
OncANP
Oncology Association of Naturopathic Physicians
FONO: Endocrine Therapy in Breast Cancer
& Naturopathic Co-management
Dr Jen Green ND, FABNO
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 Musckuloskeletal 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	
Tis	DCIS LCIS Paget nipple
T1 mic	≤ 0,1 cm
T1a	≤ 0,5 cm
T1b	> 0,5 - 1 cm
T1c	> 1 cm - 2 cm
T2	> 2 cm - 5 cm
T3	> 5 cm
T4a	Extension to chest wall (does not include pectoralis muscle invasion only)
T4b	Ulceration, ipsilateral satellite skin nodules, or skin oedema - including peau d'orange.
T4c	a+b
T4d	Inflammatory ca

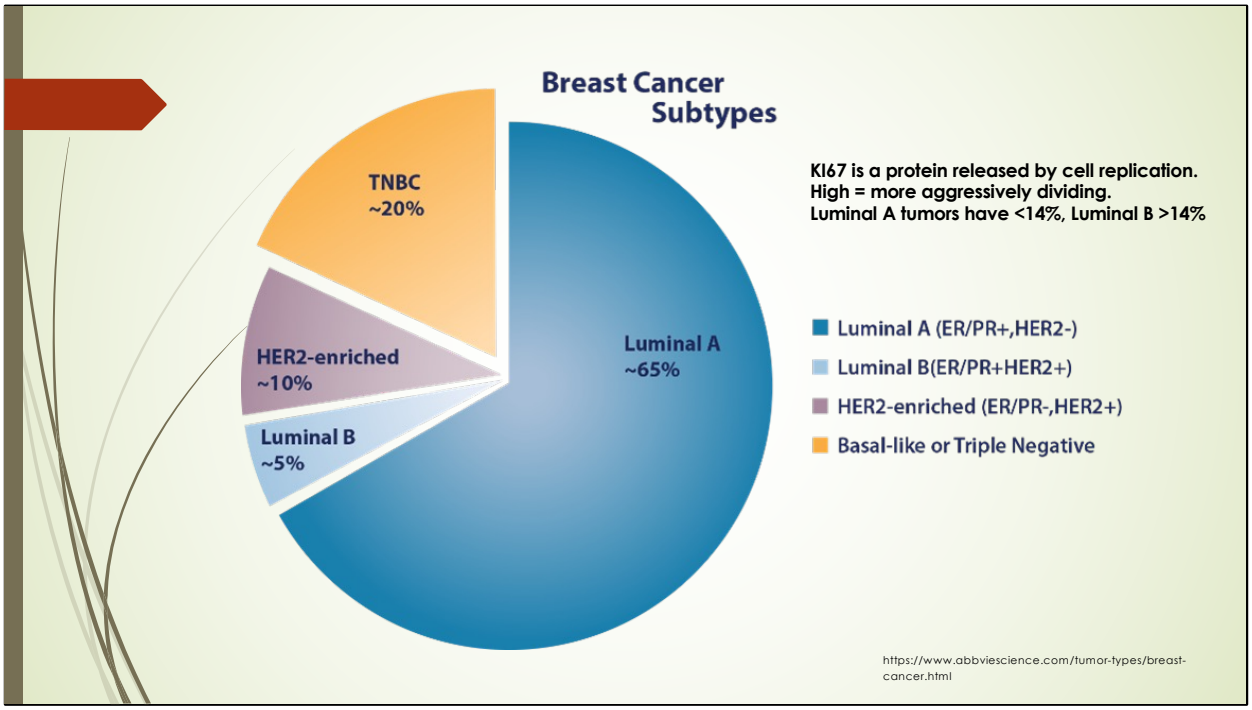
pN	
pN1mi	Micrometastasis > 0,2 mm to 2 mm
pN1a	1-3 axillary nodes
pN1b	Internal mammary nodes with microscopic/macroscopic metastasis by sentinel node biopsy but not clinically detected
pN1c	1-3 axillary nodes and internal mammary nodes and internal mammary nodes with microscopic/ macroscopic metastasis by sentinel node biopsy but not clinically detected
pN2a	4-9 axillary nodes
pN2b	Internal mammary nodes, clinically detected, without axillary nodes
pN3a	≥ 10 axillary nodes or infraclavicular
pN3b	Internal mammary nodes, clinically detected, with axillary node(s) or > 3 axillary nodes and internal axillary mammary nodes with microscopic metastasis by sentinal node biopsy but not clinically detected
pN3c	Supra-clavicular

pTNM-Stage	
0	DCIS
IA	T1N0
IB	T0-1N1mi
IIA	T0-1N1 T2N0
IIB	T2N1 T3N0
IIIA	T0-2N2 T3N1-2
IIIA	T4N0-2 T3N1-2
IIIC	anyT N3
IV	systemic

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%

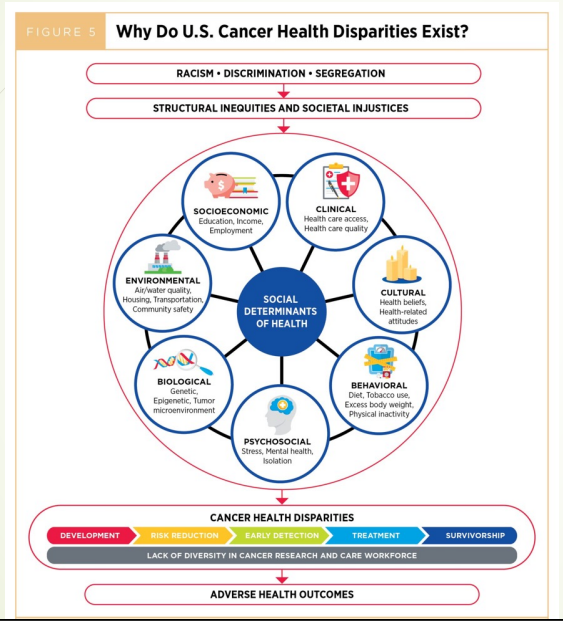
Luminal B Tumors: ER+ and/or PR +, HER2 negative, Ki-67 index greater than 14% or, are ER+ and/or PR+, HER2 positive, and have any Ki-67 index

HER2 enriched

Triple negative/basal-like

Lobular more unpredictable than ductal carcinomas

Racial & Ethnic Disparities in BC



- 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/
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4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6002943/
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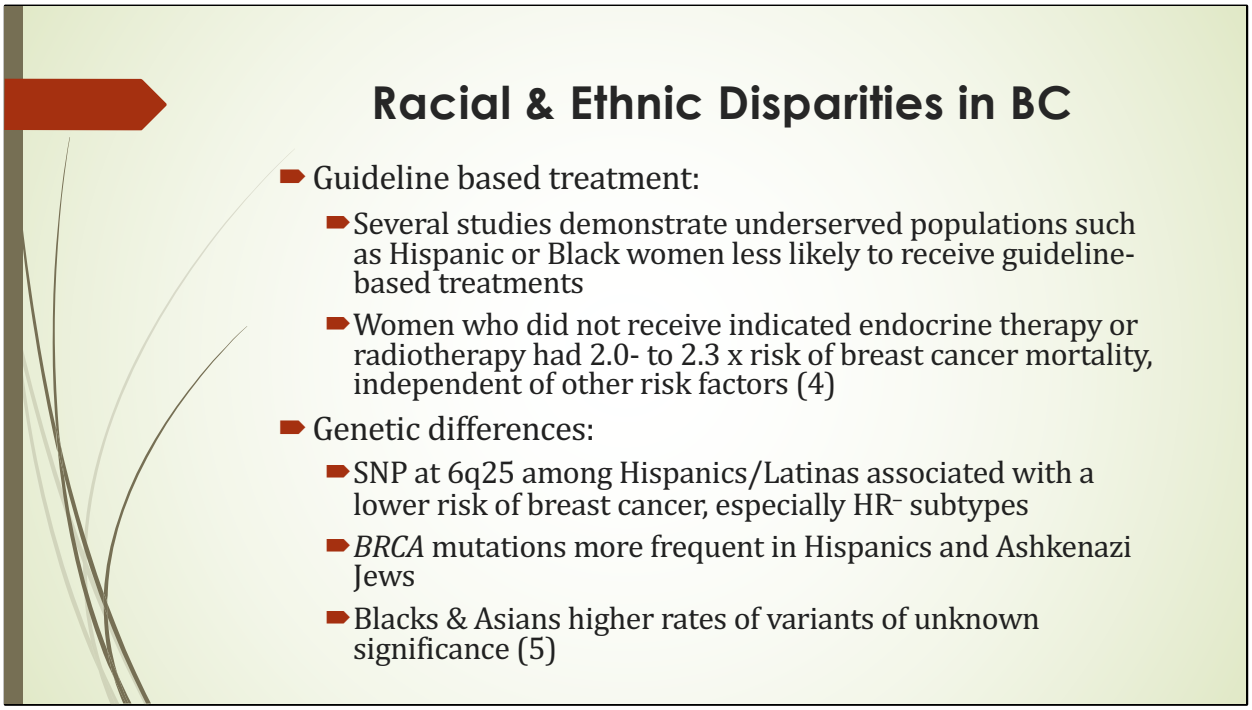

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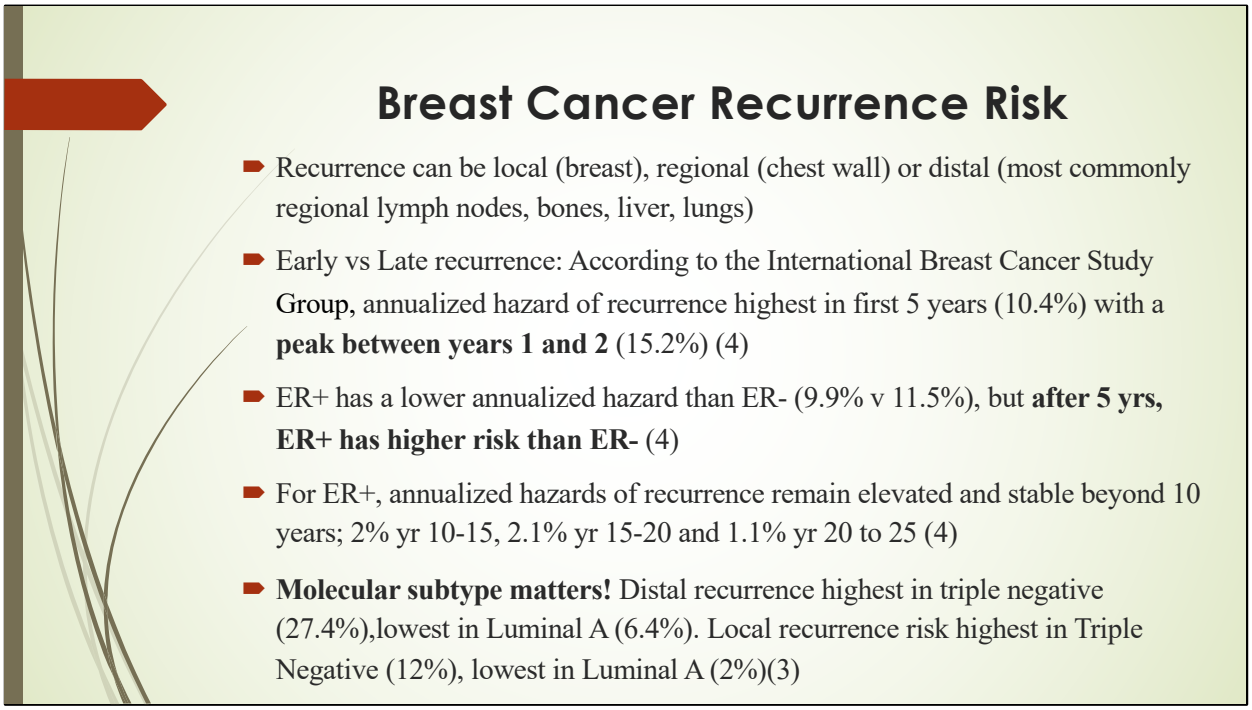


Note distal recurrence>local

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

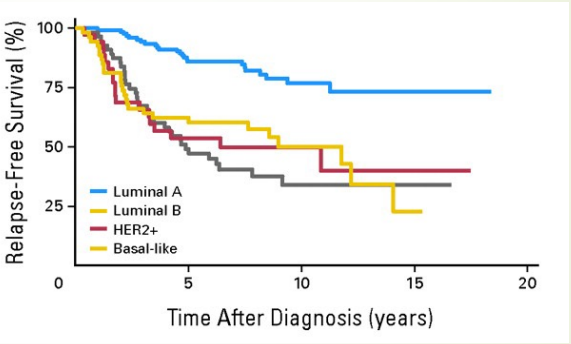
Luminal A: (characterized by hormone receptors (ER)-positive tumor cells and low Ki-67 expression; human epithelial growth factor receptor 2 (HER2)-negative status)

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)

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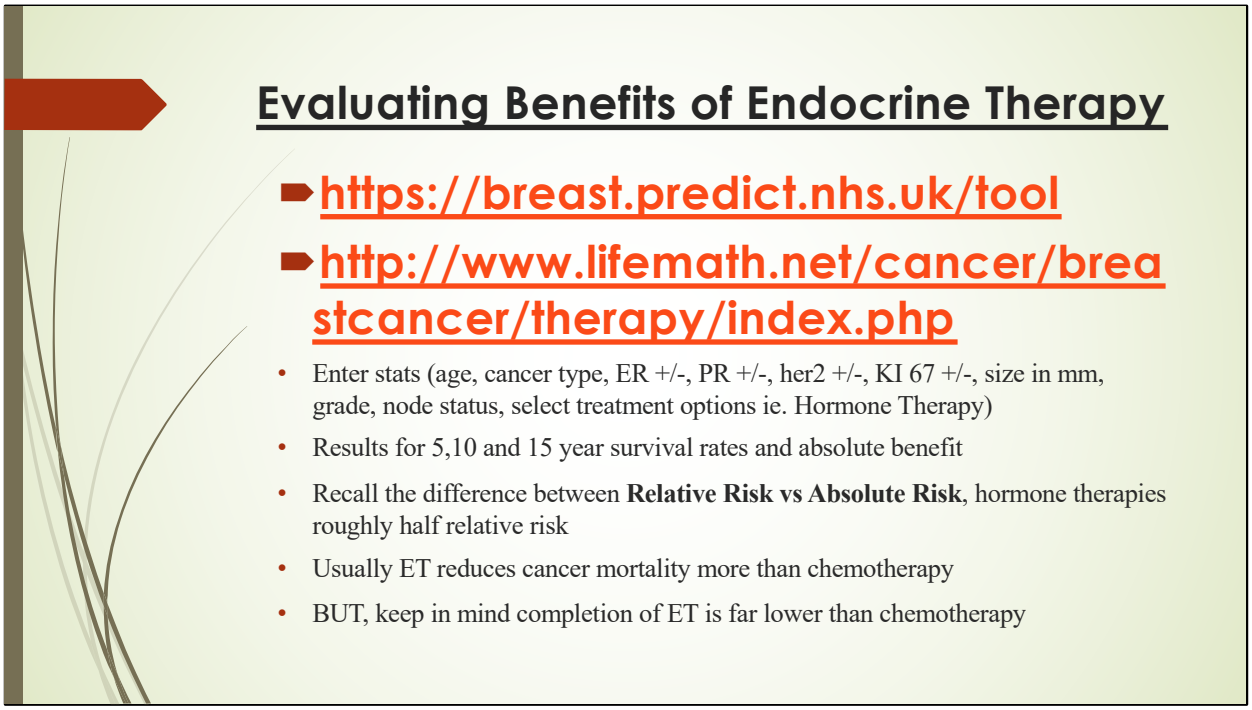
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933127/
5. https://pubmed.ncbi.nlm.nih.gov/36988749/
6. https://cancerchoices.org/handbook/breast-cancer/reducing-your-risk-of-breast-cancer/
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6002943/



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/
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3. https://www.bmj.com/content/349/bmj.g6501
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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
- "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/

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4650202/
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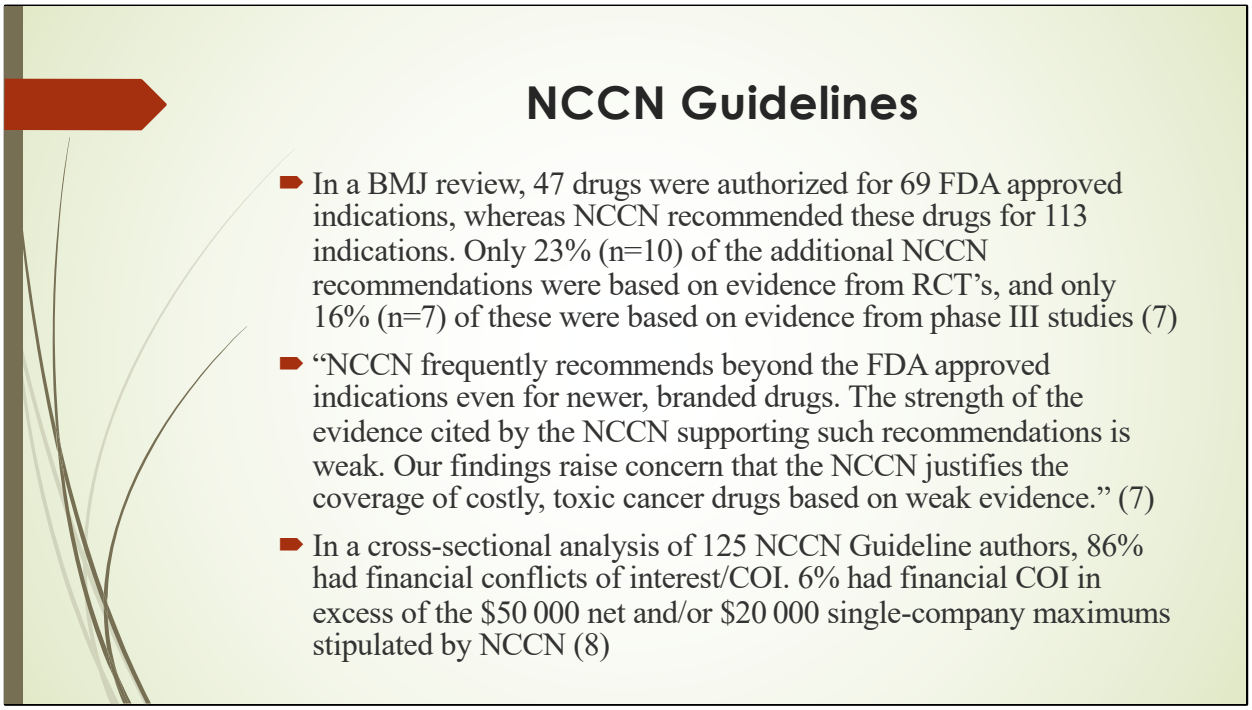
6. https://pubmed.ncbi.nlm.nih.gov/19826357/
7. https://www.bmj.com/content/360/bmj.k668
8. https://jamanetwork.com/journals/jamaoncology/fullarticle/2546172
9. https://www.nccn.org/guidelines/guidelines-process/about-nccn-clinical-practice-guidelines accessed 7/1/23



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

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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

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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

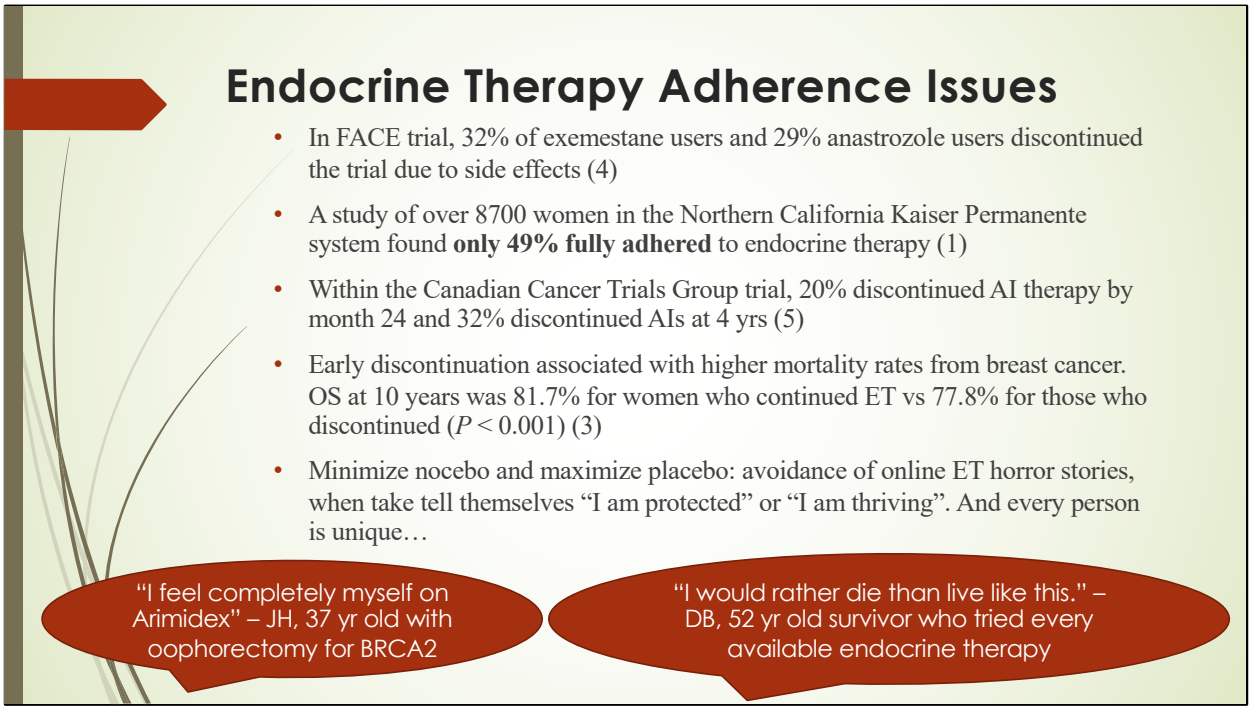
Types of Endocrine Therapies

- 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

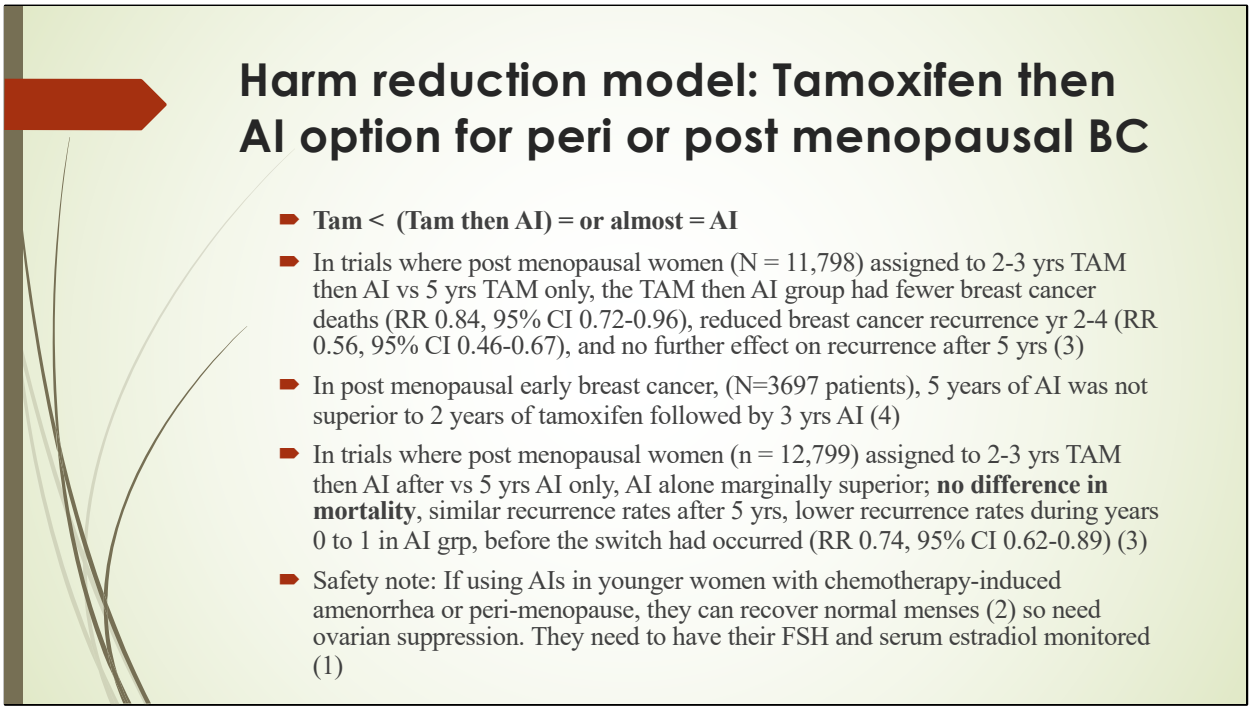
Comparing & Contrasting Endocrine Therapies

	Tamoxifen/Nolvadex	Arimidex/Anastrozole Aromasin/Exemestane & Femara/Letrozole rough equivalents[1]	Faslodex/ Fulvestrant	Lupron/ leuprolide Zoladex/ Goserelin
Mechanism, FDA approval & Considerations	SERM/Selective Estrogen Receptor Modifier (doesn't block estrogen everywhere). Antiestrogen in breast, estrogenic in bone and uterus. Indications; premenopausal women, post menopausal women, men, metastatic brCA, high risk women/previvors.[2] mucinous or tubular/cribriform histologies[3] Raloxifene/Evita sister drug with 76% of the effectiveness of Tam.[4] Need to use with birth control or ovarian suppression bec fertility can remain and toxic to fetus	AI's/Aromatase Inhibitors suppress synthesis of estrogen by inhibiting aromatase, the enzyme that coverts peripheral androgens to estrogens. Indications; post menopausal women, metastatic brCA in combos; letrozole + tykerb/lapatinib, letrozole + Ibrance/palbociclib[5] AI's are inactive in women with intact ovarian function. Must combine with ovarian suppression in younger women	Degrades/down regulates estrogen receptors post menopausal women, premenopausal women who have had ovarian ablation advanced or previously treated resistant with other hormone blockers[6] IM injection monthly	LHRH agonist (luteinizing hormone-releasing hormone), suppresses ovaries Monthly injections. Indications; combined with Tam or AI for premenopausal breast cancer. Also used for prostate cancer. SubQ vs IM options[7]
Trial evidence	In pre and post menopausal 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<0·0001. [8]	Compared to Tam, lower 10-year breast cancer mortality (RR 0.85, 95% CI 0.75-0.96)[9] and slightly lower recurrence rates yr 0-1, 2-4 but not after 5 yrs.[10] Comparing AI's; Multiple trials, no difference between them in 5 yr DFS[11][12][13]	Best option for metastatic brCA, improves OS[14]	https://www.cancernetwork.com/article/point-lhrh-agonists-vs-ovarian-ablation-suppression-ovarian-function-premenopausal-breast

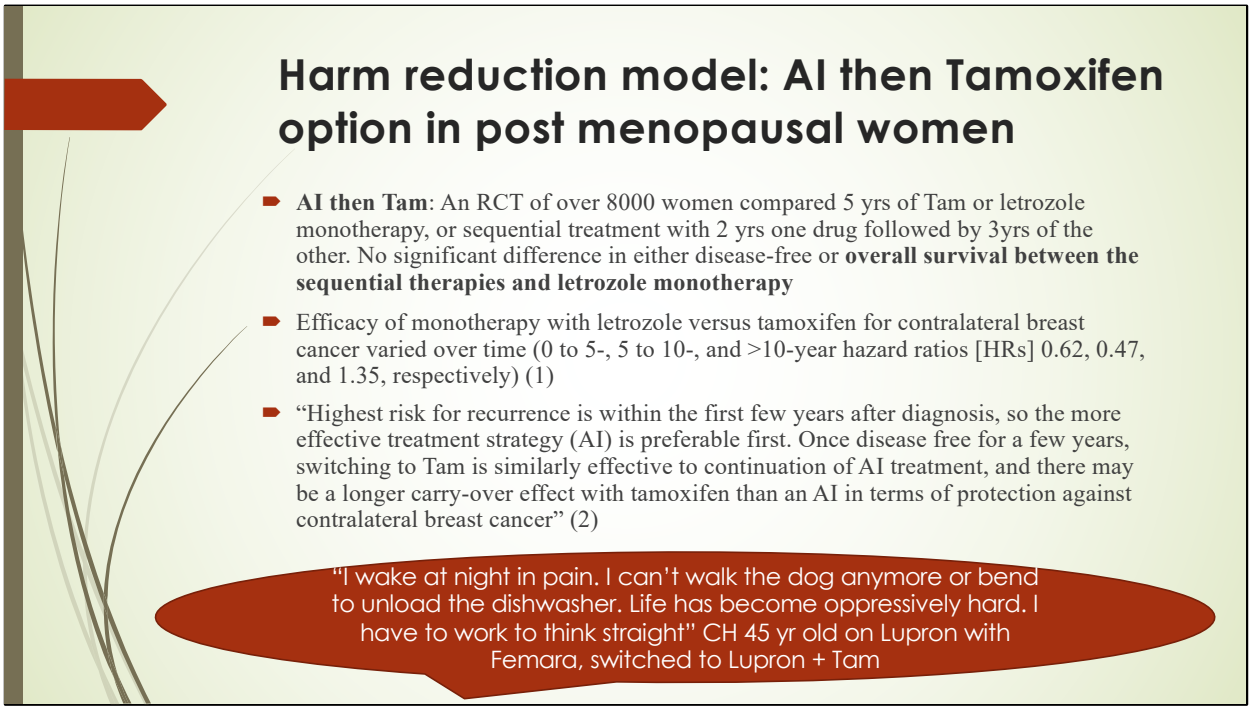
See accompanying Quick Reference Guide



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
5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6092930/



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
4. https://linkinghub.elsevier.com/retrieve/pii/S1470-2045(18)30116-5

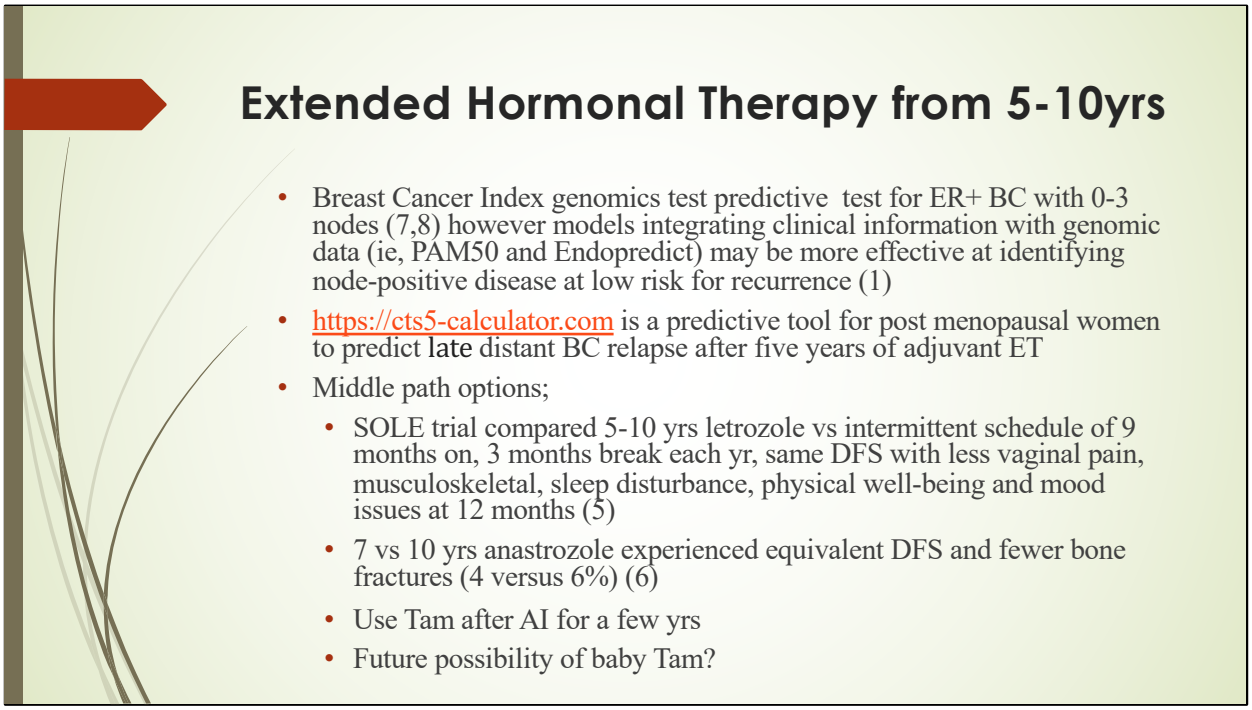


1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6325353/
2. **Adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer. UpToDate. Accessed 5/17/20.**

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
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/



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
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/
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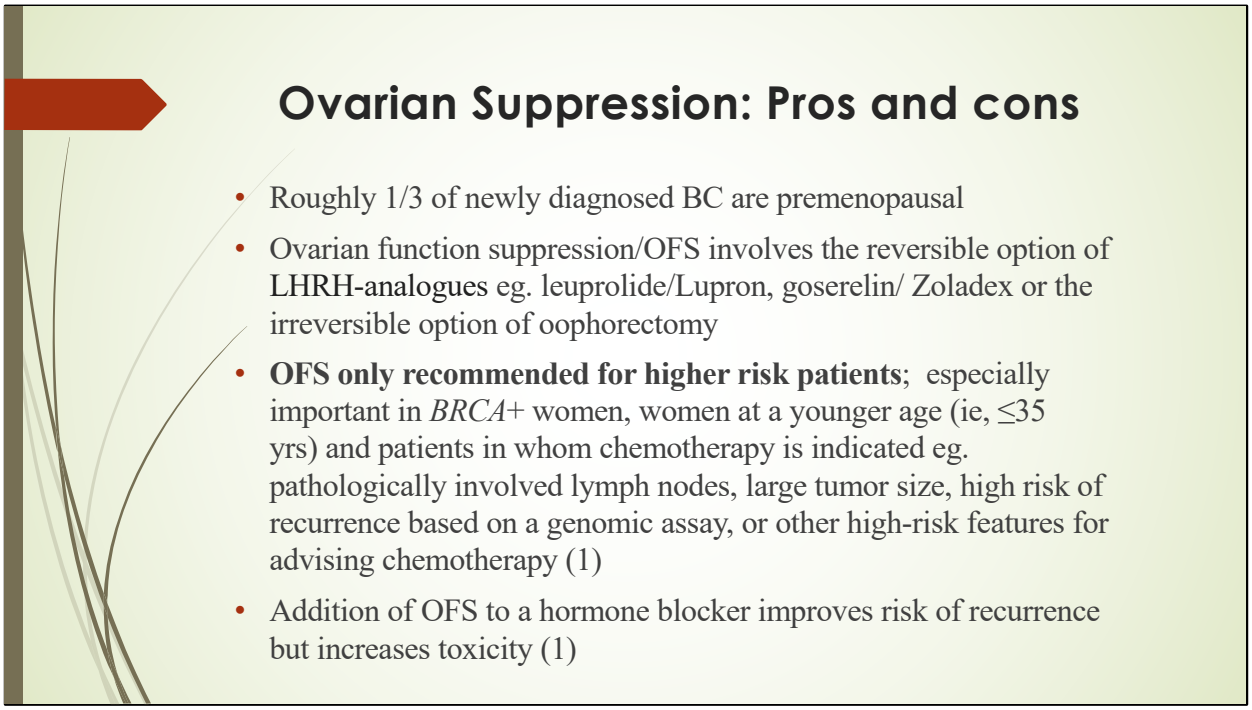
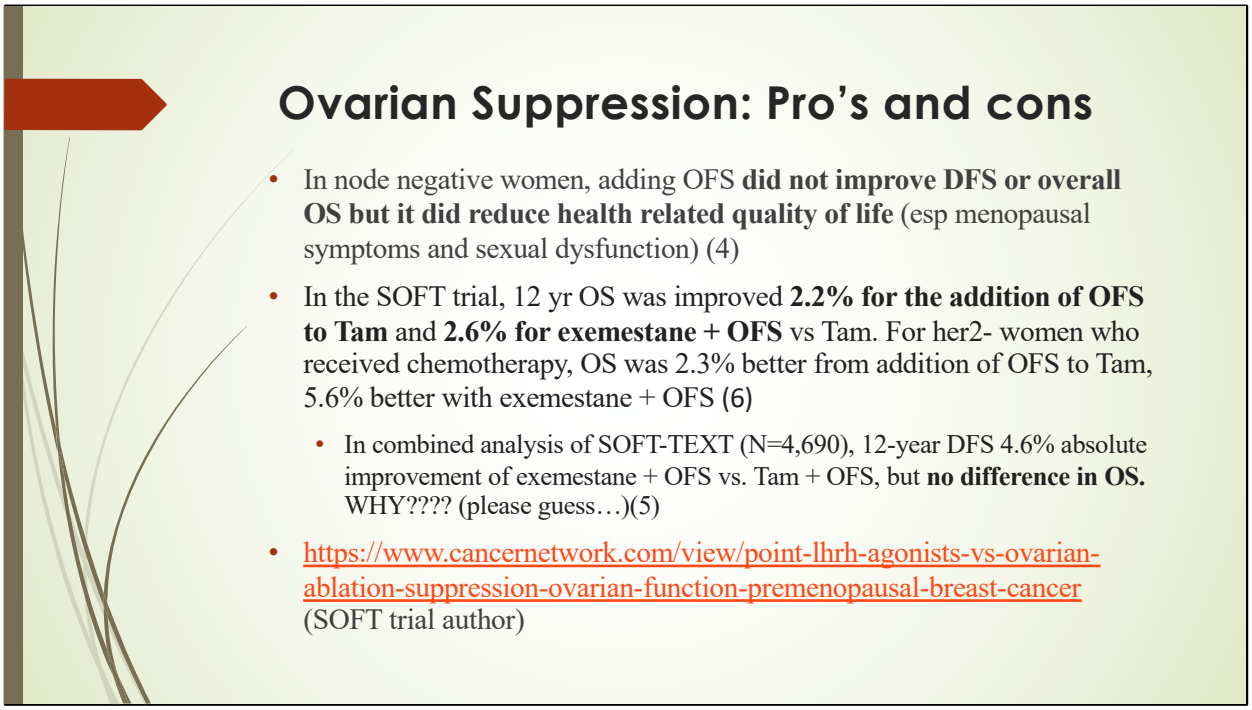


1. **UpToDate.** Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer. Accessed 4/30/20. Claudine Isaacs, MD
2. https://ascopubs.org/doi/abs/10.1200/JCO.19.00126?rfr_dat=cr_pub%3Dpubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&journalCode=jco
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6193457/:
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



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

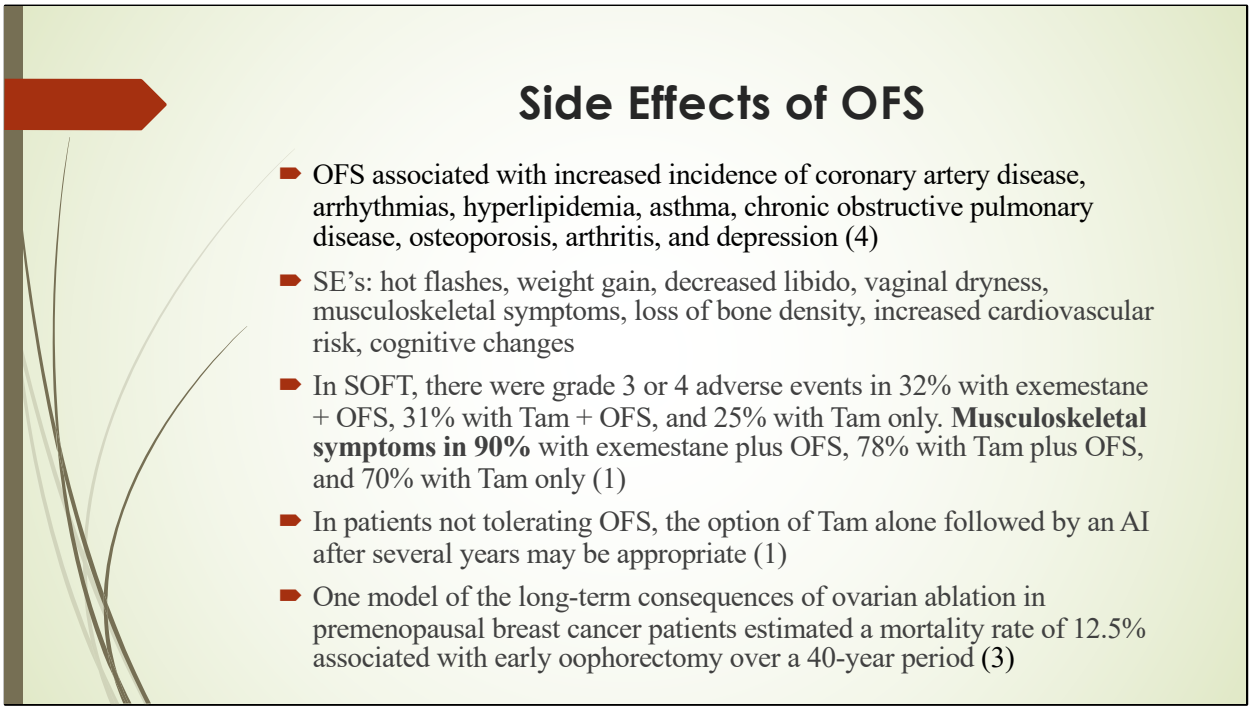
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6193457/: In SOFT trial, 8 yr OS was and 93.3% in the Tam + OFS vs 91.5% in Tam only vs 92.1% with exemestane + OFS . This means the absolute benefit **was 2.1% for the addition of OFS to tamoxifen** and **4.5% for the use of exemestane plus OFS** vs Tam. **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!



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/