamoxifen/Nolvadex</u>	<u>Arimidex/Anastrozole, Aromasin/Exemestane &amp; Femara/Letrozole rough equivalents<sup>1</sup></u>	<u>Faslodex/Fulvestrant</u>	<u>Lupron/leuprolide</u> <u>Zoladex/Goserelin</u>
<b>Mechanism, FDA approval &amp; Considerations</b>	<p>SERM/Selective Estrogen Receptor Modifier (doesn't block estrogen everywhere). Antiestrogen in breast, estrogenic in bone and uterus.</p> <p>Indications: premenopausal women, postmenopausal women, men, metastatic bCAs, high risk women/previvors.<sup>2</sup> mucinous or tubular/ciribriform histologies<sup>3</sup></p> <p>Raloxifene/Evita sister drug with 76% of the effectiveness of Tam.<sup>4</sup></p> <p>Need to use with birth control or ovarian suppression bec fertility can remain and toxic to fetus</p>	<p>AI's/Aromatase Inhibitors suppress synthesis of estrogen by inhibiting aromatase, the enzyme that converts peripheral androgens to estrogens.</p> <p>Indications: postmenopausal women, metastatic bCAs in combos: letrozole + tykerb/lapatinib, letrozole + Ibrance/palbociclib<sup>5</sup></p> <p>AI's are inactive in women with intact ovarian function. Must combine with ovarian suppression in younger women</p>	<p>Degrades/down regulates estrogen receptors</p> <p>postmenopausal women, premenopausal women who have had ovarian ablation advanced or previously treated resistant with other hormone blockers<sup>6</sup></p> <p>IM injection monthly</p>	<p>LHRH agonist (luteinizing hormone-releasing hormone), suppresses ovaries</p> <p>Monthly injections.</p> <p>Indications: combined with Tam or AI for premenopausal breast cancer. Also used for prostate cancer.</p> <p>SubQ vs IM options<sup>7</sup></p>
<b>Trial evidence</b>	<p>In pre and postmenopausal women, tam for 5 yrs reduced breast cancer mortality by about a third throughout the first 15 years (RR 0.71 [0.05] during years 0-4, 0.66 [0.05] during years 5-9, and 0.68 [0.08] during years 10-14; p&lt;0.0001.<sup>8</sup></p>	<p>Compared to Tam, lower 10-year breast cancer mortality (RR 0.85, 95% CI 0.75-0.96)<sup>9</sup> and slightly lower recurrence rates yrs 0-1, 2-4 but not after 5 yrs.<sup>10</sup></p> <p>Comparing AI's: Multiple trials, no difference between them in 5 yrs. DFS<sup>11,12,13</sup></p>	<p>Best option for metastatic bCAs, improves OS<sup>14</sup>.</p>	<p><a href="https://www.cancer-network.com/article/point-lhrh-agonists-vs-ovarian-ablation-suppression-ovarian-function-premenopausal-breast">https://www.cancer-network.com/article/point-lhrh-agonists-vs-ovarian-ablation-suppression-ovarian-function-premenopausal-breast</a></p>

See accompanying Quick Reference Guide

## Endocrine Therapy Adherence Issues

- In FACE trial, 32% of exemestane users and 29% anastrozole users discontinued the trial due to side effects (4)
- A study of over 8700 women in the Northern California Kaiser Permanente system found **only 49% fully adhered** to endocrine therapy (1)
- Within the Canadian Cancer Trials Group trial, 20% discontinued AI therapy by month 24 and 32% discontinued AIs at 4 yrs (5)
- Early discontinuation associated with higher mortality rates from breast cancer. OS at 10 years was 81.7% for women who continued ET vs 77.8% for those who discontinued ( $P < 0.001$ ) (3)
- Minimize nocebo and maximize placebo: avoidance of online ET horror stories, when take tell themselves “I am protected” or “I am thriving”. And every person is unique...

“I feel completely myself on Arimidex” – JH, 37 yr old with oophorectomy for BRCA2

“I would rather die than live like this.” – DB, 52 yr old survivor who tried every available endocrine therapy

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2953970/>
2. <https://www.ncbi.nlm.nih.gov/pubmed/30465157>
3. <https://www.ncbi.nlm.nih.gov/pubmed/20803066/>
4. [https://ascopubs.org/doi/full/10.1200/JCO.2016.69.2871?url\\_ver=Z39.88-2003&rfr\\_id=ori:rid:crossref.org&rfr\\_dat=cr\\_pub%3dpubmed](https://ascopubs.org/doi/full/10.1200/JCO.2016.69.2871?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6092930/>



## Harm reduction model: Tamoxifen then AI option for peri or post menopausal BC

- Tam < (Tam then AI) = or almost = AI
- In trials where post menopausal women (N = 11,798) assigned to 2-3 yrs TAM then AI vs 5 yrs TAM only, the TAM then AI group had fewer breast cancer deaths (RR 0.84, 95% CI 0.72-0.96), reduced breast cancer recurrence yr 2-4 (RR 0.56, 95% CI 0.46-0.67), and no further effect on recurrence after 5 yrs (3)
- In post menopausal early breast cancer, (N=3697 patients), 5 years of AI was not superior to 2 years of tamoxifen followed by 3 yrs AI (4)
- In trials where post menopausal women (n = 12,799) assigned to 2-3 yrs TAM then AI after vs 5 yrs AI only, AI alone marginally superior; **no difference in mortality**, similar recurrence rates after 5 yrs, lower recurrence rates during years 0 to 1 in AI grp, before the switch had occurred (RR 0.74, 95% CI 0.62-0.89) (3)
- Safety note: If using AIs in younger women with chemotherapy-induced amenorrhea or peri-menopause, they can recover normal menses (2) so need ovarian suppression. They need to have their FSH and serum estradiol monitored (1)

1. **UpToDate.** Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer. Accessed 4/30/20. [Claudine Isaacs, MD](#)
2. <https://www.ncbi.nlm.nih.gov/pubmed/23108951>
3. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(15\)61074-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)61074-1/fulltext)
4. [https://linkinghub.elsevier.com/retrieve/pii/S1470-2045\(18\)30116-5](https://linkinghub.elsevier.com/retrieve/pii/S1470-2045(18)30116-5)

## Harm reduction model: AI then Tamoxifen option in post menopausal women

- **AI then Tam:** An RCT of over 8000 women compared 5 yrs of Tam or letrozole monotherapy, or sequential treatment with 2 yrs one drug followed by 3yrs of the other. No significant difference in either disease-free or **overall survival between the sequential therapies and letrozole monotherapy**
- Efficacy of monotherapy with letrozole versus tamoxifen for contralateral breast cancer varied over time (0 to 5-, 5 to 10-, and >10-year hazard ratios [HRs] 0.62, 0.47, and 1.35, respectively) (1)
- “Highest risk for recurrence is within the first few years after diagnosis, so the more effective treatment strategy (AI) is preferable first. Once disease free for a few years, switching to Tam is similarly effective to continuation of AI treatment, and there may be a longer carry-over effect with tamoxifen than an AI in terms of protection against contralateral breast cancer” (2)

“I wake at night in pain. I can't walk the dog anymore or bend to unload the dishwasher. Life has become oppressively hard. I have to work to think straight” CH 45 yr old on Lupron with Femara, switched to Lupron + Tam

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6325353/>
2. **Adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer. UpToDate. Accessed 5/17/20.**

## Extended Hormonal Therapy from 5-10 yrs

- UpToDate recommends including Patient Preference (1)
- “What would make you rest easier, staying on a hormonal therapy or discontinuing it?”
- Women with smaller, node-negative tumors have no benefit of extended therapy
- Multiple studies show use of AI from 5-10 yrs after an AI or Tam improves RFS but not OS (4) while increasing bone pain, bone fractures, osteoporosis, myalgia, and treatment discontinuation for adverse events (11)
- Extending tamoxifen from 5 to 10 years lowered absolute breast cancer mortality by about 2.8% but also increased absolute risk of endometrial cancer by 1.7% (2,10)

1. **UpToDate.** Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer. Accessed 4/30/20. [Claudine Isaacs, MD](#)

2. <https://pubmed.ncbi.nlm.nih.gov/23219286/>

3. <https://pubmed.ncbi.nlm.nih.gov/22042967/>

4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5024713/>

5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6734915/>

6. [http://www.kongresshighlights.com/uploads/media/ABCSG-16\\_p.pdf](http://www.kongresshighlights.com/uploads/media/ABCSG-16_p.pdf)

7. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6927322/>

8. <https://pubmed.ncbi.nlm.nih.gov/31504126/>

9. <https://cco.amegroups.com/article/view/3462/4340>

10. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9320044/>

11. <https://pubmed.ncbi.nlm.nih.gov/31606823/>

## Extended Hormonal Therapy from 5-10yrs

- Breast Cancer Index genomics test predictive test for ER+ BC with 0-3 nodes (7,8) however models integrating clinical information with genomic data (ie, PAM50 and Endopredict) may be more effective at identifying node-positive disease at low risk for recurrence (1)
- <https://cts5-calculator.com> is a predictive tool for post menopausal women to predict late distant BC relapse after five years of adjuvant ET
- Middle path options;
  - SOLE trial compared 5-10 yrs letrozole vs intermittent schedule of 9 months on, 3 months break each yr, same DFS with less vaginal pain, musculoskeletal, sleep disturbance, physical well-being and mood issues at 12 months (5)
  - 7 vs 10 yrs anastrozole experienced equivalent DFS and fewer bone fractures (4 versus 6%) (6)
  - Use Tam after AI for a few yrs
  - Future possibility of baby Tam?

1. **UpToDate.** Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer. Accessed 4/30/20. [Claudine Isaacs, MD](#)

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## Ovarian Suppression: Pros and cons

- Roughly 1/3 of newly diagnosed BC are premenopausal
- Ovarian function suppression/OFS involves the reversible option of LHRH-analogues eg. leuprolide/Lupron, goserelin/ Zoladex or the irreversible option of oophorectomy
- **OFS only recommended for higher risk patients**; especially important in *BRCA*+ women, women at a younger age (ie,  $\leq 35$  yrs) and patients in whom chemotherapy is indicated eg. pathologically involved lymph nodes, large tumor size, high risk of recurrence based on a genomic assay, or other high-risk features for advising chemotherapy (1)
- Addition of OFS to a hormone blocker improves risk of recurrence but increases toxicity (1)

1. **UpToDate.** Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer. Accessed 4/30/20. [Claudine Isaacs, MD](#)

2.

[https://ascopubs.org/doi/abs/10.1200/JCO.19.00126?rfr\\_dat=cr\\_pub%3Dpubmed&url\\_ver=Z39.88-2003&rfr\\_id=ori%3Arid%3Acrossref.org&journalCode=jco](https://ascopubs.org/doi/abs/10.1200/JCO.19.00126?rfr_dat=cr_pub%3Dpubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&journalCode=jco)

3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6193457/>:

4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4251958/>

5.

<https://ascopubs.org/doi/abs/10.1200/JCO.22.01064?md5=5e0912e5a155ff17479e6383b13d7ea7&cid=DM12337&bid=228912817>



## Ovarian Suppression: Pro's and cons

- In node negative women, adding OFS **did not improve DFS or overall OS but it did reduce health related quality of life** (esp menopausal symptoms and sexual dysfunction) (4)
- In the SOFT trial, 12 yr OS was improved **2.2% for the addition of OFS to Tam** and **2.6% for exemestane + OFS** vs Tam. For her2- women who received chemotherapy, OS was 2.3% better from addition of OFS to Tam, 5.6% better with exemestane + OFS (6)
  - In combined analysis of SOFT-TEXT (N=4,690), 12-year DFS 4.6% absolute improvement of exemestane + OFS vs. Tam + OFS, but **no difference in OS**. WHY???? (please guess...)(5)
- <https://www.cancernetwork.com/view/point-lhrh-agonists-vs-ovarian-ablation-suppression-ovarian-function-premenopausal-breast-cancer> (SOFT trial author)

### SOFT had non OFS arm whereas TEXT did not

**1.UpToDate.** Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer. Accessed 4/30/20. [Claudine Isaacs, MD](#)

2.

[https://ascopubs.org/doi/abs/10.1200/JCO.19.00126?rfr\\_dat=cr\\_pub%3Dpubmed&url\\_ver=Z39.88-2003&rfr\\_id=ori%3Arid%3Acrossref.org&journalCode=jco](https://ascopubs.org/doi/abs/10.1200/JCO.19.00126?rfr_dat=cr_pub%3Dpubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&journalCode=jco)

3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6193457/>: In SOFT trial, 8 yr OS was and 93.3% in the Tam + OFS vs 91.5% in Tam only vs 92.1% with exemestane + OFS . This means the absolute benefit was **2.1% for the addition of OFS to tamoxifen** and **4.5% for the use of exemestane plus OFS** vs Tam. **No OS benefit for women who did not undergo chemotherapy** (3)

4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4251958/>

5.

<https://ascopubs.org/doi/abs/10.1200/JCO.22.01064?md5=5e0912e5a155ff17479e6383b13d7ea7&cid=DM12337&bid=228912817>

6. <https://pubmed.ncbi.nlm.nih.gov/36493334/>

DFS does not equal overall survival!



## Side Effects of OFS

- ▶ OFS associated with increased incidence of coronary artery disease, arrhythmias, hyperlipidemia, asthma, chronic obstructive pulmonary disease, osteoporosis, arthritis, and depression (4)
- ▶ SE's: hot flashes, weight gain, decreased libido, vaginal dryness, musculoskeletal symptoms, loss of bone density, increased cardiovascular risk, cognitive changes
- ▶ In SOFT, there were grade 3 or 4 adverse events in 32% with exemestane + OFS, 31% with Tam + OFS, and 25% with Tam only. **Musculoskeletal symptoms in 90%** with exemestane plus OFS, 78% with Tam plus OFS, and 70% with Tam only (1)
- ▶ In patients not tolerating OFS, the option of Tam alone followed by an AI after several years may be appropriate (1)
- ▶ One model of the long-term consequences of ovarian ablation in premenopausal breast cancer patients estimated a mortality rate of 12.5% associated with early oophorectomy over a 40-year period (3)

1. **UpToDate.** Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer. Accessed 4/30/20. [Claudine Isaacs, MD](#)
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4251958/>
3. <https://pubmed.ncbi.nlm.nih.gov/27236562/>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5097693/>