SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ADDARII
ONCOLOGIA MEDICA
S.ORSOLA-MALPIGHI BOLOGNA



La donna dopo il cancro: il parere dell'oncologo

Claudio Zamagni
Direttore SSD Oncologia Medica Addarii

Our Voice

MANIFESTO ON BEHALF of YOUNG WOMEN AFFECTED BY BREAST CANCER

For the first time, at the 2016 BCY3 conference the voice of young women affected by breast cancer (YBC) was shared by over twenty patient advocates representing many countries from around the world. Key issues were identified along the continuum of a young woman's journey: from the newly diagnosed, post treatment, long term survivorship and those living with advanced disease.

Advocates identified **five** priority areas of concern for YBC. It is important to note that many of these issues are often amplified for young women diagnosed with metastatic breast cancer:

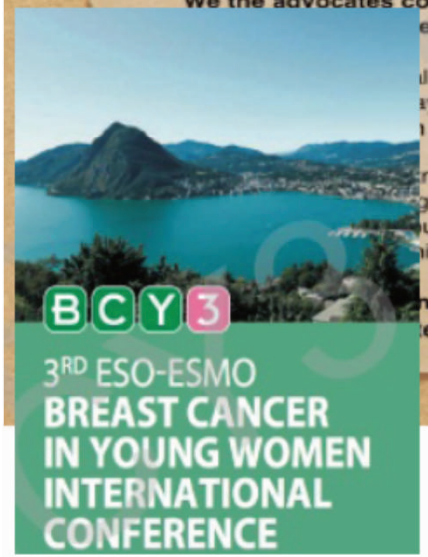
- Quality of life during treatment; importance of a woman's individual needs and preferences guiding treatment decision making
- Post-treatment survivorship and consideration of cancer as a social condition that affects a woman's life beyond diagnosis (financial stability, returning to work, long-term side effects particularly menopausal, fatigue, impact on sexuality and relationships...)
- Fertility preservation and pregnancy related issues for all women, including women with advanced disease
- Clinical trials and research for YBC: ensuring young women with breast cancer are not excluded from RCTs on the basis of age alone
- Professional and/or peer-to-peer psychosocial care for the patient and her immediate network (spouse, partner, family member, friend, children etc.) delivered by a range of modalities that consider individual needs and preferences

We the advocates conclude, if a young woman has consistent and reliable communication with her healthcare provider, e she can overcome many of these areas of concern – no matter where she is in her journey.

l to you, the healthcare provider (physician, nurse, social worker, psychologist, etc.), to recognize the y and be prepared to listen to, advocate for and share resources with the young woman who wants to be her care.

nowledge your contributions and tireless efforts in caring for young women after their diagnosis. We thank ge to continue our advocacy efforts in our respective countries through networking, sharing resources and utreach. Our collaborative efforts aim to empower young women with breast cancer around the world to igh quality care that extends both quality and quantity of life.

ns our conversation. We believe together we are stronger and we thank you for your commitment to ed by breast cancer.



Rango	Maschi			Femmine		
	Età			Età		
	0-49	50-69	70+	0-49	50-69	70+
1°	Testicolo (12%)	Prostata (22%)	Prostata (20%)	Mammella (41%)	Mammella (35%)	Mammella (22%)
2°	Cute (melanomi) (9%)	Polmone (14%)	Polmone (17%)	Tiroide (15%)	Colon-retto (12%)	Colon-retto (17%)
3°	Linfoma non-Hodgkin (8%)	Colon-retto (13%)	Colon-retto (14%)	Cute (melanomi) (7%)	Utero corpo (7%)	Polmone (7%)
4°	Colon-retto (8%)	Vescica* (10%)	Vescica* (12%)	Colon-retto (4%)	Polmone (7%)	Pancreas (5%)
5°	Tiroide (8%)	Vie aerodigestive superiori** (5%)	Stomaco (5%)	Utero cervice (4%)	Tiroide (5%)	Stomaco (5%)

TABELLA 7. Primi cinque tumori in termini di frequenza e proporzione sul totale dei tumori incidenti (esclusi i carcinomi della cute) per sesso e fascia di età. Pool AIRTUM 2008-2013.

*Comprende sia tumori infiltranti sia non infiltranti.

**Comprende lingua, bocca, orofaringe, rinofaringe, ipofaringe, faringe NAS, laringe.

Rango	Maschi	Femmine	Tutta la popolazione
1°	Polmone (27%)	Mammella (17%)	Polmone (20%)
2°	Colon-retto (11%)	Colon-retto (12%)	Colon-retto (11%)
3°	Prostata (8%)	Polmone (11%)	Mammella (8%)
4°	Fegato (7%)	Pancreas (7%)	Stomaco (6%)
5°	Stomaco (6%)	Stomaco (6%)	Pancreas (6%)

TABELLA 9. Prime cinque cause di morte oncologica e proporzione sul totale dei decessi oncologici per sesso. Pool AIRTUM 2008-2013.

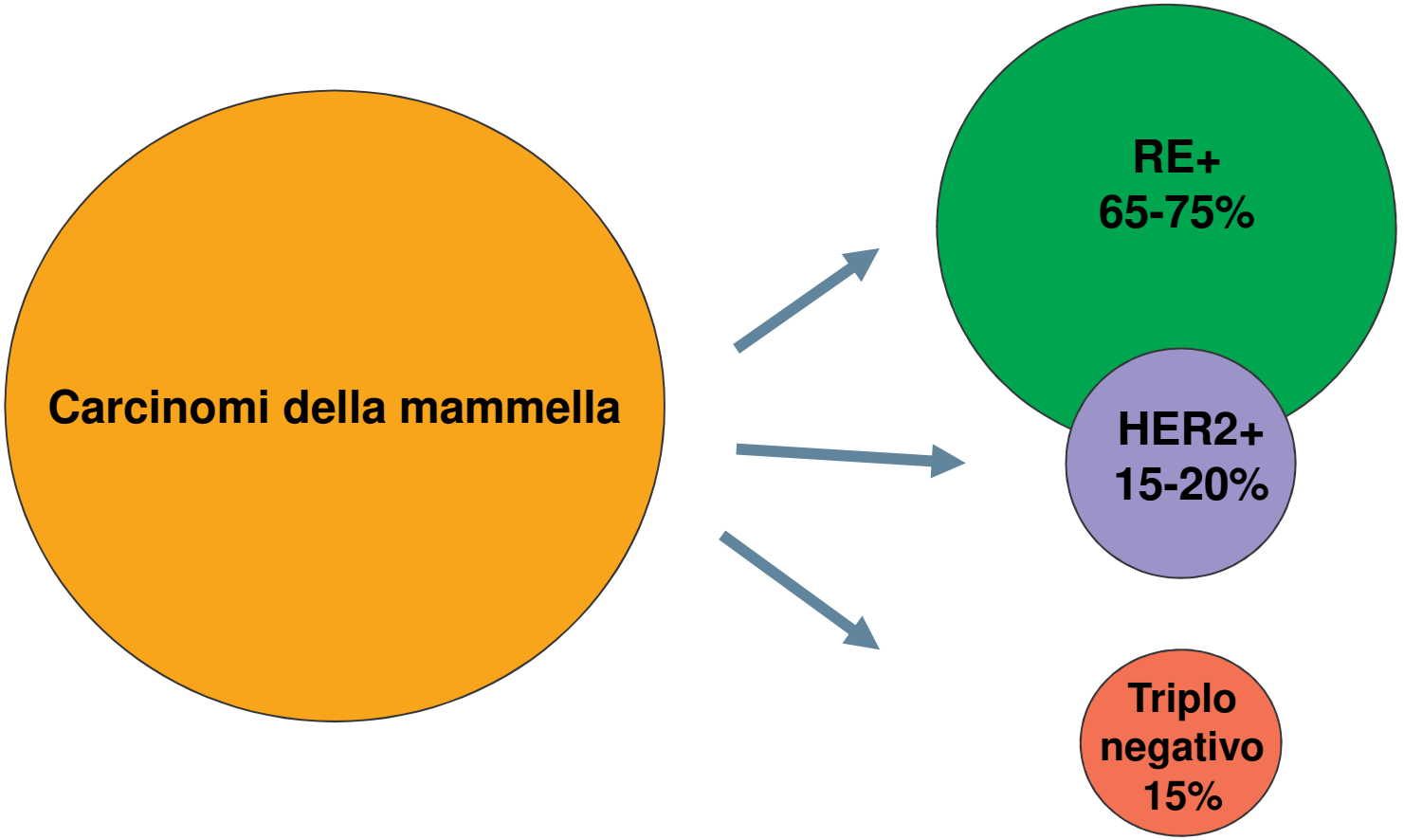
Femmine		
Età		
0-49	50-69	70+
Mammella (29%)	Mammella (22%)	Mammella (15%)
Polmone (9%)	Polmone (14%)	Colon-retto (13%)
Colon-retto (7%)	Colon-retto (10%)	Polmone (10%)
Ovaio (6%)	Pancreas (7%)	Pancreas (8%)
Sistema nervoso centrale (6%)	Ovaio (7%)	Stomaco (7%)

I numeri del cancro della mammella in Italia

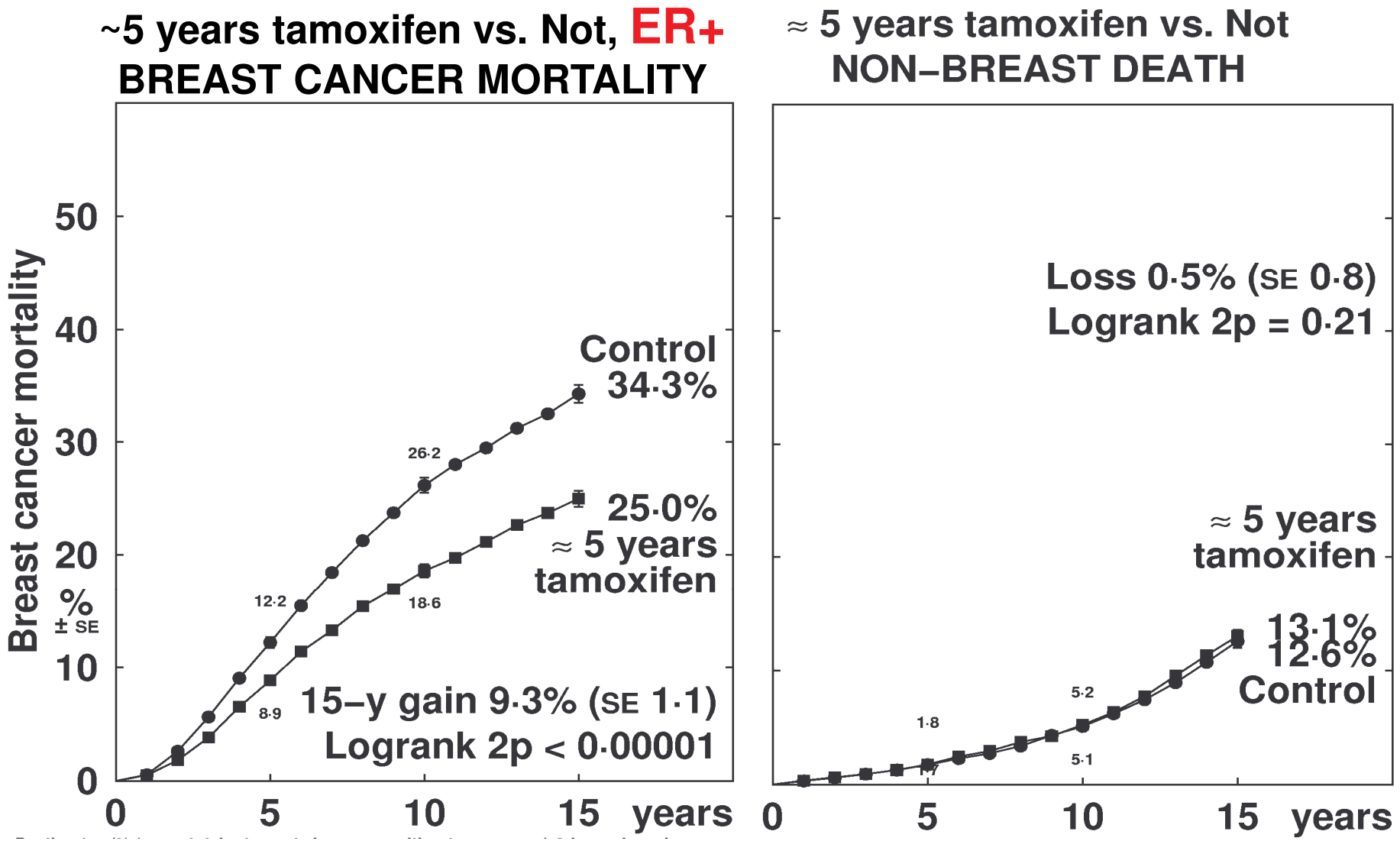
1 donna su	8
nuovi casi/anno	50.000
decessi/anno	12.000
sopravvivenza a 5 a.	87%
sopravvivenza a 10 a.	80%
donne vive con diagnosi	760.000

AIOM/AIRTUM 2017

Non una, ma diverse malattie



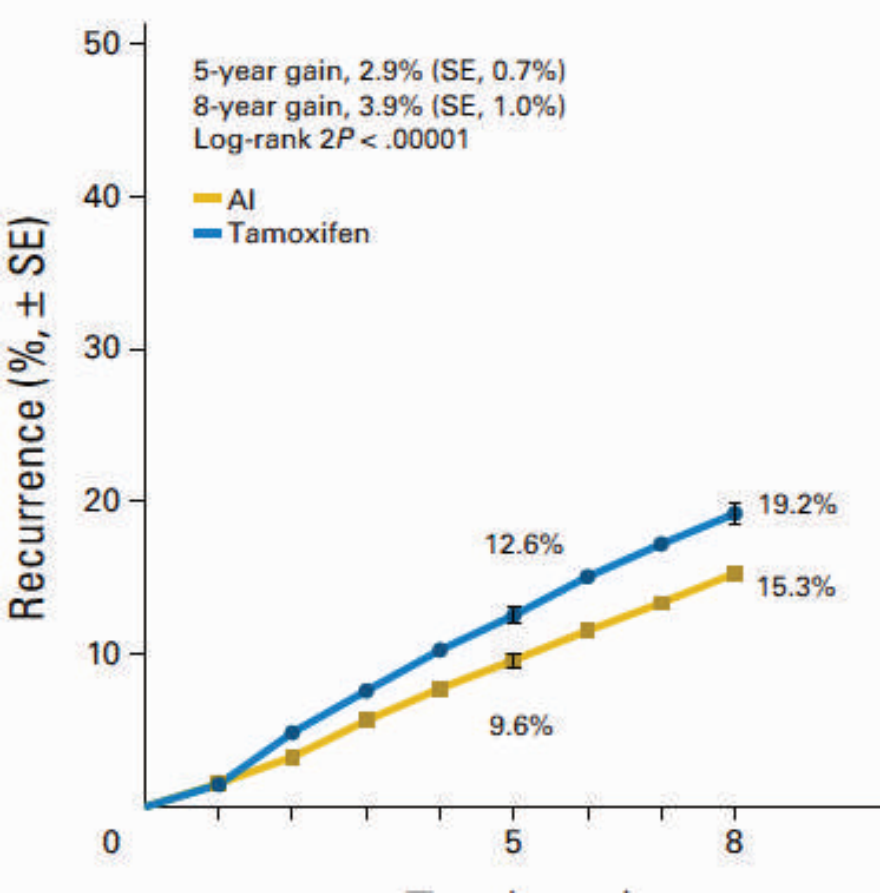
~5 years tamoxifen vs not: MORTALITY



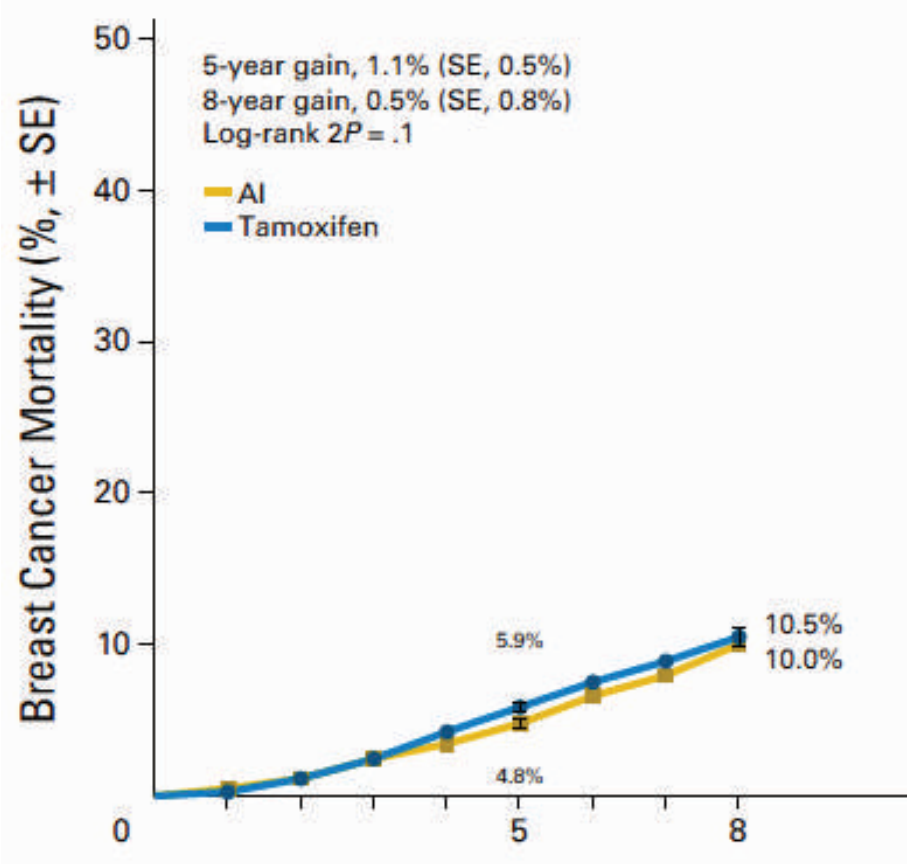
EBCTCG

~5 years of AI vs. ~5 years of tamoxifen:

Recurrence

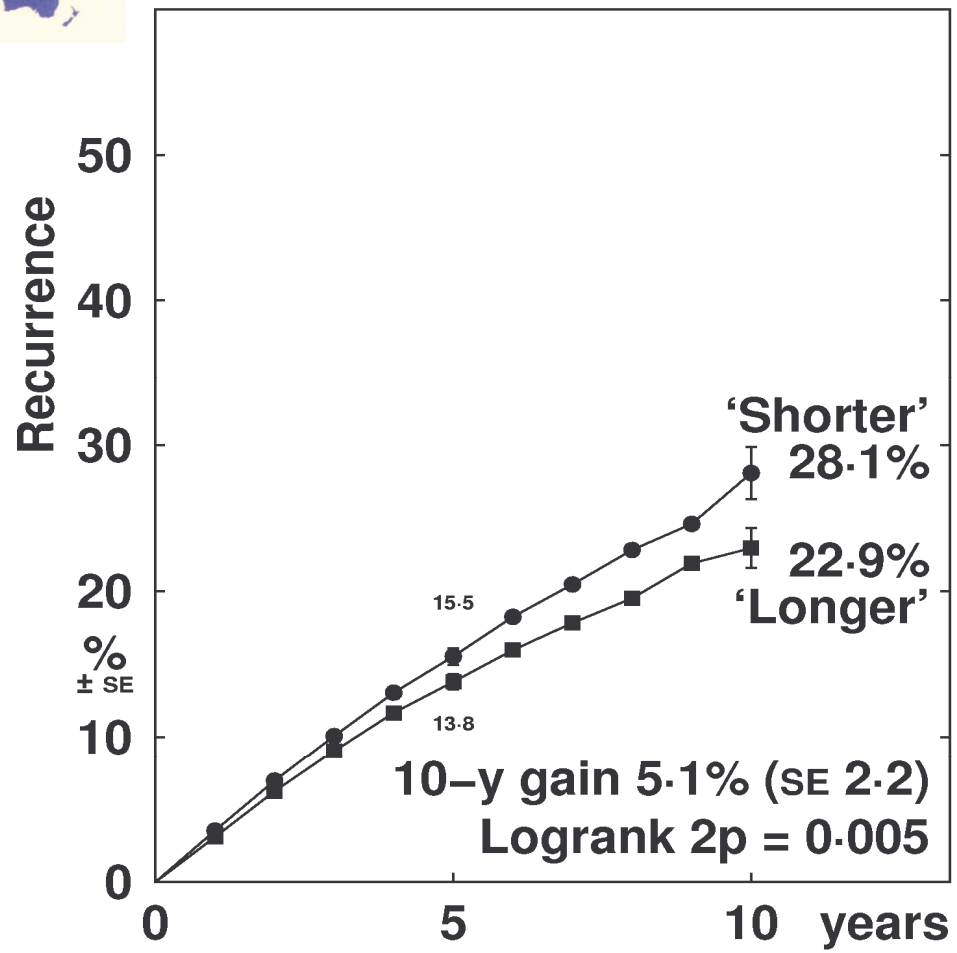


Breast cancer death



AIOG, J Clin Oncol 2011

ATLAS alone: ~10 vs ~5 years: recurrence in ER+ / ER?



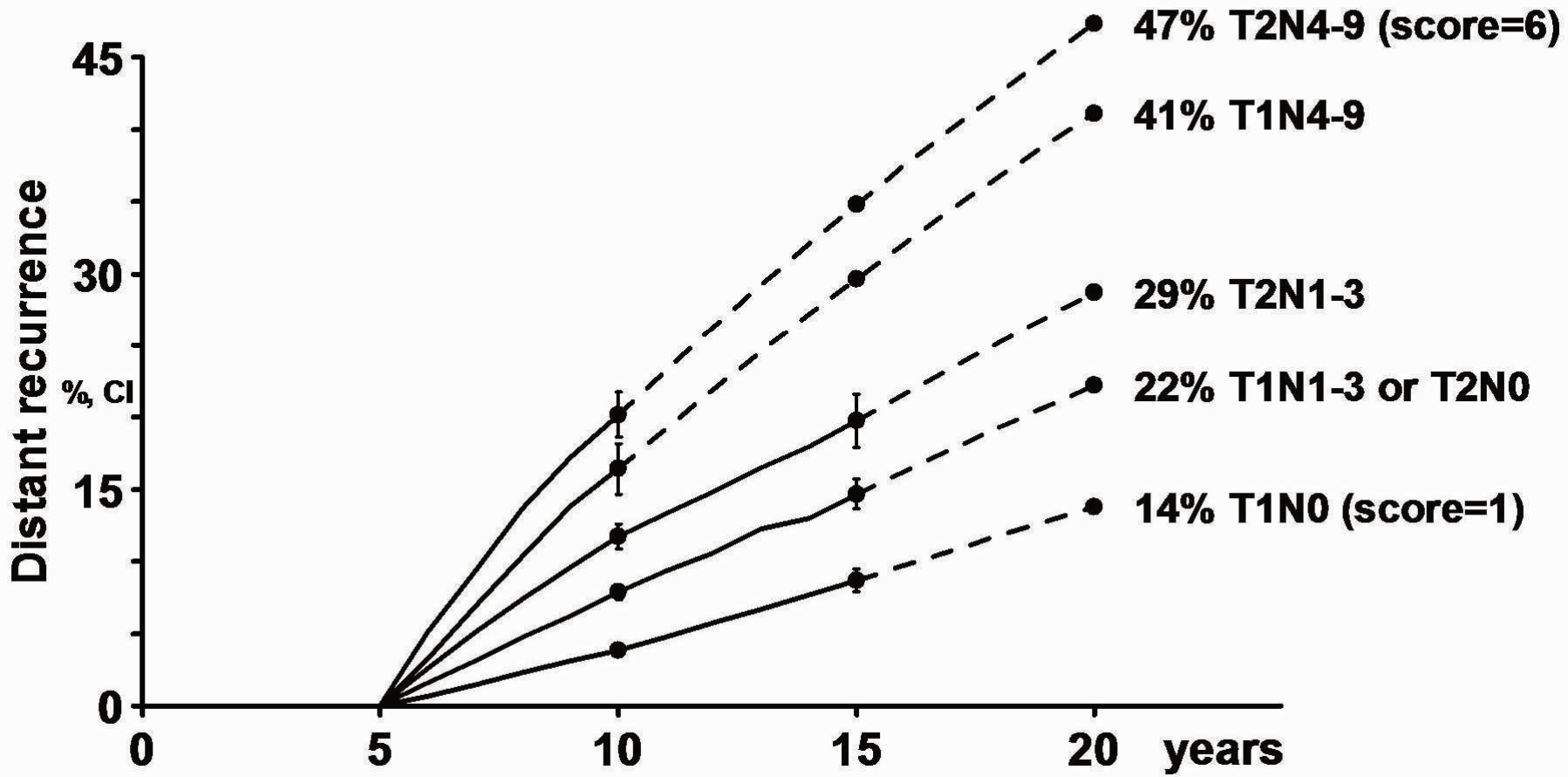
Recurrence rates (% / year) and logrank analyses

	Years 0 – 4	Years 5 – 9	Year 10+
'Longer'	3·03 (643 / 21196)	2·42 (95 / 3919)	4·17 (1 / 24)
'Shorter'	3·45 (710 / 20585)	3·03 (114 / 3767)	5·56 (1 / 18)
Rate ratio, from	0·88 SE 0·05	0·78 SE 0·12	0·32 SE 0·95
(O–E) / V	–41·2 / 326·8	–12·6 / 50·7	–0·4 / 0·4

R. Gray Addarii Lecture 2015

Effect of additive "T+N score" (range 1-6)

Score: 1/ 2 for T1/ T2, plus 0/ 1/ 4 for N0/ N1-3/ N4-9



Presented By Hongchao Pan at 2016 ASCO Annual Meeting

2018 Ormonoterapia adiuvante (solo RE+)
5-10 anni

PRE/PERIMENOPAUSA

Tamoxifene +/- LHRHa

IA + LHRHa

TAM → IA (+/- LHRHa)

POSTMENOPAUSA

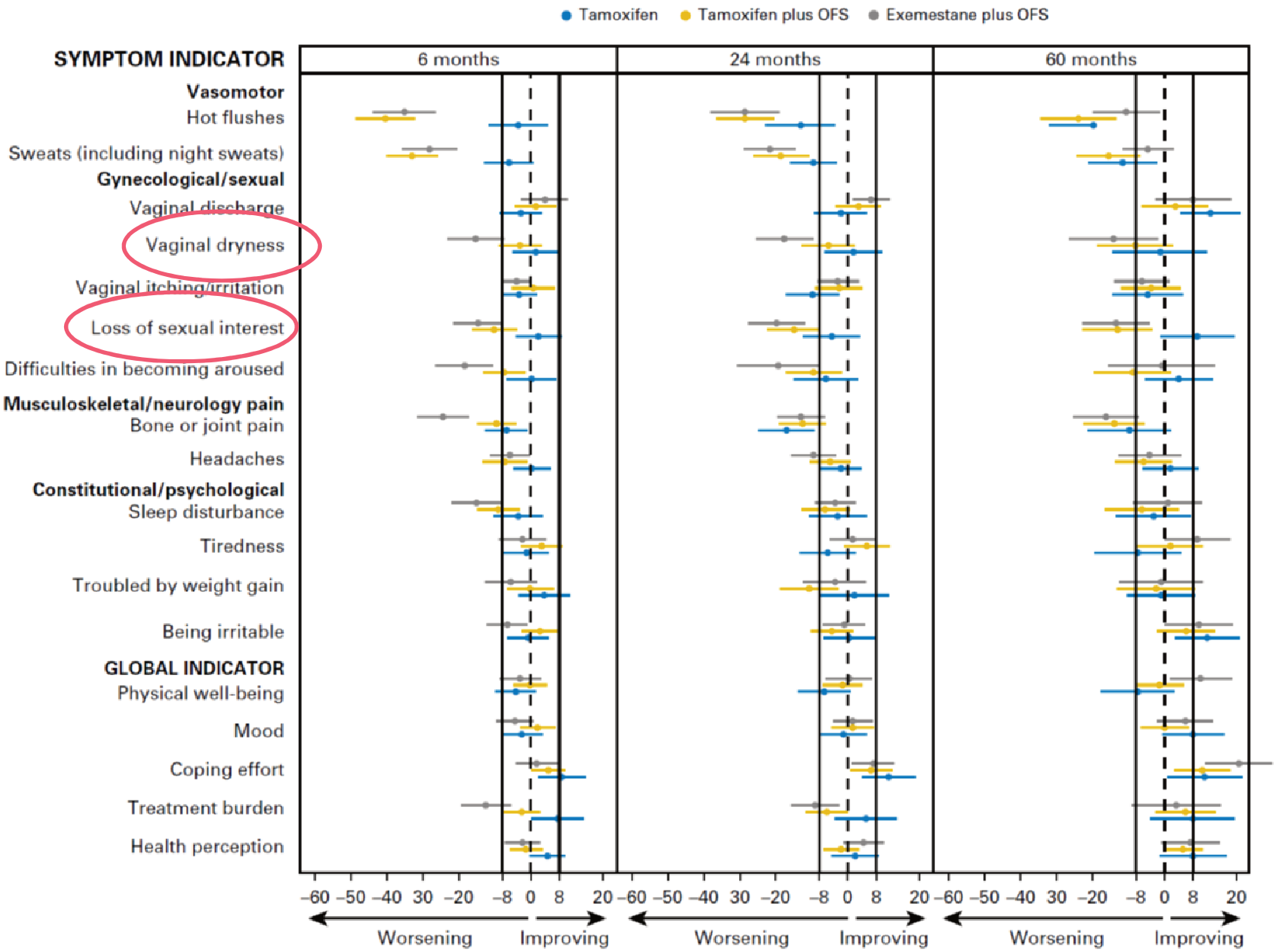
IA

TAM

TAM → IA

IA: inibitori aromatasi anastrozolo, letrozolo, exemestane
LHRHa: goserelin, leuprorelin, triptorelin

Patient-Reported Outcomes in the SOFT and TEXT trial

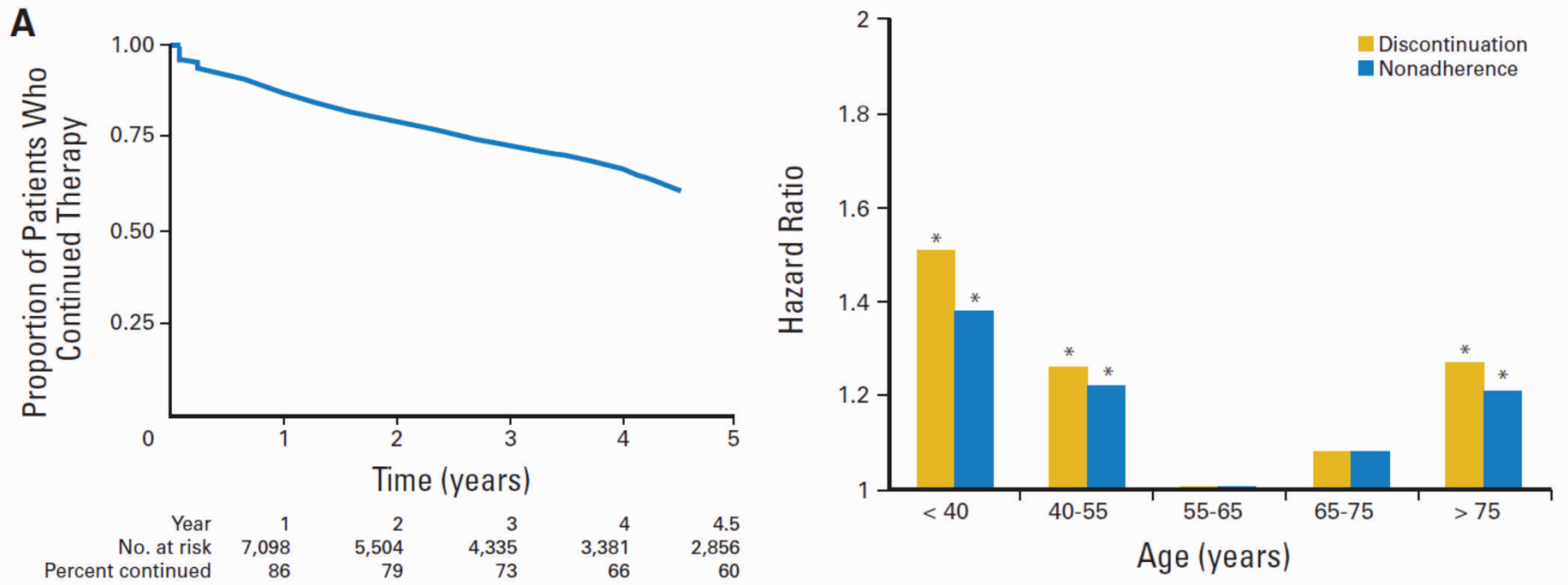


TEXT and SOFT Trials: Grade 3/4 AEs With OFS + Tamoxifen or Exemestane

Adverse Event, %	Exe + OFS SOFT[1]	Tam + OFS SOFT[1]	Tam + OFS TEXT[2]	Tam SOFT[2]
Any	30.6	29.4	31.3	23.7
Musculoskeletal	11.0	5.2	5.5	6.3
Insomnia	3.8	4.3	2.9	4.6
Hot flashes	10.0	12.0	13.2	7.6
Osteoporosis	0.4	0.3	0.3	0.1
Decreased libido (any grade)	45.0	40.9	47.5	42.4
Vaginal dryness (any grade)	52.4	47.4	49.8	41.8
Depression	3.8	4.4	4.4	3.8

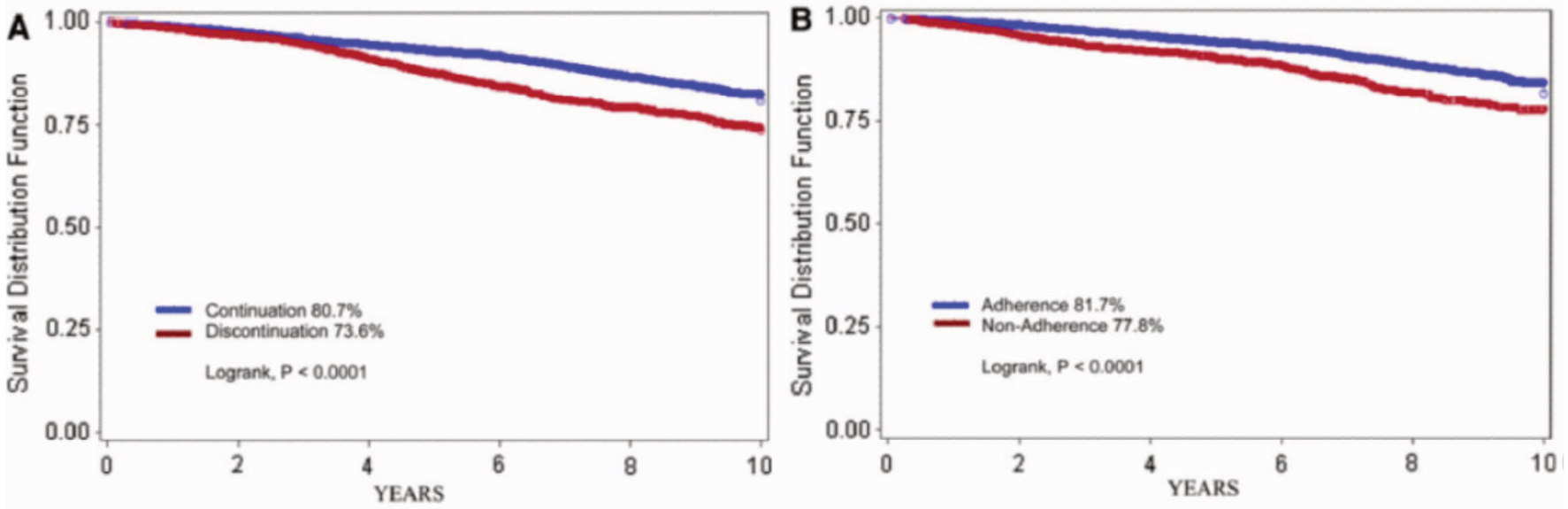
1. Pagani O, et al. N Engl J Med. 2014;371:107-118. 2. Francis PA, et al. N Engl J Med. 2015;372:436-446.

Early Discontinuation and Nonadherence to Adjuvant Hormonal Therapy in a Cohort of 8,769 Early-Stage Breast Cancer Patients



Hershman DL et al JCO 2010

Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer Dawn L. Hershman, *Breast Cancer Res Treat.* 2011 April ; 126(2): 529–537.



Both early discontinuation and non-adherence to HT were common and associated with increased mortality. Interventions to improve continuation of and adherence to HT may be critical to improve BC survival.

Review Article

Sexuality, fertility and pregnancy following breast cancer treatment

Mary Lopresti[1,2], Tina Rizack[2], Don S. Dizon[1,2]

[1]Lifespan Cancer Institute, [2]The Warren Alpert Medical School of Brown University, Providence, RI, USA

Gland Surgery, Vol 7, No 4 August 2018

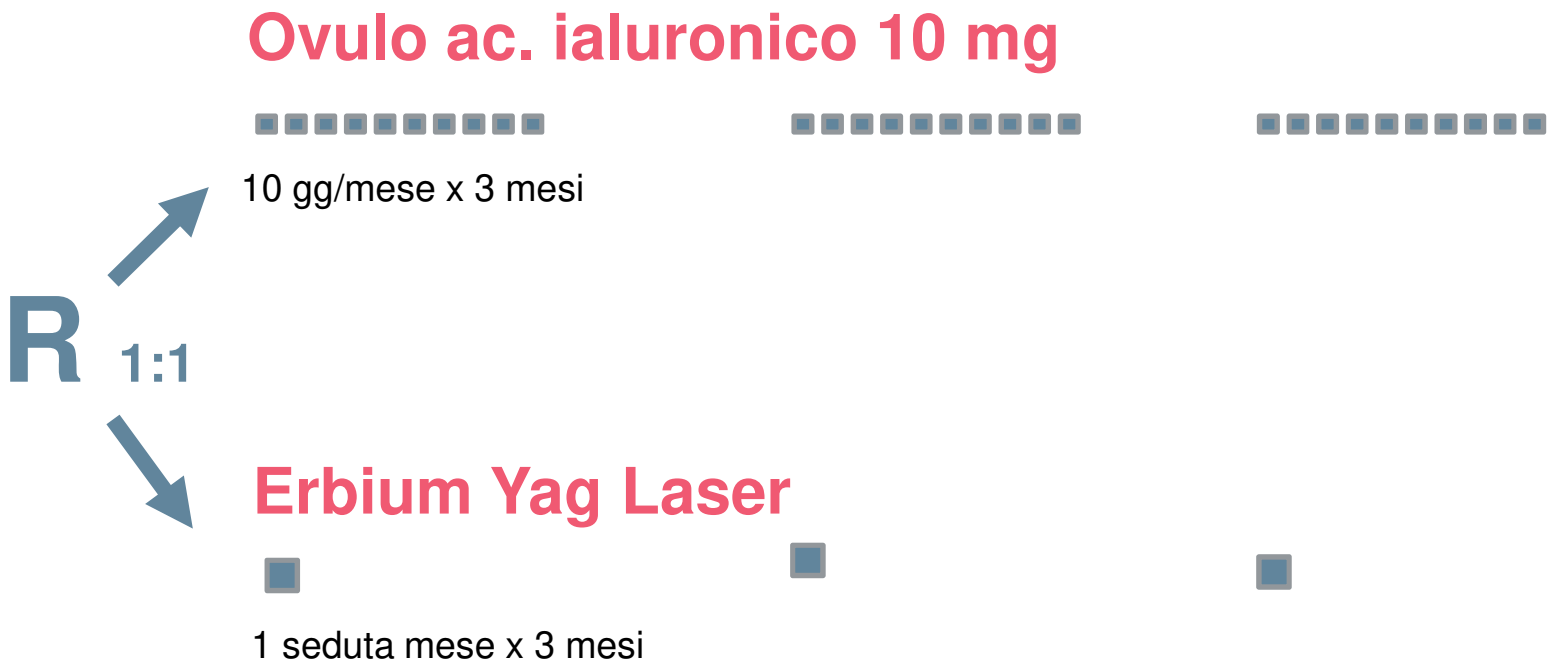
Table 1 An approach to sexual health concerns in women following a diagnosis and treatment of cancer

Symptom	Therapeutic intervention
Genitourinary symptoms of menopause (GSM)	Vaginal moisturizers;
	Vaginal dehydroepiandrosterone (DHEA);
	Low-dose vaginal estrogen;
	Testosterone;
	Experimental: CO_2-laser therapy
Sexual dysfunctions	
Vestibular tenderness	4% aqueous lidocaine
Vaginal dyspareunia	Vaginal dilators (plus lubricant)
Intimacy	Sensate focusing

ELISA

Studio prospettico randomizzato di confronto tra laserterapia **E**rbium Yag Fotona ed applicazione **L**ocale di acido **I**aluronico nel trattamento della disfunzione **S**essuale da **A**trofia vaginale indotta dall'ormonoterapia adiuvante in donne operate per carcinoma mammario

Pz eligibili: OT adiuvante per ca.mammella, secchezza vulvo-vaginale e FSFI ≤ 26.55, consenso informato



P.I: S. Alfieri, C. Zamagni

Carcinoma mammario e gravidanza

- Carcinoma mammario *in* gravidanza
- Gravidanza *dopo* il carcinoma mammario

Breast cancer *during* pregnancy

Pregnancy-Associated Breast Cancer (PABC) is defined as

breast cancer diagnosed during pregnancy or within 1 year of delivery

Carcinoma mammario *in* gravidanza

Incidenza del cancro durante la gravidanza: 1/1.000

Incidenza del cancro della mammella in gravidanza 1/3.000 – 1/10.000

0.2 – 3.8% dei cancri mammari diagnosticati in donne < 50 anni

10-20% dei cancri mammari diagnosticati in donne < 30 anni

Viswanathan S and Ramaswamy Clin Obstet Gynecol 2011
Turchi JJ et al Cancer 1988
Anderson JM Br Med J 1979

Rischio di amenorrea con i più comuni regimi di chemioterapia adiuvante

Trattamento	% donne con amenorrea indotta		
	Età < 30	Età 30-40	Età > 40
nessuno	0	<5	20-25
AC x 4		13	57-63
CMF x 6	19	31-38	76-96
CAF/CEF x 6	23-47		80-89
TAC x 6	51		
AC x 4, T x 4	38 (15% età <40)		

Goodwin JCO 1999, Burstein NEJM 2000, Nabholz ASCO 2002, Parulekar JCO 2005, Fornier Cancer 2005, Petrek JCO 2006

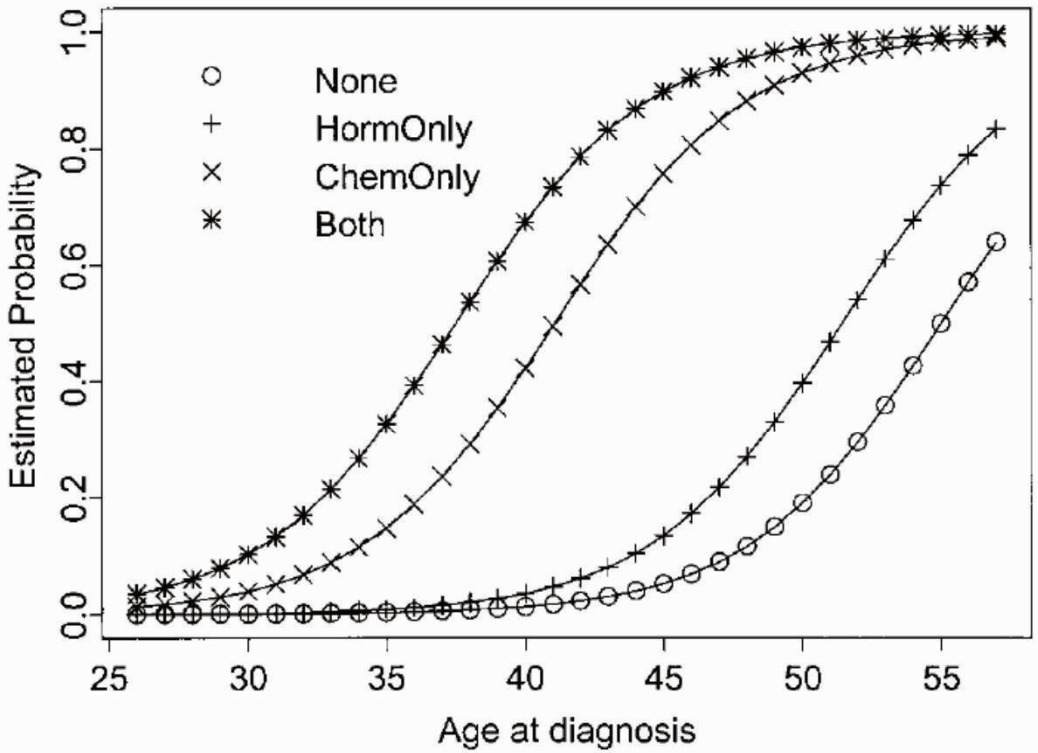


Fig 1. Probability of menopause during the first year after diagnosis (from model shown in Table 3).

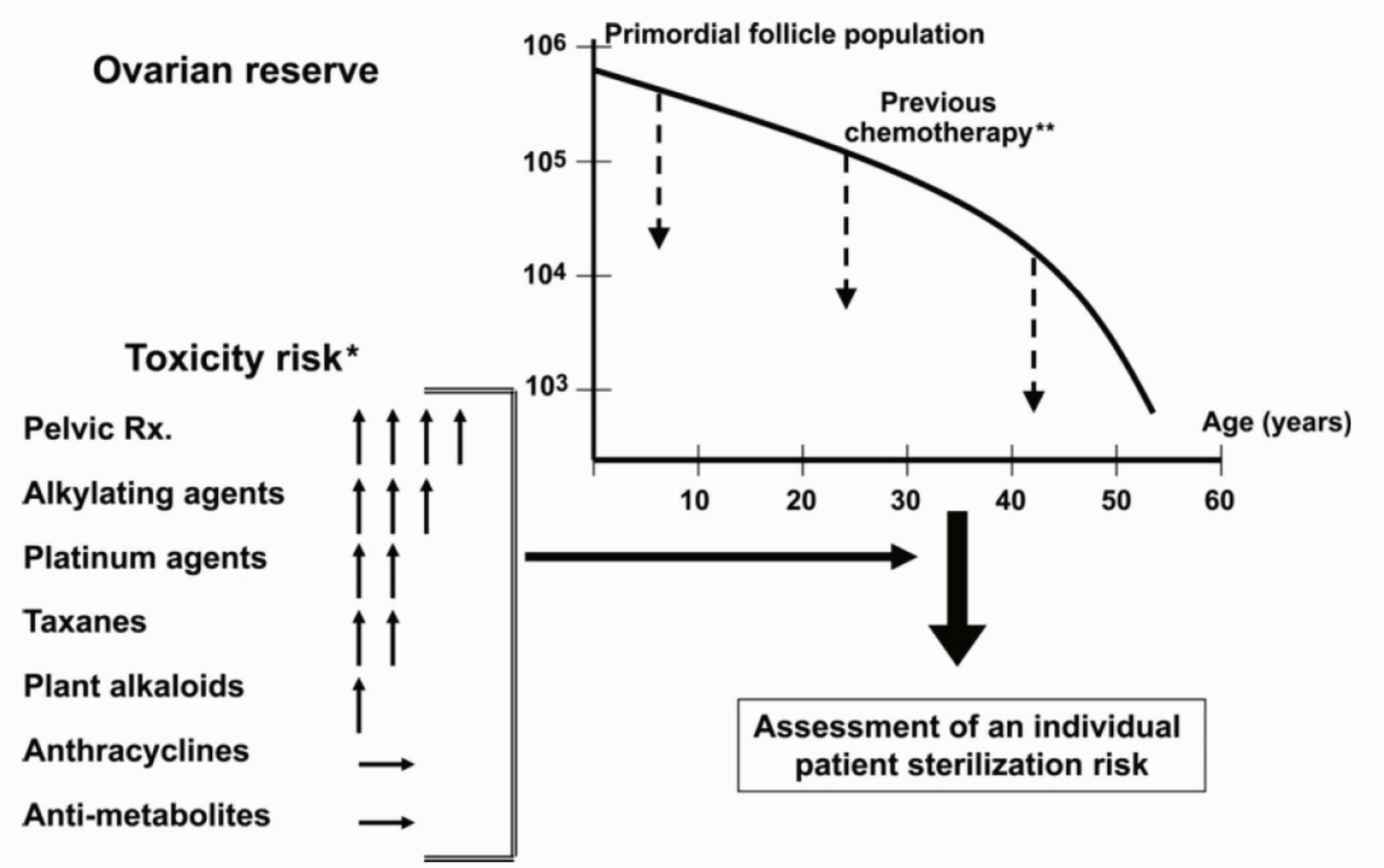
Table 3. Final Multivariate Model

Variable*	*P*
Age	< .00001
Chemotherapy (CMF or CEF)†	< .00001
Tamoxifen	.034

*No interaction terms were significant.
†CMF did not differ from CEF.

Goodwin PJ et al J Clin Oncol 1999

Danno ovarico da chemioterapia: età e classe di chemioterapici



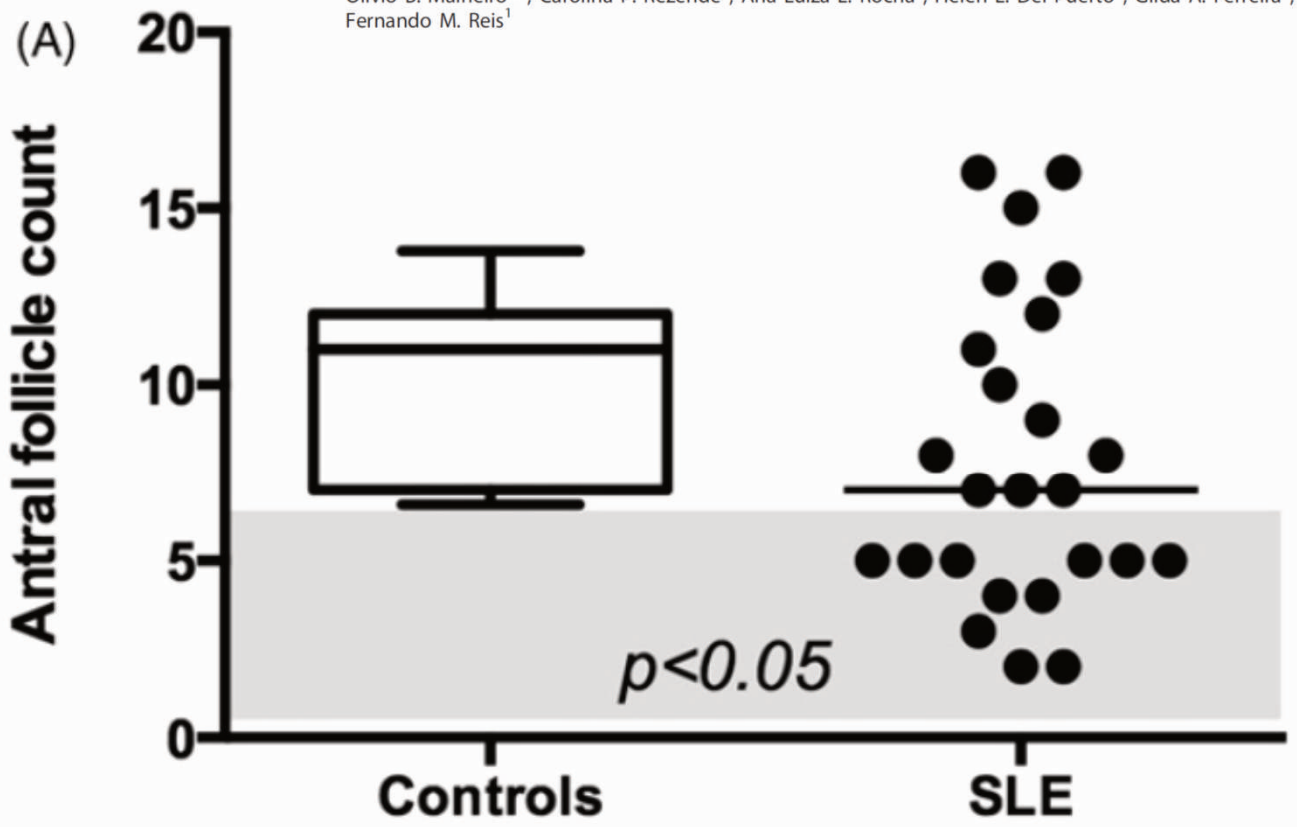
Roness H et al Hum Reprod Update 2014

GYNECOLOGICAL ENDOCRINOLOGY
http://informahealthcare.com/gye
ISSN: 0951-3590 (print), 1473-0766 (electronic)
Gynecol Endocrinol, 2014; 30(10): 701–704
© 2014 Informa UK Ltd. DOI: 10.3109/09513590.2014.922949
informa healthcare

OVARIAN DAMAGE AND SYSTEMIC LUPUS ERYTHEMATOSUS

Regular menstrual cycles do not rule out ovarian damage in adult women with systemic lupus erythematosus

Olivio B. Malheiro[1,2], Carolina P. Rezende[1], Ana Luiza L. Rocha[1], Helen L. Del Puerto[1], Gilda A. Ferreira[2], and Fernando M. Reis[1]



AFC inversely correlated with the cumulative dose of CTX
(r= -0-387, p= 0.028)

Gravidanza dopo il carcinoma della mammella

Al *dopo* si deve pensare *prima*

Linee guida AIOM 2017 per la preservazione della fertilità nelle Pazienti oncologiche

	RACCOMANDAZIONE
CRIOPRESERVAZIONE OVOCITARIA	POSITIVA FORTE
CRIOPRESERVAZIONE TESSUTO OVARICO	POSITIVA DEBOLE Da riservare a chi non può criopreservare ovociti
OVAROPROTEZIONE CON LHRH ANALOGHI	POSITIVA FORTE

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi160–vi170, 2013
doi:10.1093/annonc/mdt199
Published online 27 June 2013

Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. A. Peccatori[1], H. A. Azim Jr[2], R. Orecchia[3], H. J. Hoekstra[4], N. Pavlidis[5], V. Kesic[6] & G. Pentheroudakis[5], on behalf of the ESMO Guidelines Working Group*

[1]*Fertility and Procreation Unit, Division of Gynaecologic Oncology, European Institute of Oncology, Milan, Italy;* [2]*Department of Medicine, BrEAST Data Centre, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium;* [3]*Department of Radiotherapy, European Institute of Oncology, Milan, Italy;* [4]*Department of Surgical Oncology, University Medical Centre Groningen, Groningen, The Netherlands;* [5]*Department of Medical Oncology, University of Ioannina, Ioannina, Greece;* [6]*Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;*

These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

Fertility preservation methods in cancer patients

Females:

(i) Young women desiring future fertility should be counselled on available fertility preserving options before starting anti-cancer treatment. Counselling should be implemented soon after diagnosis to allow prompt referral to fertility specialists.
(ii) The use of GnRH analogues concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility.
(iii) Embryo or oocyte cryopreservation is the main method to preserve female fertility.
(iv) Ovarian stimulation should be carried out before commencing chemotherapy.
(v) The use of gonadotropins and letrozole or tamoxifen for ovarian stimulation is suggested for cancer patients. Consideration of such an approach in patients with ER-positive breast cancer should be made during a discussion with the patient and requires intensive interdisciplinary discussion including oncologists, radiotherapists and reproductive medicine specialists.
(vi) Chemotherapy and radiotherapy-induced sterility can be prevented also by freezing ovarian tissue before treatment. This is still experimental.

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update

Kutluk Oktay, Brittany E. Harvey, Ann H. Partridge, Gwendolyn P. Quinn, Joyce Reinecke, Hugh S. Taylor, W. Hamish Wallace, Erica T. Wang, and Alison W. Loren

Adult Women

Recommendation 3.1. Embryo cryopreservation: Embryo cryopreservation is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization.

Recommendation 3.2. Cryopreservation of unfertilized oocytes: Cryopreservation of unfertilized oocytes is an option, and may be especially well suited to women who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing. Oocyte cryopreservation should be performed in centers with the necessary expertise. As of October 2012, the American Society for Reproductive Medicine no longer deems this procedure

Recommendation 3.5 (updated). Ovarian suppression: There is conflicting evidence to recommend GnRHa and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods.

Recommendation 3.6 (updated). Ovarian tissue cryopreservation and transplantation: Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation and can be performed immediately. In addition, it does not require sexual maturity and hence may be the only method available in children. Finally, this method may also restore global ovarian function. However, it should be noted further investigation is needed to confirm whether it is safe in patients with leukemias.

Qualifying statement. As of the time of this publication, ovarian tissue cryopreservation remains experimental. However, emerging data may prompt reconsideration of this designation in the future (this technique is already considered nonexperimental in some countries, and its experimental status is undergoing evaluation in the United States).

J Clin Oncol 36. © 2018 by American Society of Clinical Oncology

Gravidanza *dopo* il carcinoma mammario

Dobbiamo scoraggiare la gravidanza in donne trattate per carcinoma della mammella?

Biological mechanisms are much more complex than commonly believed

Historical dogma: pregnancy is detrimental after breast cancer diagnosis and treatment , because of high levels of estrogens, progestins, prolactin and placental lactogens during pregnancy

However, clinical and preclinical data do not support the detrimental effect of pregnancy, but possibly a bidirectional time-dependent effect of pregnancy on breast cancer

- Reduced expression of ER-alfa and PgR and two-fold espression of ER-beta in parous women compared to nulliparous (Asztalos et al, 2010)

- Foetal cells and breast cancer cells share common antigens: during pregnancy immune response exerted by maternal immunity against circulating foetal cells could act against dormant cancer cells (Janerich DT el, 2001)

- In the short term the process of breast remodelling following pregnancy is associated with angiogenesis, inflammation, extracellular matrix alterations that could have stimulatory effect on incipient breast lesions (Polyak K et al 2006)

Pregnancy *following* breast cancer diagnosis: a meta-analysis of 14 studies

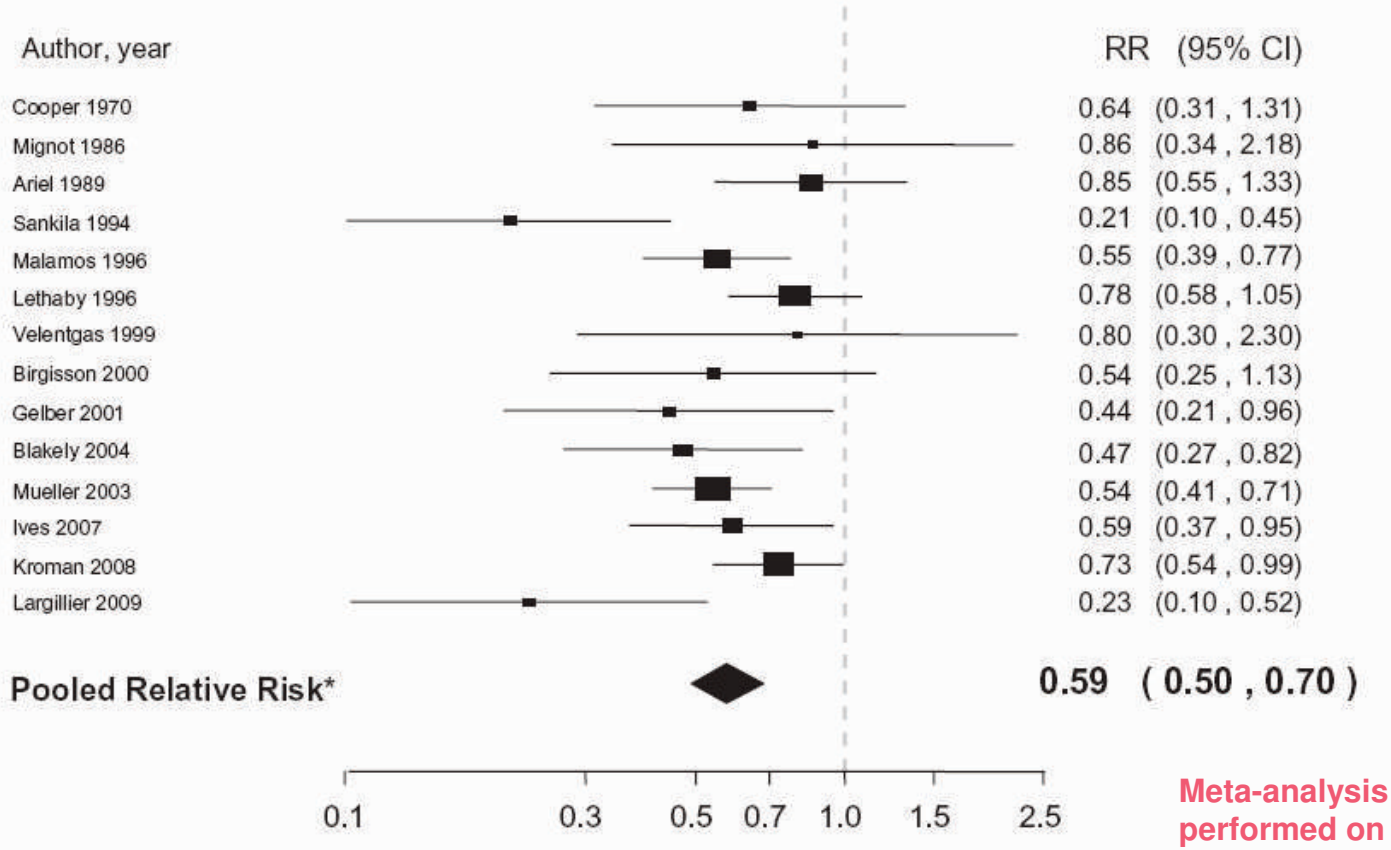


Fig. 2 – Overall survival analysis.

Meta-analysis performed on published data rather than on individual patients data

No information on ER and HER2 status

Azim HA et al Eur J Cancer 2011

The Healthy Mother Effect

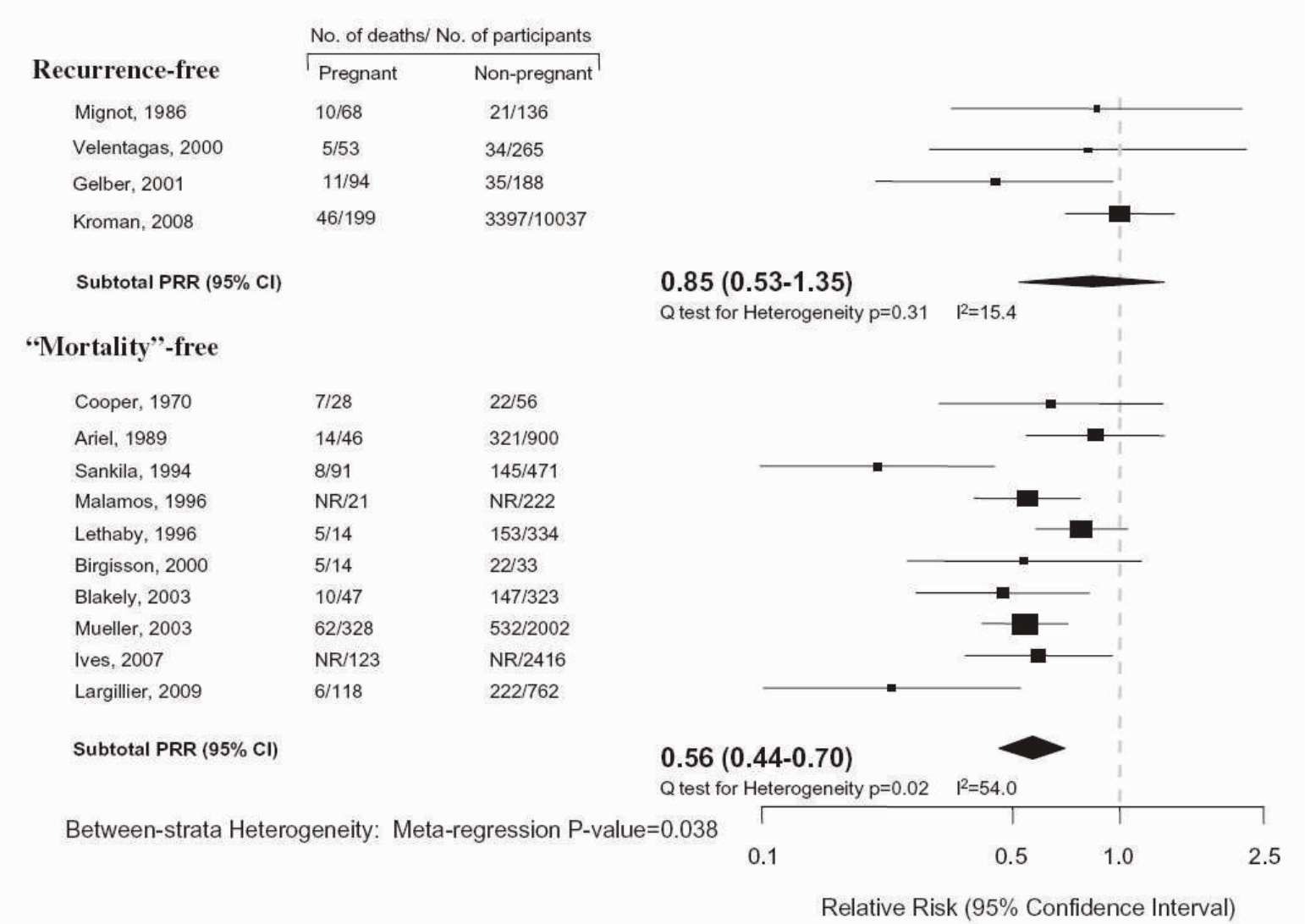
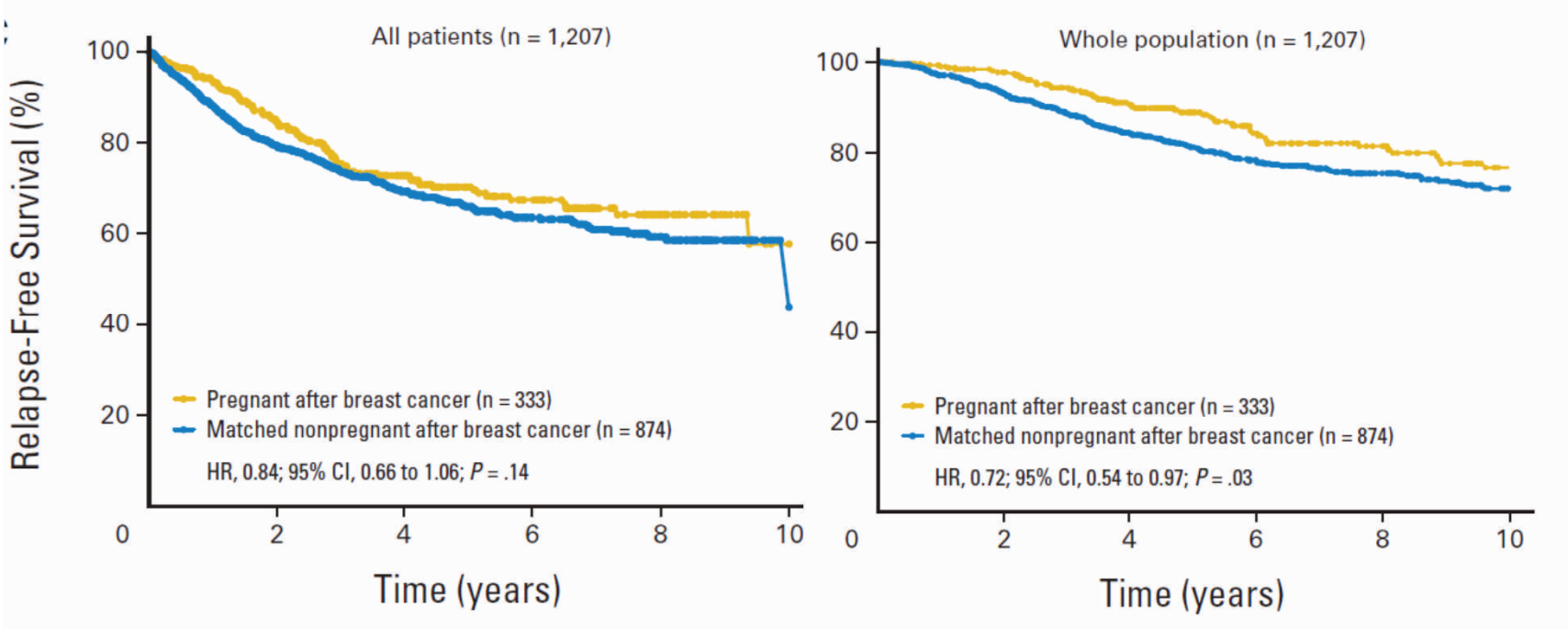


Fig. 3 – Healthy Mother Effect subgroup analysis.

Azim HA et al Eur J Cancer 2011

Correct for Healthy Mother Effect

Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

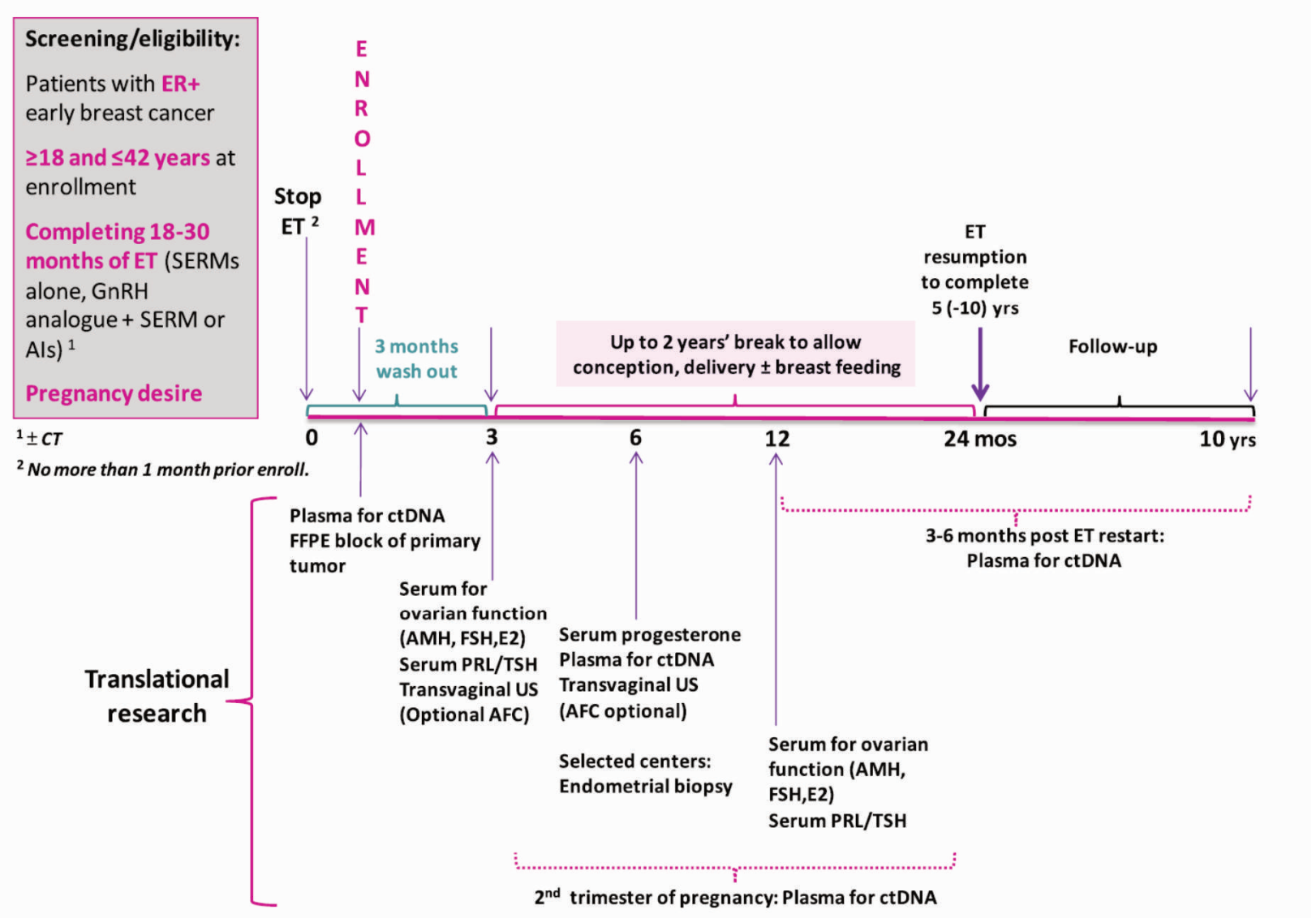


Hazim HA et al JCO 2013

Breast cancer *after* pregnancy: clinical practice

- Pregnancy after breast cancer should not be discouraged, providing adequate multidisciplinary counselling
- Adequate data to provide accurate prediction on individual basis are not available
- In common clinical practice it is generally suggested to wait at least 2 years from diagnosis before attempting a conception, mainly to allow early recurrences to manifest
- Taking into account the timing of oocyte maturation it is reasonable to wait at least 6 months from the end of chemo
- The impact of temporary adjuvant hormonal treatment interruption to allow conception is not known
- Practical advice is to wait at least 3-6 months after withdrawal from endocrine therapy before attempting conception
- Trials are strongly needed (BIG-NABCG project)

POSITIVE Trial Design



Pagani O et al Breast 2015