

Case #5 – Breast Cancer Management during Pregnancy: A Difficult Challenge



Nadia Harbeck

Dept. OB&GYN

**Interdisciplinary Breast Center
Technische Universität München
Munich, Germany**



Frauenklinik und Poliklinik der
Technischen Universität München
Klinikum rechts der Isar
Direktorin: Prof. Dr. M. Kiechle



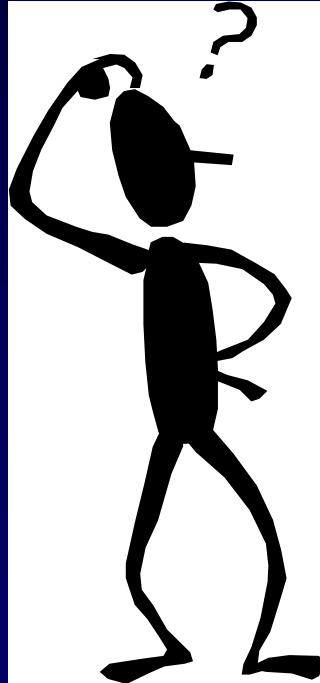
Case #5:

39-year-old professor of sociology, 16 weeks pregnant, pT2, pN1 (1/10), endocrine responsive, HER2 negative

Clinical Questions:

- Terminate pregnancy?
- How to treat BC in pregnancy?
- Endocrine Therapy in premenopausal patients
- Genetic counseling and testing

Case #5: Terminate Pregnancy?



Pregnancy-Associated Breast Cancer: Histopathologic Features

Tumor size, nodal status, and biological features

	BCdP (n = 21)	BCdL (n = 17)
Tumour size, median (range), cm	2.4 (0.8-12)	2.5 (0.2-5.5)
pN0	11	6
pN positive	10	11
ER and PgR negative, %	6	9
ER or PgR positive, %	7	2
G1	2/15	0/16
G2-G3	13/15	16/16
Ki-67 >20%	15/20	14/16
HER2/ <i>neu</i> overexpression	5	3
Peritumoral vascular invasion	9	6

Pregnancy-Associated Breast Cancer*: Outcome

Oxford

LoE

BC during pregnancy / lactation

- **Outcome not compromised**

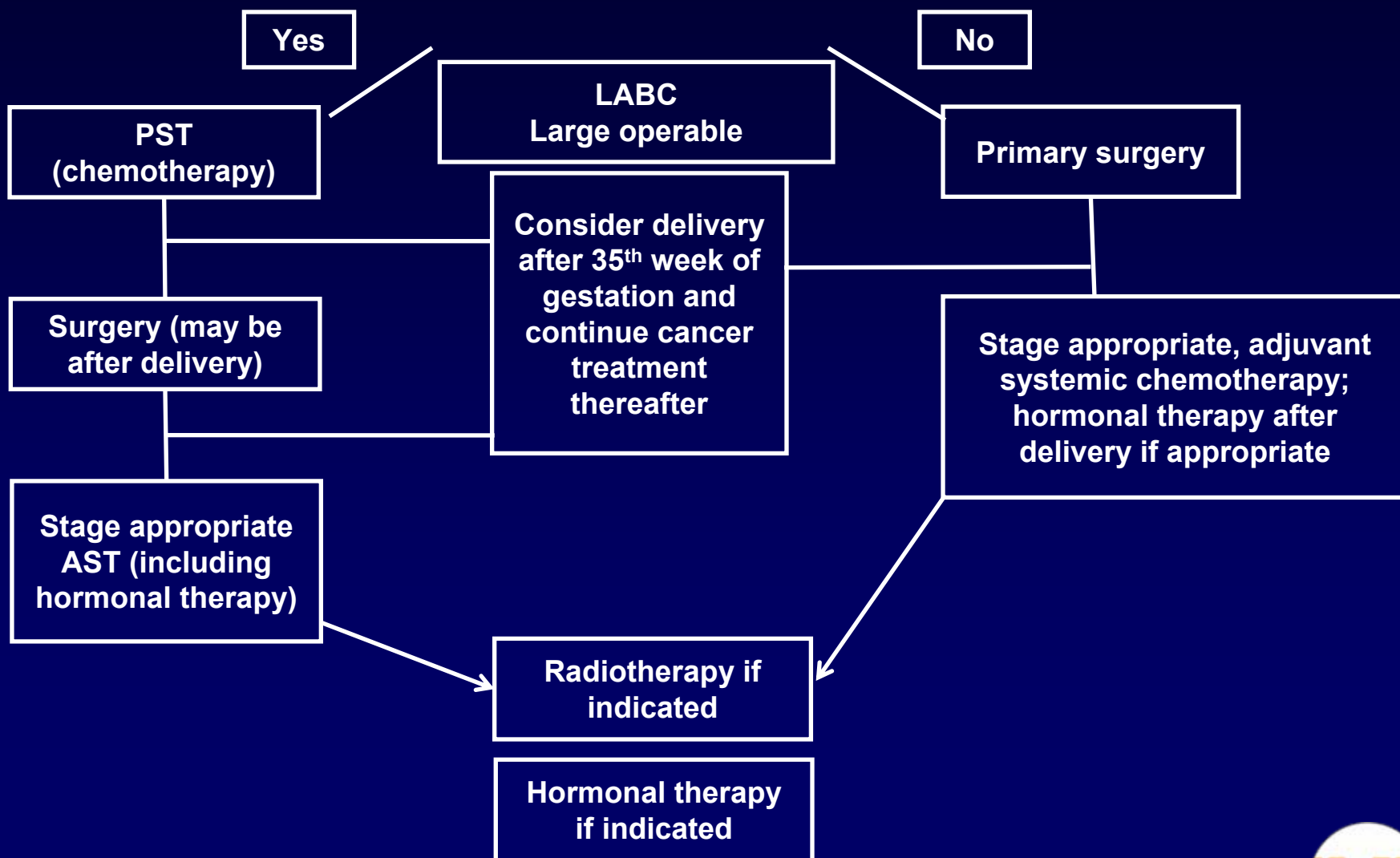
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Pregnancy and lactation after BC

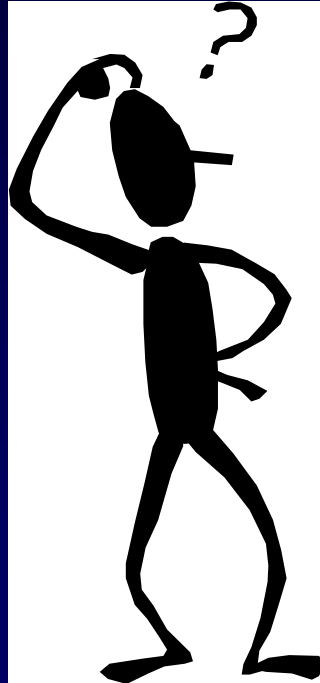
- **Outcome not compromised**

3b

Treatment Algorithm for Breast Cancer During Pregnancy



Case #5: Which Chemotherapy Regimen?



Breast Cancer During Pregnancy*

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➤ Breast imaging & biopsy like in non-pregnant	4	C	++
➤ Staging: ultrasound, chest X-ray if indicated	5	D	+/-
➤ Surgery like in nonpregnant patients	4	C	++
➤ Sentinel node excision (technetium only)	4	C	+/-
➤ Radiation therapy during pregnancy	4	C	-
➤ (Neo)adjuvant chemotherapy only after first trimester (indication as in nonpregnant)			++
➤ AC, FAC, (FEC)	3b	C	++
➤ MTX (eg, CMF)	4	D	--
➤ Taxanes	4	D	-
➤ Endocrine treatment	4	D	--
➤ Trastuzumab	4	D	-

* Participation in register study recommended

Breast Cancer During Pregnancy*

Oxford / AGO

LoE / GR

Delivery should be postponed until sufficient fetal maturation since termination of pregnancy does not improve maternal outcome

4 C ++

**Delivery mode like in nonpregnant;
Avoid delivery ≤ 3 weeks of prior chemotherapy**

4 C ++

If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities

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* Participation in register study recommended

Chemotherapy During Pregnancy

VOLUME 23 · NUMBER 18 · JUNE 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chemotherapy for Breast Cancer During Pregnancy: An 18-Year Experience From Five London Teaching Hospitals

Alistair E. Ring, Ian E. Smith, Alison Jones, Catherine Shannon, Eleni Galani, and Paul A. Ellis

Chemotherapy During Pregnancy

	No of Patients			
	Adjuvant	Neoadjuvant	Palliative	Total
Doxorubicin and cyclophosphamide*	5	4	2	11
Epirubicin and cyclophosphamide†	3	0	2	5
Cyclophosphamide, methotrexate, and fluorouracil‡	9	3	0	12
Total	17	7	4	28

Abbreviation: iv, intravenously

*doxorubicin 50-60 mg/m² iv day 1, cyclophosphamide 600 mg/m² iv day 1, every 3 weeks

†Epirubicin 60-100 mg/m² iv day 1, cyclophosphamide 600 mg/m² iv day 1, every 3 weeks

‡Cyclophosphamide 100-150 mg orally days 1-14, methotrexate 40 mg/m² iv days 1 and 8, fluorouracil 600 mg/m² iv days 1 and 8; every 4 weeks.

Chemotherapy During Pregnancy

Initiation of Epirubicin	First Trimester	Second and Third Trimesters
No. of patients	3	47
Chemotherapy regimen (n)	FEC (2) EC (1)	FEC (9) EC (9) PEV (2) EP (1) VEM (1) Not precised (23)
Median cumulative dose of epirubicin, mg/m ² (range)	100 (100-270)	150 (75-480)

Chemotherapy During Pregnancy (table cont'd)

Initiation of Epirubicin	First Trimester	Second and Third Trimesters
No. of patients	3	47
Pregnancy outcomes		
Spontaneous abortion	2	0
Stillbirth	0	1
Neonatal death, unknown cause	0	1
Malformations	0	1*
Normal	1	44
Delivery		
Vaginal	0	9
C-section	1	22
Not reported	0	16
Prematurity (birth <37 weeks)	1	12

Chemotherapy During Pregnancy: Taxanes

review

Annals of Oncology 19: 607–613, 2008
doi:10.1093/annonc/mdm460
Published online 5 October 2007

Emerging therapeutic options for breast cancer chemotherapy during pregnancy

O. Mir^{1,2*}, P. Berveiller⁴, S. Ropert¹, F. Goffinet³, G. Pons², J.-M. Treluyer² & F. Goldwasser¹

¹Department of Medical Oncology; ²Department of Clinical Pharmacology; ³Department of Obstetrics, Université Paris Descartes—Faculté de Médecine, Hôpital Cochin, Assistance Publique—Hôpitaux de Paris, Paris; ⁴Department of Obstetrics, Hôpital André Mignot, Versailles, France

Received 10 August 2007; revised 16 August 2007; accepted 21 August 2007

Chemotherapy During Pregnancy: Taxanes

References	De Santis et al ¹	Gainford et al ²	Potluri et al ³	Nieto et al ⁴	Sekar et al ⁵	
Age, years	34	44	29	38	35	28
Malignancy	Breast carcinoma	Breast carcinoma	Breast carcinoma stage IIIA	Breast carcinoma stage IIIA	Breast carcinoma	Breast carcinoma
Treatment received during pregnancy	V 25 mg/m ² then D 100 mg/m ² (three cycles)	D 35 mg/m ² weekly (5 weeks)	AC then D 75 mg/m ² q 15 days (four cycles)	Doxorubicine 60 mg/m ² + D 75 mg/m ² (six cycles)	FAC then D 100 mg/m ² (four cycles)	D 190 mg + trastuzumab (three cycles)
Treatment setting	Metastatic	Metastatic	Adjuvant	Neoadjuvant	Neoadjuvant	Metastatic
Initiation of docetaxel, weeks	NR	32	26	14	25	23

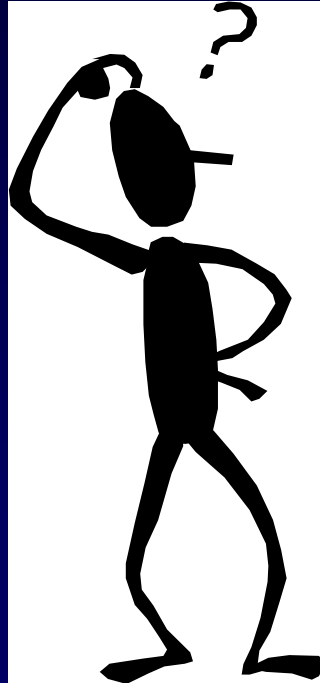
¹De Santis M, et al. *Eur J Cancer Care* 2000;9:235–237. ²Gainford MC, et al. *J Clin Oncol* 2006;18:159. ³Potluri V, et al. *Clin Breast Cancer* 2006;7:167–170. ⁴Nieto Y, et al. *Clin Breast Cancer* 2006;6:533–534. ⁵Sekar R, et al. *Obstet Gynecol* 2007;110:507–510.

Chemotherapy During Pregnancy: Taxanes (table cont'd)

References	De Santis et al ¹	Gainford et al ²	Potluri et al ³	Nieto et al ⁴	Sekar et al ⁵	
Newborn						
Sex	Female	Male	NR	NR	Male	Male
Birth Weight	1620 g (30 th percentile)	NR	NR	NR	3080 g (30 th percentile)	2230 g (5 th percentile)
Neonatal status	Apgar 8, 9	“Healthy”	Hydrocephalia	“Healthy”	“Healthy”	Apgar 7, 9
Follow-up of the offspring	Healthy at 20 months	Healthy at 15 months	Healthy at 28 months	Healthy at 9 months	NR	NR

¹De Santis M, et al. *Eur J Cancer Care* 2000;9:235–237. ²Gainford MC, et al. *J Clin Oncol* 2006;18:159. ³Potluri V, et al. *Clin Breast Cancer* 2006;7:167–170. ⁴Nieto Y, et al. *Clin Breast Cancer* 2006;6:533–534. ⁵Sekar R, et al. *Obstet Gynecol* 2007;110:507–510.

Case #5: Endocrine Therapy?



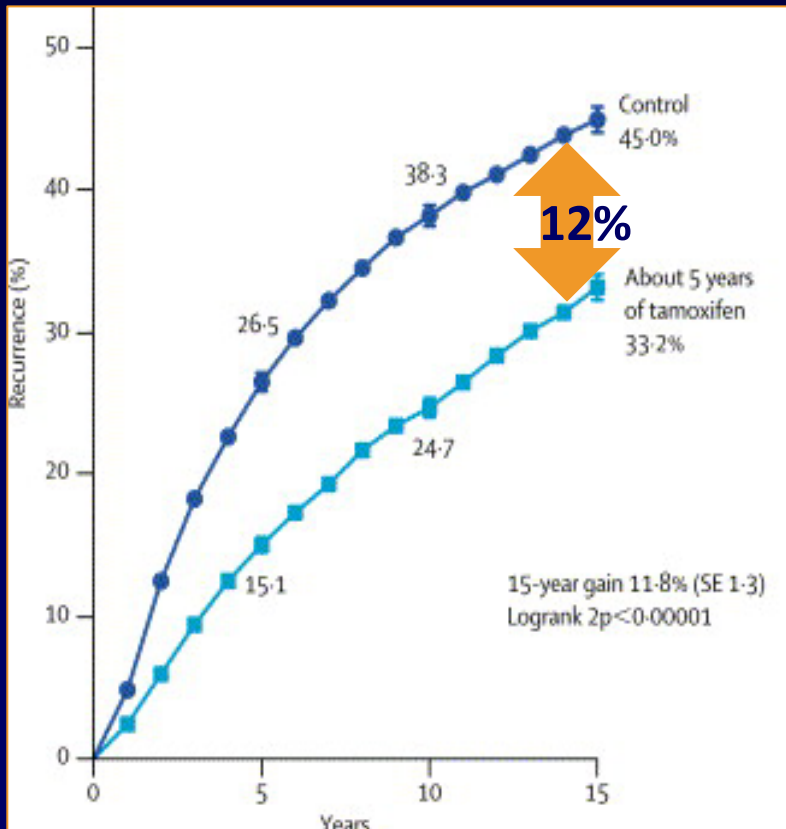
Tamoxifen Efficacy Does Not Differ Significantly According to Patient Age

	Annual Risk Ratio \pm SE			
	Breast Cancer Recurrence Rate		Breast Cancer Death Rate	
	Risk Ratio	SE	Risk Ratio	SE
For all age groups	0.59	0.03	0.66	0.04
Age, years				
<40	0.56	0.10	0.61	0.12
40-49	0.71	0.07	0.76	0.09
50-59	0.66	0.05	0.76	0.07
60-69	0.55	0.05	0.65	0.06
≥ 70	0.49	0.12	0.63	0.15

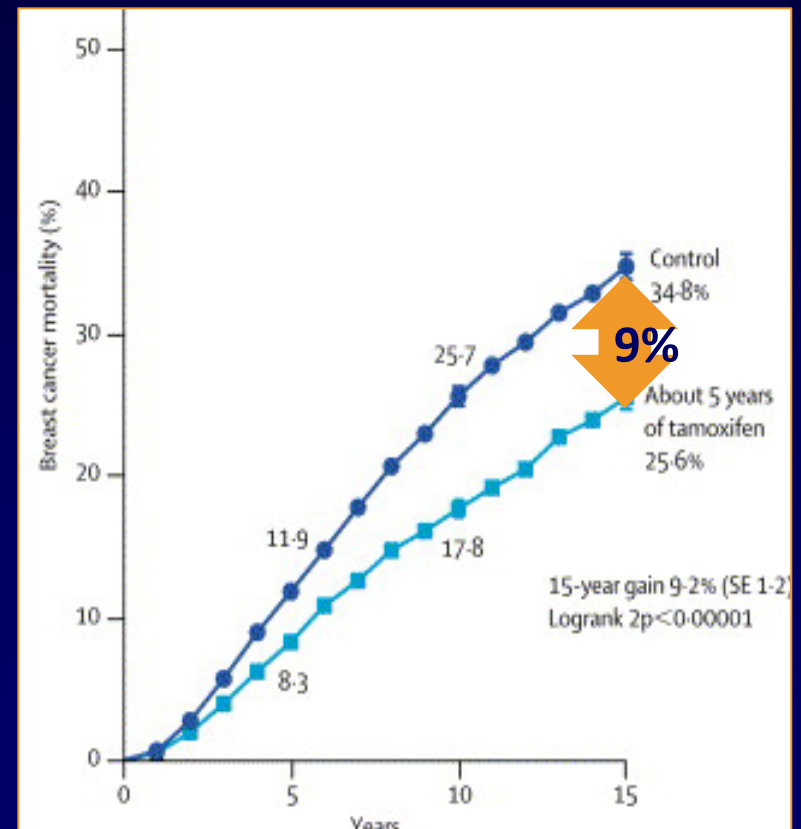
Abbreviation: ER, estrogen receptor

EBCTCG – Tamoxifen

Recurrence



Breast Cancer Mortality



(Chemo-)Endocrine Treatment in Premenopausal Patients

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- **Standard therapy**
- **Chemotherapy** 1a A ++
- **Endocrine responsive tumors**
- **and / or endocrine therapy** 1a A ++

**Indication for endocrine or chemo-endocrine
therapy depends on the individual risk of
recurrence**

(Chemo-)Endocrine Therapy of Premenopausal Patients with Endocrine Responsive Tumors

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➤ High or intermediate risk

➤ Chemo → TAM	1a	A	++
➤ Chemo → TAM + GnRHa	1b	B	+/-*
➤ <40 yrs	2a	C	+*

➤ Low or intermediate risk

➤ TAM alone	1a	A	++
➤ TAM + GnRHa	1b	B	+*
➤ GnRHa alone	1b	B	+/-

* Study participation recommended

Use of Aromatase Inhibitors in Perimenopause: Royal Marsden Experience

45 women, median age 47 (39-52) years with chemotherapy-induced amenorrhea and treated with aromatase inhibitors (AIs) (33 biochemically confirmed ovarian suppression)

- Recovery of ovarian function: 12 (27%)
- Pregnancies 1
- Median duration of amenorrhea: 12 (4-59) months
- Median time on AI: 6 (3-18) months

(Chemo-)Endocrine Therapy of Premenopausal Patients with Endocrine Responsive Tumors

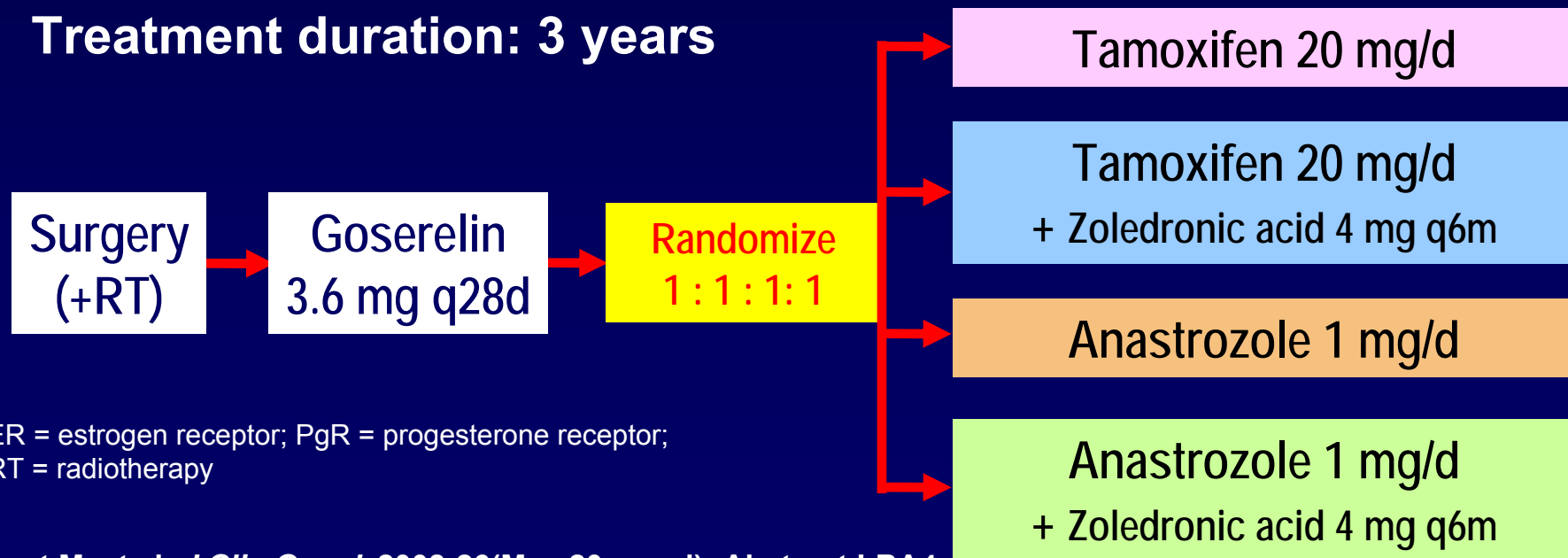
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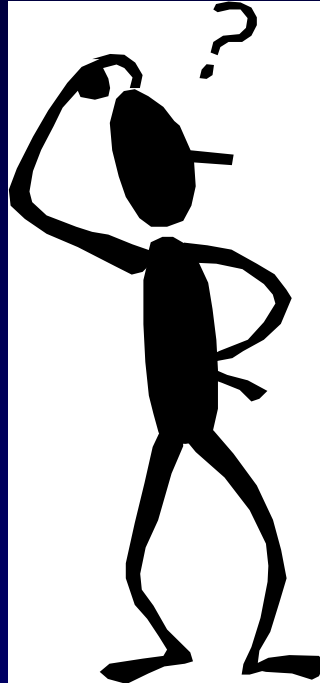
	Oxford LoE / GR	/	AGO
GnRH + AI	5	D	+/-*
AI alone	1c	A	--
AI after GnRHa (induced amenorrhea)	5	D	--
Upfront AI in patients with chemotherapy-induced amenorrhea	4	C	--

Trial ABCSG-12: AIs in Premenopausal Patients/ Does Zoledronic Acid Improve Patients' Outcome?

- Accrual 1999-2006
- 1803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



Case #5: Prophylactic Surgery in BRCA 1/2 Mutation Carriers ?



Who Should be Tested for BRCA1/2 Mutations?

Oxford LoE: 2b

GR: B

AGO: ++

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Families with*

at least two women with breast cancer, one < 51 years

at least one woman affected by breast and one by ovarian cancer

at least one woman affected by breast and ovarian cancer

at least two women affected by ovarian cancer

at least one woman affected by bilateral breast cancer < 51 years

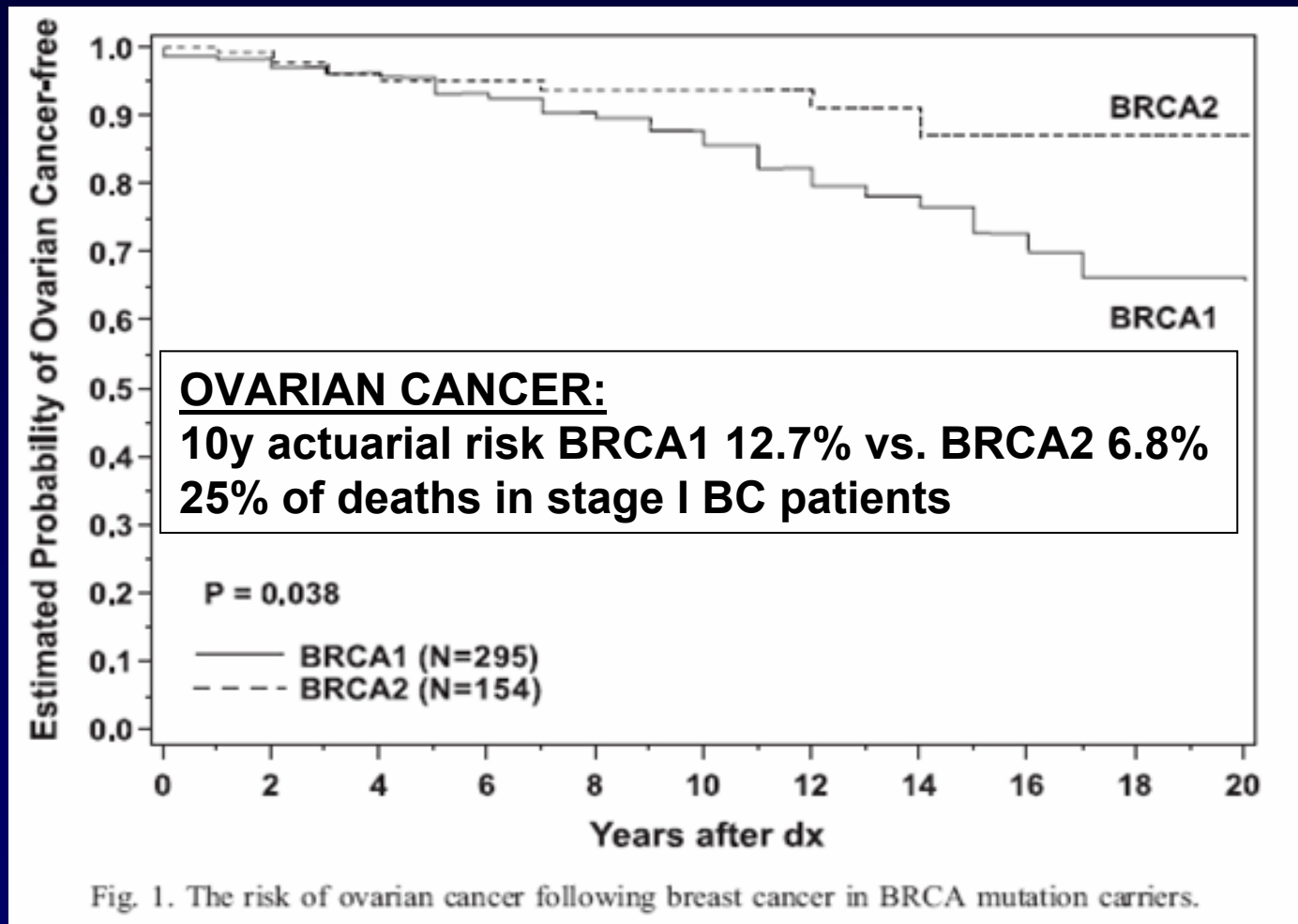
at least one woman affected by breast cancer < 36 years

**at least one man affected by breast cancer and one additional
relative affected by breast or ovarian cancer**

***Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a mutation detection rate $\geq 10\%$**

Risk of Ovarian Cancer in Patients with Primary Breast Cancer (n = 491, MACA Stage I-II; 1975-2000)

Risk of ovarian cancer following breast cancer in BRC mutation carriers



Therapy of BRCA1/2-Associated Breast Cancer

Limited prospective cohort studies with short follow-up time

	Oxford / AGO LoE / GR		
➤ Breast conserving therapy:			
➤ adequate local tumor control (10 years observation)	2a	B	+
➤ Contralateral (cl) mastectomy⁺ :			
➤ reduction of cl BrCa incidence	2b	B	+/-
➤ PBSO⁺:			
➤ reduction of ovarian cancer incidence	2b	B	+
➤ reduction of cl BrCa incidence if performed around the age of 40 years	2b	B	+
➤ Systemic therapy according to sporadic breast cancer	2b	B	+
➤ Platinum-based regimens	3	C	+/-*

+ Overall prognosis has to be considered

* Study participation recommended

In-Breast Recurrence in Women with BRCA1/2 Mutation

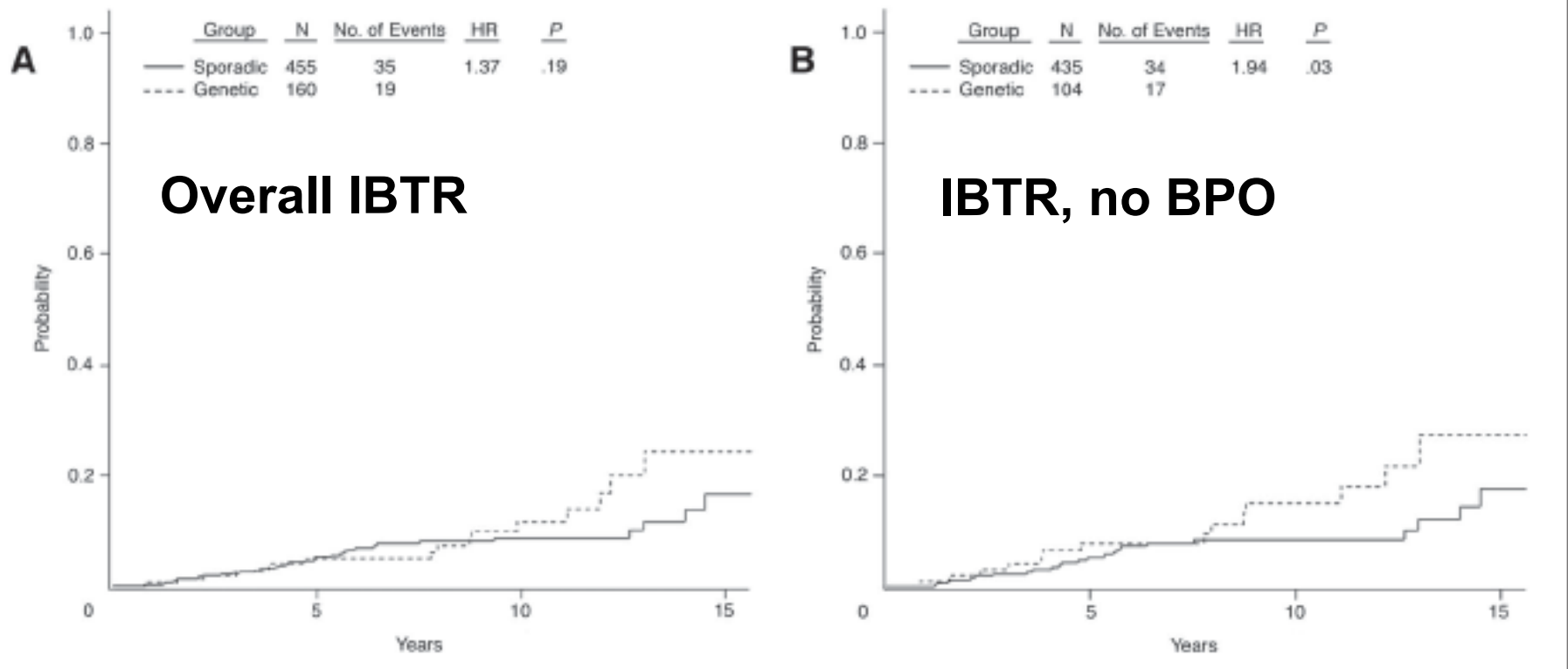


Fig 1. (A) Overall in-breast tumor recurrence in BRCA1/2[r] mutation carriers and sporadic controls. (B) In-breast tumor recurrence in BRCA 1/2 mutation carriers and sporadic controls who have not undergone bilateral prophylactic oophorectomy. HR, hazard ratio.



Contralateral Recurrence in Women with BRCA1/2 Mutation

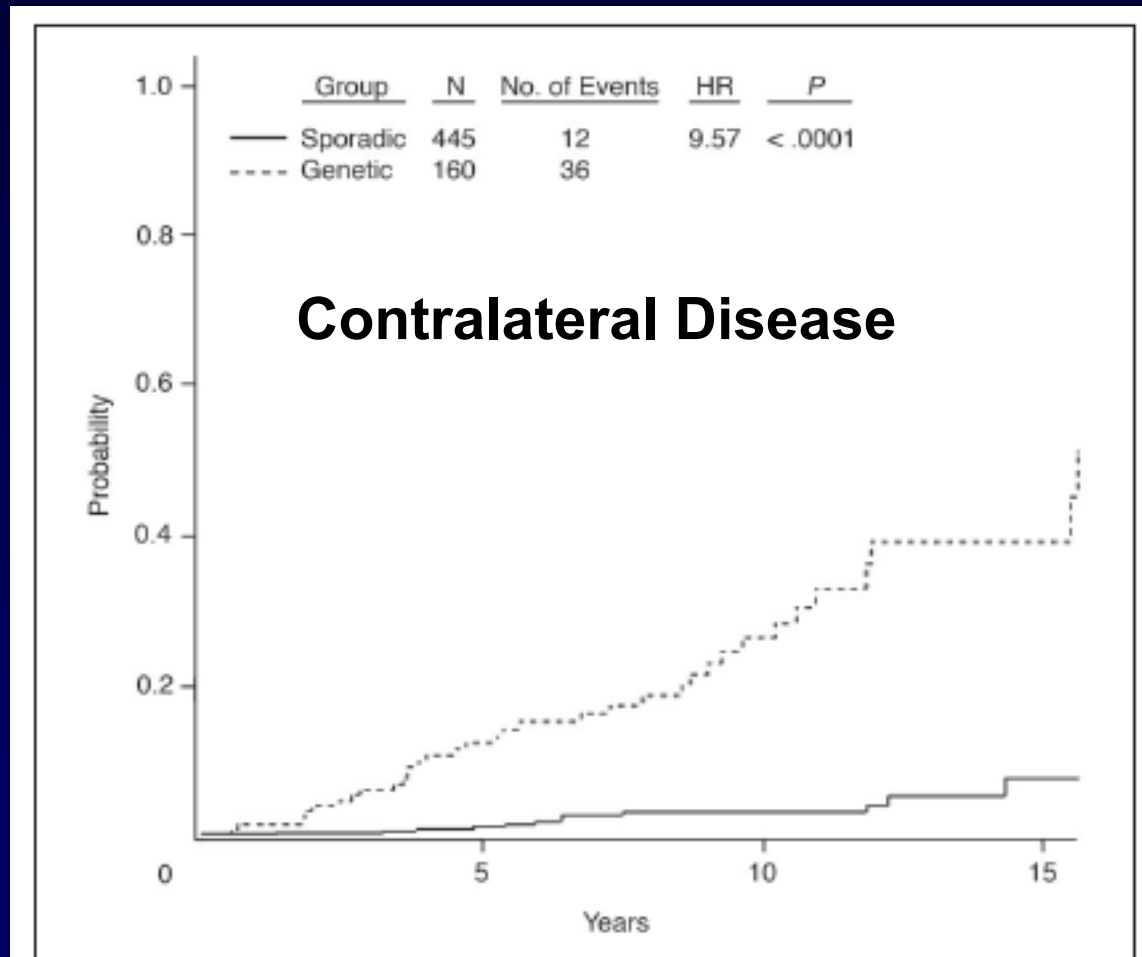
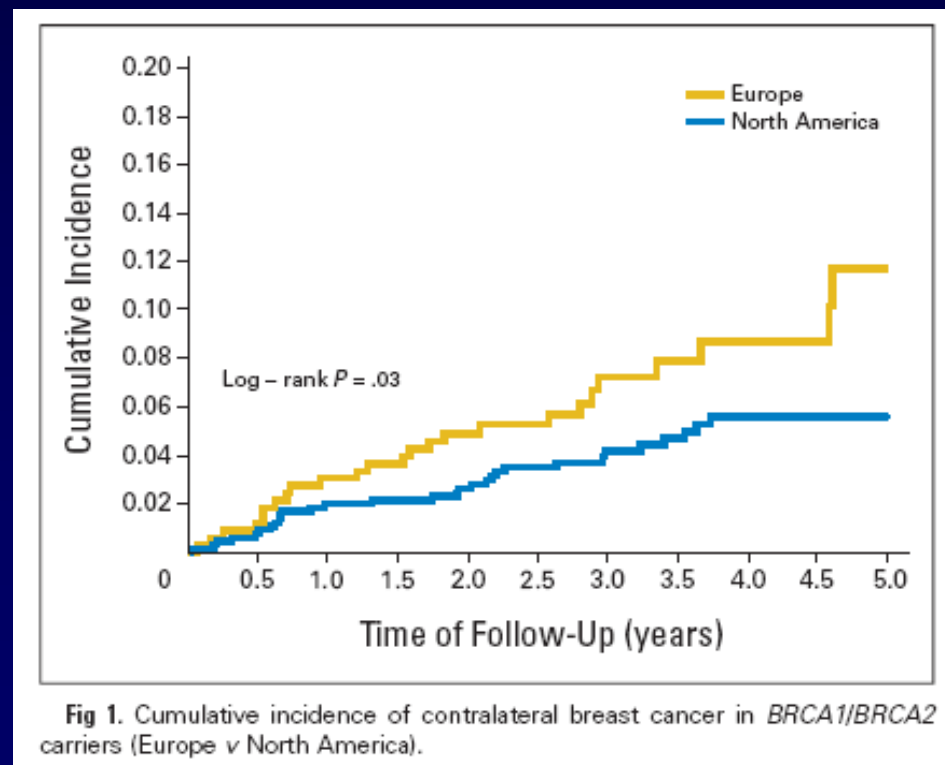


Fig 2. Overall contralateral breast cancers in BRCA1/2[r] mutation carriers and sporadic controls. HR, hazard ratio.

Contralateral Mastectomy in Breast Cancer Patients with Known BRCA1/2 Mutations (n = 927)

- Age, type of initial breast cancer surgery, and prophylactic oophorectomy predictive of prophylactic contralateral mastectomy.
- Acceptance of contralateral preventive mastectomy was much higher in North America (38%) than in Europe (5%).



Risk of Contralateral Breast Cancer

Women with breast cancer have an increased risk for a second primary

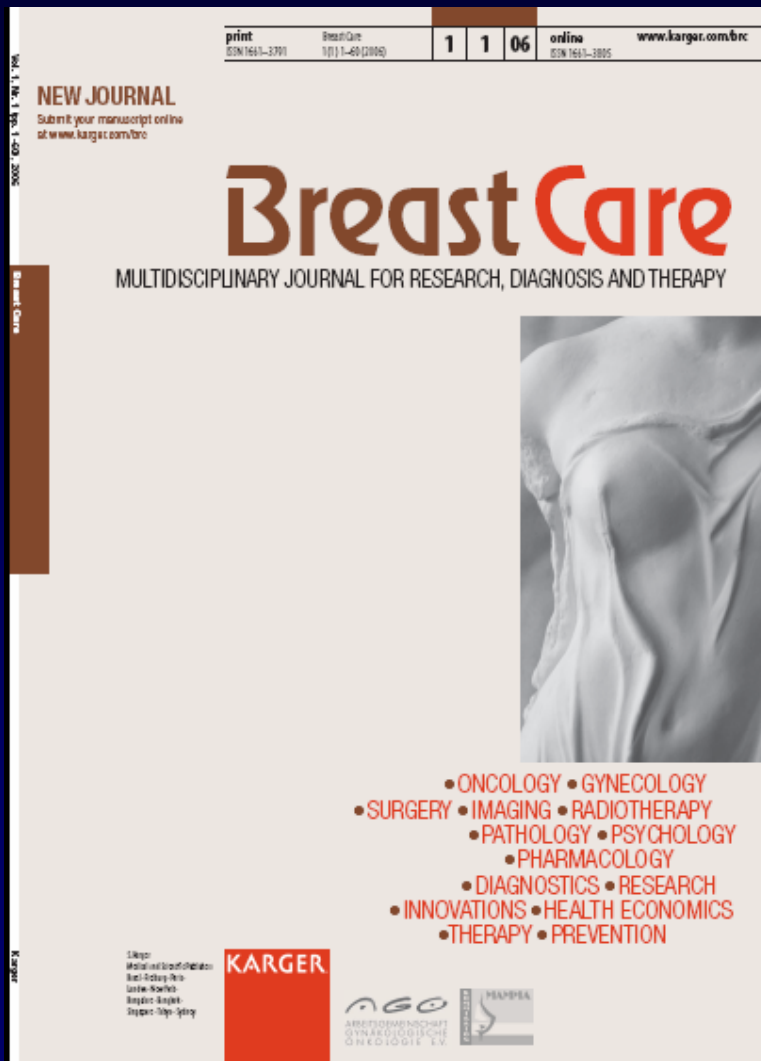
	Oxford / AGO LoE / GR
➤ Tamoxifen*	1a A +
➤ Aromatase inhibitors*	1a A +
➤ Ovarian function* suppression + Tamoxifen	1b B +

***Only proven for HR positive primary sporadic BrCa**

Case #5: My Opinion

- 39-year-old professor of sociology, 16 weeks pregnant, pT2, pN1 (1/10), ER/PR positive, HER2 negative
- **Continue pregnancy**
 - Treat BC according to guidelines
 - Regular prenatal check-ups in specialized center
- **Chemotherapy**
 - Anthracycline-Taxane sequential regimen in N+ patient
 - Taxane after delivery
- **Endocrine therapy**
 - Tamoxifen is gold standard in premenopausal/perimenopausal patients
 - GnRH an additional option in patients < 40 years (after CTx)
 - Consider adjuvant bisphosphonates
- **Genetic testing and counseling**
 - Mutation carriers: Increased surveillance vs prophylactic surgery

Evidence-Based Breast Cancer Therapy



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www.ago-online.org

www.karger.com/brc