



American Society of Clinical Oncology

Making a world of difference in cancer care

***ASCO Clinical Practice
Guideline Update on
Pharmacologic Interventions for
Breast Cancer Risk Reduction***

Update Committee of the Breast Cancer Risk Reduction Expert Panel

Introduction

- The American Society of Clinical Oncology (ASCO) first published evidence-based clinical practice guidelines for breast cancer risk reduction in 1999
- ASCO guidelines are updated at intervals by an Update Committee of the original Expert Panel; the last update was 2002
- For the 2009 update, the Update Committee reviewed literature published since 2002

Guideline Methodology: Systematic Review

- The Update Committee completed a review and analysis of the medical literature available from January 2002 to July 2007 on breast cancer risk reduction.
 - ✓ Medline
 - ✓ Cochrane Collaboration Library

Clinical Questions

This guideline update addresses the following clinical questions:

- In women who were not previously diagnosed with breast cancer, do tamoxifen, raloxifene, aromatase inhibitors, and/or fenretinide reduce the risk of developing breast cancer (invasive or non-invasive) compared to no pharmacologic intervention?
- Factors considered include: disease-specific and overall mortality, type or stage of breast cancer diagnosed, and net health benefit*.

*Net benefit = the potential benefit of chemoprevention after taking into consideration potential harms

Clinical Questions (cont'd)

- What is the comparative efficacy of tamoxifen, raloxifene, aromatase inhibitors, and fenretinide?
- What constitutes effective and responsible communication by physicians of issues regarding breast cancer risk reduction to women eligible to consider use of these agents?

Major clinical trials reviewed

Agent	Trial
Tamoxifen	National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP-P1)
	International Breast Intervention Study (IBIS-I)
	Italian Breast Cancer Prevention Trial
	Royal Marsden Tamoxifen Trial
Raloxifene	Multiple Outcomes of Raloxifene Evaluation (MORE)
	Continuing Outcomes Relevant to Evista (CORE)
	Raloxifene Use for The Heart (RUTH)
Tamoxifen vs. Raloxifene	NSABP Study of Raloxifene and Tamoxifen (STAR)

2009 Recommendation: Tamoxifen

- May be offered to reduce the risk of estrogen receptor (ER) positive invasive breast cancer for **either** premenopausal or postmenopausal women with a 5-year projected breast cancer risk $\geq 1.66\%$ (according to the NCI Breast Cancer Risk Assessment Tool), or with lobular carcinoma in situ (LCIS).
- Risk reduction benefit continues for at least 10 years.
- Impact on breast cancer mortality is unknown.

2009 Recommendation: Tamoxifen (cont'd)

- Tamoxifen may be offered 20 mg/d for five years.
- Tamoxifen is not recommended for women with a prior history of deep venous thrombosis, pulmonary embolus, stroke, or transient ischemic attack.
- Vascular and vasomotor events do not persist post-treatment across all ages.
- Follow-up should include a baseline gynecological examination prior to initiation of treatment and annually thereafter, with a timely work-up of abnormal vaginal bleeding.

2009 Recommendation: Tamoxifen (cont'd)

- Given the inconsistent findings across trials, combined use of tamoxifen with menopausal hormone therapy is not currently recommended, pending results from ongoing trials for clarification.
- Risks and benefits associated with tamoxifen use should be carefully considered during the decision-making process.

Tamoxifen – Efficacy Evidence (tamoxifen vs. placebo trials)

Results	NSABP-P1			IBIS-I			Royal Marsden			Italian
Sample size	6576 (tam) 6599 (pla)			3579 (tam) 3575 (pla)			1238 (tam) 1233 (pla)			2700 (tam) 2708 (pla)
BC Incidence	RR (95% CI)	AR per 1000 **	NNT ***	RR (95% CI)	AR per 1000 **	NNT ***	HR (95% CI)	AR per 1000 **	NNT ***	RR **** (95% CI)
BC overall	NR			0.73 (0.58-0.91)	15	68	0.84 ¹ (0.64-1.10)			0.84 (0.60-1.17)
Invasive BC	0.51 (0.39-0.66)*	15	66	0.74 (0.58-0.94)	12	81	0.78 ¹ (0.58-1.04)			0.80 (0.56-1.15)
ER+	0.31 (0.22-0.45)*	16	63	0.66 (0.50-0.87)	13	80	0.61¹ (0.43-0.86)	26	38	0.77 (0.51-1.16)
ER-	1.22 (0.74-2.03)*			1.00 (0.61-1.65)			1.4 ¹ (0.7-2.6)			1.10 (0.59-2.05)
Non-invasive BC	0.50 (0.33-0.77)*	6	154	0.63 (0.32-1.2) [for DCIS]			NR			1.50 (0.53-4.20)

IBIS-I, Royal Marsden, Italian entire follow-up period; *NSABP-P1 initial follow-up period only (due to unblinding);
 ** AR=Absolute risk difference; ***NNT = number needed to treat; ****Italian – AR/NNT not calculated for NS events
¹Refers to HR

Tamoxifen: Side Effects Evidence (tamoxifen vs. placebo trials)

SIDE EFFECT	Statistic (95% CI)	AR ¹	NNH ²	DETAILS	Trial
VTE	RR=1.72 (1.27-2.36)	14	73	Increase did not persist after treatment	IBIS-I entire period**
Stroke	RR=1.25 (0.55-2.93)			Particular to women ≥ 50	IBIS-I entire period
Endometrial cancer*	RR=2.4 (1.5-4.0) p=.0005 RR=2.53 (1.35-4.97)	6	158	Majority stage 1 adenocarcinomas Seen primarily during active treatment	Cuzick et al. meta-analysis NSABP-P1 initial period***
Cataracts*	RR=1.14 (1.01-1.29) RR=1.92 (1.12 to 3.29)	14	71	During active treatment After treatment	NSABP-P1 initial period IBIS-I post tx. period
Gyn./ Vasomotor symptoms*	RR=1.08 (1.06-1.10)	64	16	Increase did not persist after treatment	IBIS-I entire period
Breast Complaints	RR=0.77 (0.70-0.84)	58	17	Decrease seen in both active and post-tx. periods	IBIS-I entire period

¹ AR=Absolute risk difference; ²NNH = number needed to harm

*significant results versus placebo in ≥1 trial; **IBIS-I entire period – 10 year follow-up (median 8.0 years) - includes 5 years of active treatment; ***NSABP-P1 initial period (median 5 years)

©American Society of Clinical Oncology 2009



2009 Recommendation: Raloxifene

- May be offered to reduce the risk of ER-positive invasive breast cancer in postmenopausal women with a 5-year projected breast cancer risk $\geq 1.66\%$ (according to the NCI Breast Cancer Risk Assessment Tool), or with LCIS.
- Impact on breast cancer mortality is unknown.
- Should not be used for breast cancer risk reduction in premenopausal women.
- May be offered 60 mg/d for five years.

2009 Recommendation: Raloxifene (cont'd)

- May be used longer than five years in women with osteoporosis, in whom breast cancer risk reduction is a secondary benefit.
- Is not recommended for use in women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack.
- Risks and benefits associated with raloxifene use should be carefully considered during the decision-making process.

Raloxifene: Efficacy Evidence (raloxifene vs. placebo trials)

Results	CORE	MORE	RUTH	AR per 1000**	NNT** *
Sample size	5129 (ral) 2576 (pla)	5111 (ral) 2571(pla)	5044 (ral) 5057 (pla)		
BC Incidence	Statistic (95% CI)	Statistic (95% CI)	Statistic (95% CI)		
BC overall	HR=0.42 (0.29-0.60)	RR=0.38 (0.24-0.58)	HR=0.67 (0.47-0.96)	5	200
Invasive BC	HR=0.34 (0.22-0.50)	RR=0.28 (0.17-0.46)	HR=0.56 (0.38-0.83)	7	150
ER+	HR=0.24* (0.15-0.40)	RR=0.16 (0.09-0.30)	HR=0.45 (0.28-0.72)	7	150
ER-	HR=1.06 * (0.43-2.59)	NR	HR=1.44 (0.61-3.36)		
Non-invasive BC	RR=1.12 (0.46-2.73)	NR	HR=2.17 (0.75-6.24)		

*ER status known for only
73% of participants

©American Society of Clinical Oncology 2009

*AR=Absolute risk
difference; **NNT=number
needed to treat



Raloxifene: Side Effects Evidence (raloxifene vs. placebo trials)

SIDE EFFECT	Statistic	AR per 1000*	NNH* *	Study
VTE overall	HR=1.44 (95 CI%: 1.06-1.95)	7	150	RUTH entire period
DVT	P=.002			MORE entire period
PE	P=0.05			CORE entire period
Vasomotor symptoms	P<.001			CORE, MORE, RUTH**
Stroke	NS			Reported in MORE, RUTH
Endometrial cancer	NS			Reported by CORE, MORE, RUTH
Gyn symptoms	NS			Reported by CORE, MORE, RUTH
Cataracts	NS			Reported only in RTH

POSSIBLE ADDITIONAL BENEFIT WITH RALOXIFENE– Reduction in risk of fracture: HR Vertebral Fractures HR= 0.65 (95% CI: 0.47-0.89), AR/1000=7, NNH=138 ,source: RUTH entire period; RR all fractures=0.66 (95% CI: 0.55-0.81) source: MORE entire period; all fractures p<.05 source: CORE entire period

*AR=Absolute risk difference; **NH = number needed to harm; **Entire period of all three trials

©American Society of Clinical Oncology 2009



Raloxifene versus tamoxifen: Efficacy Evidence - STAR trial

Results	Incidence	RR	95% CI
Invasive BC	168 (ral) 163 (tam)	1.02	0.82-1.28
ER+	109 (ral) 115 (tam)	0.94	0.72-1.24
ER-	51 (ral) 44 (tam)	1.15	0.75-1.77
Non-invasive BC	80 (ral) 57 (tam)	1.40	0.98-2.00
DCIS	44 (ral) 30 (tam)	1.46	0.90-2.41
LCIS	29 (ral) 21 (tam)	1.37	0.76-2.54

Raloxifene vs. tamoxifen: Comparison of side effects/QOL (STAR trial)

Side Effect	Agent with statistically significantly more events		RR or effect size	AR per 1000*
	Tamoxifen	Raloxifene		
Benign uterine complaints	X		NR	
Thromboembolic Events	X		RR = 0.70 (95% CI: 0.54-0.91)	5
Cataract	X		RR = 0.79 (95% CI: 0.68-0.92)	12
Gynecological symptoms ¹	X		0.3 (p<.001)	
Vasomotor symptoms ¹	X		0.2 (p<.001)	
Leg cramps ¹	X		0.2 (p<.001)	
Bladder control ¹	X		0.2 (p<.001)	
Musculoskeletal problems ¹		X	<0.1 (p=.002)	
Dyspareunia ¹		X	0.1 (p<.001)	
Weight gain ¹		X	0.1 (p<.001)	

¹STAR QOL analysis - differences associated with small effect sizes; *AR=Absolute risk difference

©American Society of Clinical Oncology 2009



2009 Recommendation: Aromatase Inhibitors and Retinoids

- Aromatase Inhibitor use is not recommended outside of the clinical trial setting to lower breast cancer risk.
- Fenretinide use is not recommended outside of the clinical trial setting to lower breast cancer risk.

Risk Assessment

- Risk assessment models should be used to identify women at increased risk of breast cancer who may benefit from breast cancer risk reduction strategies
- Assess risk periodically – risk estimates change over a woman's lifetime

Note: Risk models developed for population levels have modest discriminatory accuracy for individuals

Risk Assessment Models

MODEL	DETAILS
Gail	A projected 5-year risk of $\geq 1.66\%$ (used by this guideline)
NCI model	Based on the Gail model - for women ≥ 35 years of age (available at: http://dceg.cancer.gov/tools/riskassessment)
CARE	(Women's Contraceptive and Reproductive Experiences) more sensitive estimates for African American women (available at: http://dceg.cancer.gov/tools/riskassessment)

Risk Assessment Models(cont'd)

Additional Models	
MODEL	DETAILS
Women's Health Initiative (WHI)	risk of ER+ breast cancer for women who are postmenopausal
Claus	For women with family history
Tyrer-Cuzick	For women with family history

Risk Communication

Discussions with women at risk should include:

- Estimate of her future risk
 - Explain inherent uncertainties associated with individual prediction
- Expected benefits and risks of risk reduction options
 - Present in both *absolute* and *relative* terms
- Impact of agent(s) on invasive and non-invasive breast cancer and impact on ER+ and ER- breast cancer

Health Disparities

Important to be aware of:

- Disparities regarding access, quality, health insurance
- Women from non-racial/ethnic minority groups and/or insured women are more likely to seek preventive health measures
- Under-representation of non-Caucasian women in breast cancer risk reduction trials

Future directions

- Results forthcoming of trials on aromatase inhibitors and other agents to reduce ER+ invasive breast cancer

Need for:

- Preventive agents for ER- breast cancers
- Improved integration of breast cancer risk assessment and risk communication into clinical practice
- New educational efforts about breast cancer risk reduction options that are geared toward women across racial/ethnic and socioeconomic groups
- New approaches to inform women from all racial, ethnic, cultural, and socioeconomic groups of clinical trial opportunities

Additional ASCO Resources

- The full text of the guideline, this slide set, and additional clinical tools and resources can be found at: <http://www.asco.org/guidelines/bcrr>
- Patient information on the Breast Cancer Risk Reduction Guideline Update can be found at <http://www.cancer.net>



Guideline Update Committee Members

•Kala Visvanathan, MD, MHS, <i>Co-Chair</i>	•Johns Hopkins Medical Institution
•Scott M. Lippman, MD, <i>Co-Chair</i>	•MD Anderson Cancer Center, University of Texas
•Banu Arun, MD	• MD Anderson Cancer Center, University of Texas
•Powel Brown, MD, PhD	•Baylor College of Medicine
•Rowan Chlebowski, MD, PhD	•Harbor UCLA Medical Center
•Nananda F. Col, MD, MPH, MPP	•Maine Medical Center
•Deborah Collyar	•Patient Representative, Patient Advocates in Research
•Jack Cuzick, PhD	•Cancer Research UK

Guideline Update Committee Members (continued)

•Judy Garber, MD, PhD	•Dana-Farber Cancer Institute
•Barnett Kramer, MD , MPH	•National Institutes of Health
•Monica Morrow, MD	•Memorial Sloan Kettering Cancer Center
•Kathleen I. Pritchard, MD	•Sunnybrook
•Mary Ropka, PhD, RN	•Fox Chase Cancer Center
•Carolyn Runowicz, MD	•Neag Comprehensive Cancer Center
•Victor Vogel III, MD	•American Cancer Society
•James L. Wade, MD	•Cancer Care Specialists of Central Illinois

ASCO Guidelines

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.