IL RUOLO DELL'ENDOCRINOLOGO NEL TEAM MULTIDISCIPILINARE: LA BREAST UNIT

Dott. Francesco Scavuzzo - AORN A. Cardarelli- Napoli

CONFLITTI DI INTERESSE

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

-Lilly

-Novartis

LA BREAST UNIT

LEGGE EUROPEA DA APPLICARE ENTRO IL 2016 - La Risoluzione del Parlamento Europeo del 2003, riconfermata nel 2006 con il sostegno di molte associazioni femminili europee, richiede a tutti gli Stati membri dell'UE che entro il 2016 sia definito nelle programmazioni sanitarie il ruolo di Breast Unit certificate. Per quanto riguarda il nostro Paese, ne sono previste 60, distribuite capillarmente lungo la penisola, in modo da garantire la disponibilità di una struttura ad hoc almeno ogni milione di abitanti.

LA BREAST UNIT

Team multidisciplinari all'interno dei quali si trovano tutte le specialità mediche, tecniche e infermieristiche, che in qualche modo interagiscono nella prevenzione, diagnosi, terapia e riabilitazione del carcinoma mammario, con le maggiori competenze specifiche e in assoluta coordinazione fra loro.

TRATTAMENTO del CA.MAMMARIO

- TRATTAMENTO CHIRURGICO:

✓ Breast-conserving surgery

✓ Modified radical mastectomy (rimozione dell'intero seno con dissezione ascellare dei livelli I e II), con o senza ricostruzione del seno

- RADIOTERAPIA:

✓ viene regolarmente impiegata dopo la Breast-conserving surgery, ma è indicata anche per i pazienti ad alto rischio post mastectomia. L'obiettivo principale è quello di eradicare la malattia residua

- ALTRE TERAPIE ADIUVANTI

✓ Lo stadio e le caratteristiche molecolari discriminano la necessità della terapia sistemica adiuvante e la scelta delle modalità da utilizzare. Le pz ER e/o PR pos. riceveranno terapia ormonale. La sovraespressione di HER2 è un'indicazione per l'uso di trastuzumab, di solito in combinazione con la chemioterapia. Se il tumore è triplo negativo, la terapia adiuvante si basa su regimi chemioterapici combinati

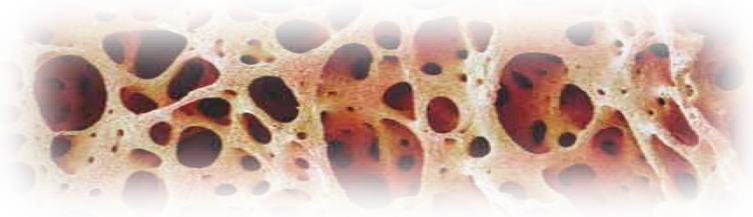
Patient Group	Treatment Options
Premenopausal, hormone receptor–positive (ER or PR)	No additional therapy
	Tamoxifen
	Tamoxifen plus chemotherapy
	Ovarian function suppression plus tamoxifen
	Ovarian function suppression plus aromatase inhibitor
Premenopausal, hormone receptor–negative (ER or PR)	No additional therapy
	Chemotherapy
Postmenopausal, hormone receptor–positive (ER or PR)	No additional therapy
	Upfront aromatase inhibitor therapy or tamoxifen followed by aromatase inhibitor with or without chemotherapy
Postmenopausal, hormone receptor–negative (ER or PR)	No additional therapy
	Chemotherapy

L'ENDOCRINOLOGO DELLA BREAST UNIT

L'Endocrinologo si inserisce esattamente in questo punto dell'iter diagnostico. Il suo ruolo è cruciale nella gestione dei potenziali effetti indotti dalle terapie adiuvanti.

In particolare sarà chiamato in consulenza per:

- gestire gli effetti della deprivazione estrogenica, in primis come bone specialist
- valutare eventuali patologie tiroidee e/o ormonali riscontrate durante la stadiazione e la terapia

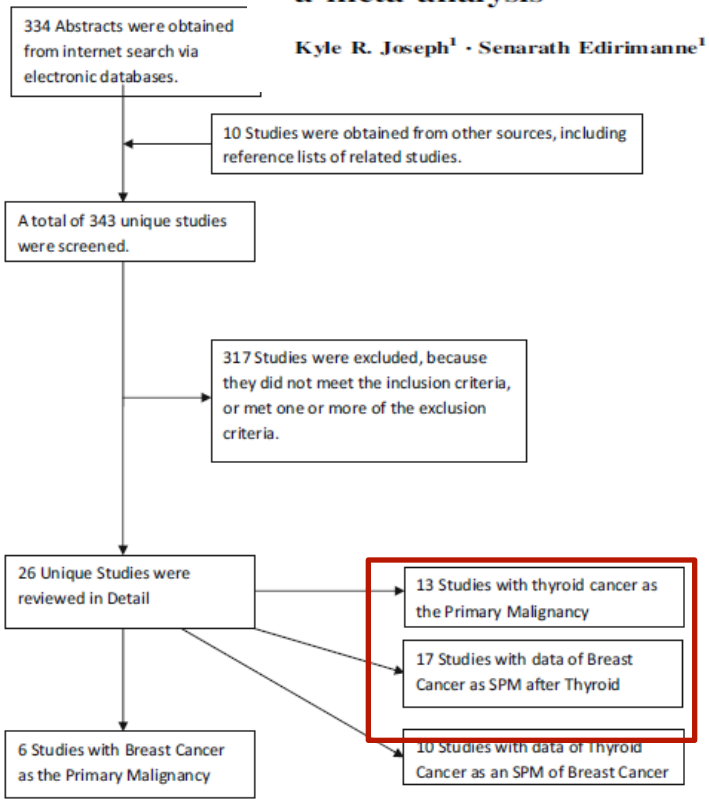


Breast Cancer Res Treat (2015) 152:173–181
DOI 10.1007/s10549-015-3456-6

EPIDEMIOLOGY

The association between breast cancer and thyroid cancer: a meta-analysis

Kyle R. Joseph[1] · Senarath Edirimanne[1] · Guy D. I



Secondly, our analysis has concluded an increased risk in the development of breast cancer following thyroid cancer in the scale of approximately 3 %. The large sample

Thirdly, our analysis observed an increased risk of developing thyroid cancer after breast cancer of 17 %, compared to most other SPMs. Large numbers of breast

Minireview

Cancer Epidemiology, Biomarkers & Prevention

The Breast–Thyroid Cancer Link: A Systematic Review and Meta-analysis

Sarah M. Nielsen[1], Michael G. White[2], Susan Hong[3], Briseis Aschebrook-Kilfoy[4], Edwin L. Kaplan[2], Peter Angelos[2], Swati A. Kulkarni[5], Olufunmilayo I. Olopade[1], and Raymon H. Grogan[2]

Minireview

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Possibili spiegazioni:

- SURVEILLANCE BIAS: le pz con Ca mammario si sottopongono a numerosi esami radiologici durante il follow up oncologico, con riscontro di lesioni incidentali, diversamente misconosciute per la natura indolente del CDT. **Contestazione:** frequenza maggiore rispetto ad altre sedi

- RUOLO DEGLI ORMONI: è stata dimostrata la presenza di recettori ER/PR sui tireociti normali, maggiormente espressi in caso di CPT. È stato dimostrato che l'E stimola la secrezione di TSH

- RADIAZIONI: l'esposizione a radiazioni esterne aumenta il rischio globale di sviluppare un secondo carcinoma nell'area irradiata. Ciò NONOSTANTE…

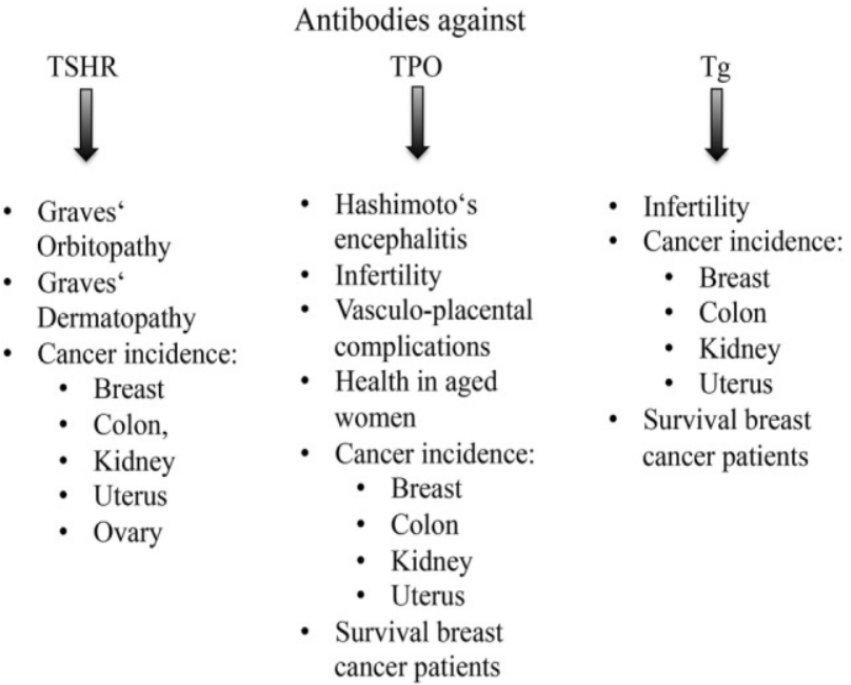
> Based on these studies, the risk for radiation-induced thyroid cancer following treatment for breast cancer is likely negligible but requires further evaluation. Special surveillance of the thyroid gland is not currently recommended for breast cancer survivors. In addition, management of thyroid nodules in women with a prior history of breast cancer should not be solely influenced by prior radiation treatment for breast cancer (19).

frontiers in Immunology

Front Immunol. 2017; 8: 521.
Published online 2017 May 9. doi: 10.3389/fimmu.2017.00521

Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases

Eleonore Fröhlich[1,2] and Richard Wahl[1,*]



Overview of extra-thyroidal effects of anti-thyroid antibodies.

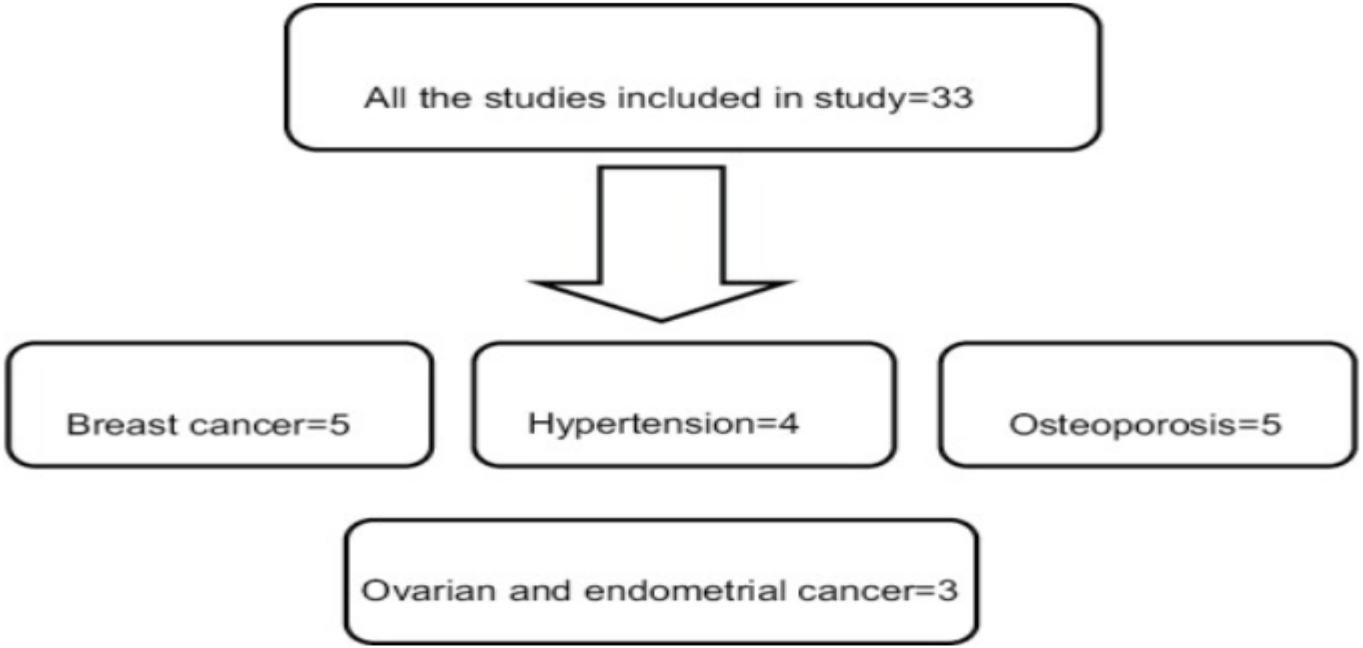
Anti-TSHR antibody levels were higher in breast cancer patients than in women with benign tumors or healthy controls

a promoting role of anti-TSHR antibodies on breast cancer has been shown, while the role of anti-Tg and anti-TPO is unclear

anti-TPO antibodies might have a beneficial effect in manifest breast cancer

Front Immunol. 2017 May 9;8:521. doi: 10.3389/fimmu.2017.00521. eCollection 2017.
Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases.

Fröhlich E[1,2], Wahl R[1].



Flowchart of conducted studies in the field of Vitamin D

J Res Med Sci. 2016 Sep 1;21:76. eCollection 2016.
The association between Vitamin D and health outcomes in women: A review on the related evidence.
Jolfaie NR[1], Rouhani MH[1], Onvani S[1], Azadbakht L[2]

Journal of Research in Medical Sciences

The association between Vitamin D and health outcomes in women: A review on the related evidence

Nahid Ramezani Jolfaie,[1] Mohammad Hossein Rouhani,[1] Shokouh Onvani,[1] and Leila Azadbakht[1,2,3]

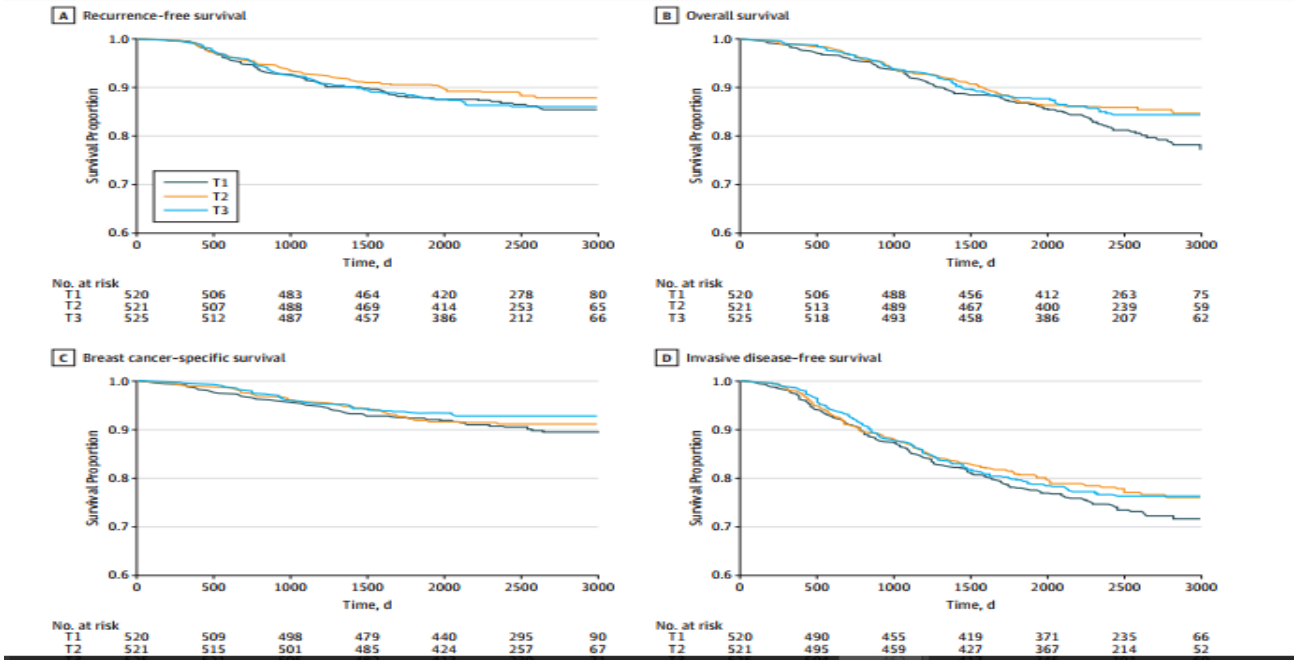
J Res Med Sci. 2016; 21: 76.
Published online 2016 Sep 1. doi: 10.4103/1735-1995.189693

Stoll *et al.*[23]	Systematic review	37 studies	The relationship between breast cancer and Vitamin D	An increased 25(OH)D level seems associated with a decreased risk of breast cancer recurrence
Maalmi *et al.*[24]	Systematic review and meta-analysis	Five studies including 4413 breast cancer patients	Serum 25(OH)D levels and survival in breast cancer patients	Higher 25(OH)D levels (>75 nmol/L) were associated with significantly reduced mortality in patients with breast cancer

JAMA Oncology | Original Investigation

Association of Serum Level of Vitamin D at Diagnosis With Breast Cancer Survival
A Case-Cohort Analysis in the Pathways Study

Song Yao, PhD; Marilyn L. Kwan, PhD; Isaac J. Ergas, MPH; Janise M. Roh, MSW, MPH; Ting-Yuan David Cheng, PhD; Chi-Chen Hong, PhD; Susan E. McCann, PhD; Li Tang, PhD; Warren Davis, PhD; Song Liu, PhD; Charles P. Quesenberry Jr, PhD; Marion M. Lee, PhD; Christine B. Ambrosone, PhD; Lawrence H. Kushi, ScD



Our findings provide compelling observational evidence for inverse associations between vitamin D levels and risk of breast cancer progression and death

EFFETTI DELLA TERAPIA ORMONALE

Sintomi menopausali

Gli effetti collaterali della terapia ormonale sono in genere lievi e sono conseguenza diretta della privazione estrogenica. I più frequenti e comuni ai preparati sono: vampate di calore, iperidrosi, ritenzione idrica, alterazioni o sospensione dei cicli mestruali, secchezza vaginale, dispareunia, variazioni di peso, nausea, dolori ossei articolari o muscolari, cefalea, stanchezza, depressione, insonnia, alterazioni della funzionalità epatica, del colesterolo e dei trigliceridi.

Volume 102, Issue 10, 1 October 2017

SINTOMI VASOMOTOR

SECCHEZZA VAGINALE
controindicato anche se in

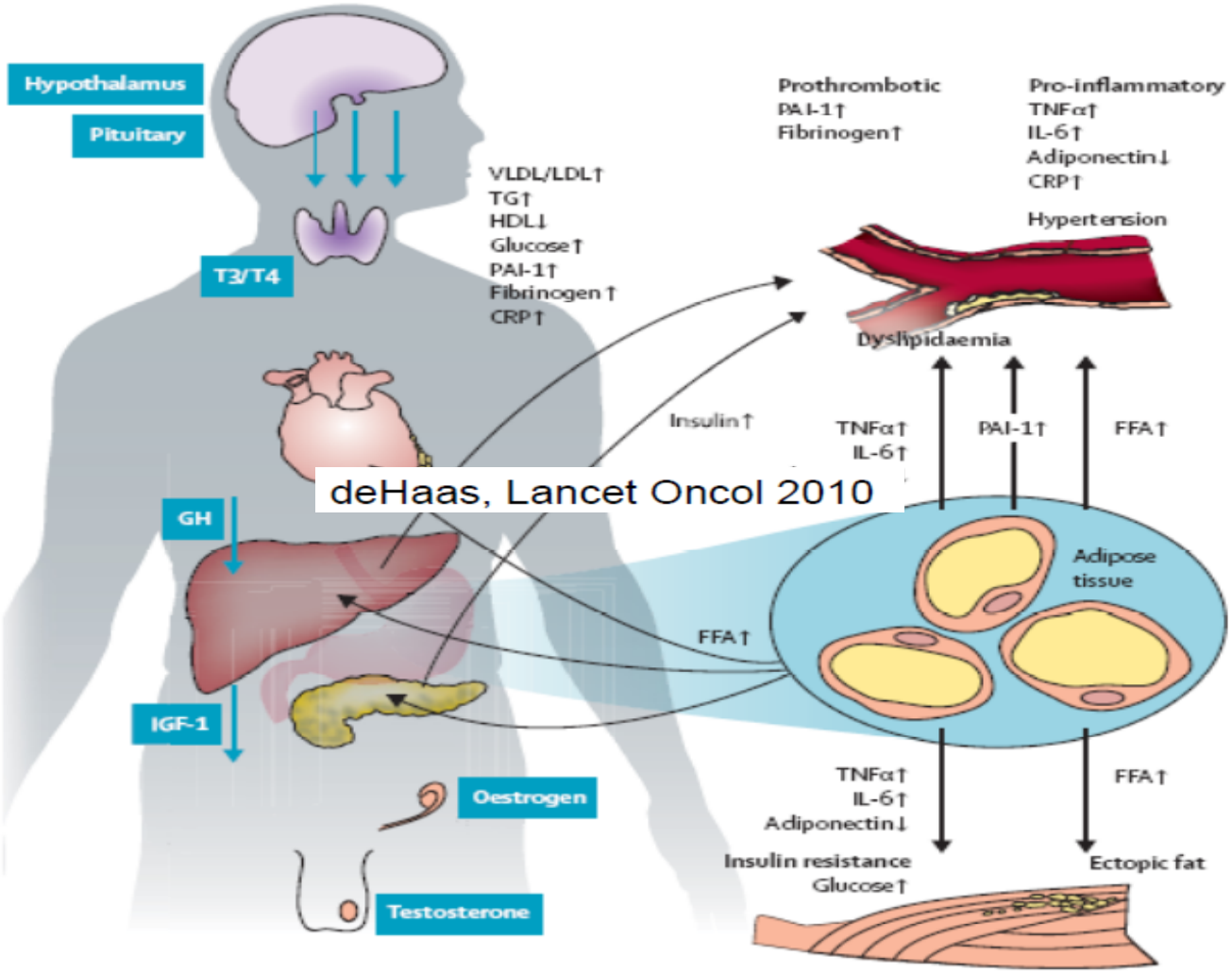
S. METABOLICA: dieta, attività fisica, eventuale uso di statine

Managing menopausal symptoms and associated clinical issues in breast cancer survivors

A recently FDA approved (i.e. November 2016) therapy for dyspareunia secondary to VVA is intravaginal dehydroepiandrosterone (DHEA).This therapy has not yet been approved beyond the USA. Nightly vaginal application of a 6.5 mg DHEA ovule has been shown to significantly improve vaginal cell maturation indices and the most bothersome symptoms of VVA. As DHEA can be enzymatically converted into both estrogen and androgens locally, this therapy theoretically provides a non-systemic hormonal approach. Carefully conducted studies with highly sensitive and specific mass spectrometry assays suggest a slight but statistically significant increase in plasma estradiol and testosterone (108). Intravaginal DHEA has not been tested in breast cancer survivors; thus there is a warning about its use due to lack of testing.

A small, double blind RCT of women without breast cancer has shown that intravaginal testosterone may be efficacious when compared with a placebo and vaginal estrogen in terms of subjective and objective VVA measures (109). A preliminary, non-controlled trial suggested that intra-vaginal testosterone may provide an effective treatment option for women with breast cancer taking an AI and experiencing symptoms of atrophic vaginitis (110). Further data on safety and efficacy are needed before this approach is recommended.

Numerosi trattamenti oncologici, attraverso un effetto sulla produzione ormonale endogena, sono associati allo sviluppo a lungo termine di SM, mediato dall' aumento di grasso viscerale



The Breast (2006) 15, 301–312
ELSEVIER
REVIEW
THE BREAST
www.elsevier.com/locate/breast

Comparative assessment of lipid effects of endocrine therapy for breast cancer: Implications for cardiovascular disease prevention in postmenopausal women

F.J. Esteva*, G.N. Hortobagyi

Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 424, Houston, Texas 77030, USA

Table 1 Lipid parameters at baseline and after 8 and 16 weeks of letrozole treatment.

Lipid parameter	Baseline ($n = 20$)	8 weeks ($n = 20$)	16 weeks ($n = 20$)
Total cholesterol (mg/dL)	239 ± 56	259 ± 58	258 ± 53*
HDL-C (mg/dL)	65.3 ± 17.9	60.8 ± 14.5	60.4 ± 13.5†
LDL-C (mg/dL)	148 ± 50	169 ± 55	170 ± 53
Triglyceride (mg/dL)	130 ± 69	148 ± 73	128 ± 56
Apolipoprotein AI (mg/dL)	185 ± 29	177 ± 21	172 ± 22
Apolipoprotein B (mg/dL)	109 ± 36	120 ± 37	117 ± 32*
Apolipoprotein E (mg/dL)	42.1 ± 14.9	52.8 ± 15.6	49.9 ± 9.5
Lipoprotein (a) (mg/dL)	13.0 ± 11.0	13.8 ± 10.5	14.0 ± 9.0
Total cholesterol: HDL-C (mg/dL)	3.94 ± 1.46	4.53 ± 1.53	4.48 ± 1.40‡
LDL-C:HDL-C (mg/dL)	2.46 ± 1.13	2.97 ± 1.24	3.00 ± 1.18§
Apolipoprotein AI:B (mg/dL)	1.91 ± 0.85	1.62 ± 0.65	1.62 ± 0.69‡

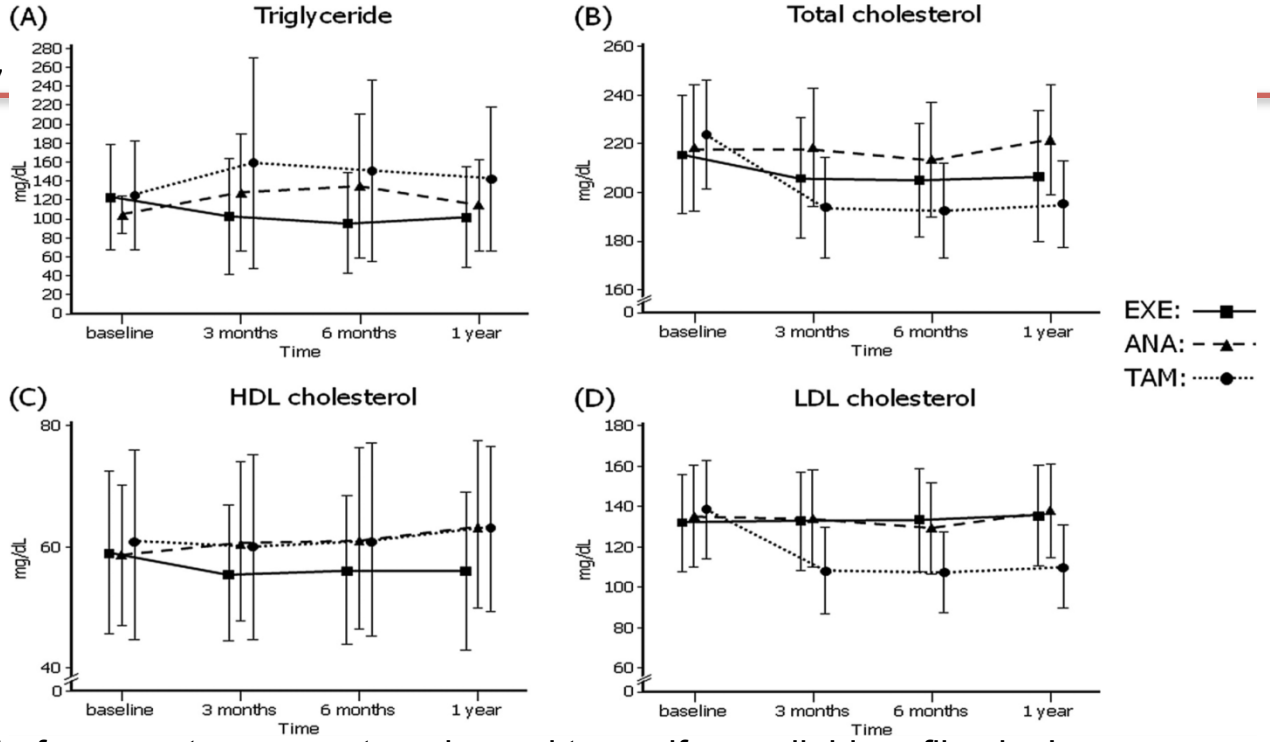
Statistical analysis carried out using repeated measures analysis of variance.[65] Reprinted from Eur J Cancer, Vol 37, Elisaf MS et al., Effect of letrozole on the lipid profile in postmenopausal women with breast cancer, pp. 1510-3, 2001, with permission from Elsevier.

*$P = 0.05$.
†$P < 0.05$.
‡$P = 0.005$.
§$P < 0.005$.

Table 2 Percentage change in lipid profiles from baseline following 12 weeks of adjuvant anastrozole, exemestane or tamoxifen treatment.[71]

Endocrine agent	Change from baseline (%)			
	Total cholesterol	HDL-C	LDL-C	Triglyceride
Anastrozole	−4.3	+1.6	−7.8	−0.3
Exemestane	−4.5	−6.8	−1.3	−6.0
Tamoxifen	−14.8*	−5.1	−22.6**	+8.1

Reprinted with kind permission of Springer Science and Business Media.
*$P < 0.005$; **$P = 0.001$ (One-Way ANOVA between groups).



From: The effect of exemestane, anastrozole, and tamoxifen on lipid profiles in Japanese postmenopausal early breast cancer patients: final results of National Surgical Adjuvant Study BC 04, the TEAM Japan sub-study

Ann Oncol. 2011;22(8):1777-1782. doi:10.1093/annonc/mdq707

Fertility Preservation in Female Patients with Breast Cancer – a Current Overview

Veronika Guenther[1], Ibrahim Alkatout[1], Wiebe Junkers[2], Dirk Bauerschlag[1], Nicolai Maass[1], Soeren von Otte[2]

Chemotherapy	Age (years)	Number of patients	Amenorrhoea rate (%)	Study
EC/Pac	mean age: 42	n = 80	46.6	Zhou, 2012
EC/Doc	<35	n = 166	15	Fornier, 2005
TAC	premenopausal	n = 109	57.7	Martin, 2005
FAC	premenopausal	n = 409	52	Martin, 2005

EC = epirubicin, cyclophosphamide; Pac = paclitaxel; Doc = docetaxel; TAC = docetaxel, doxorubicin, cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide

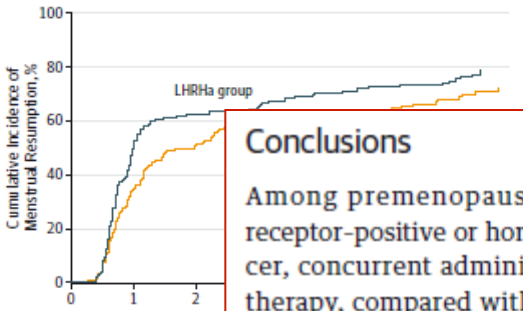
Original Investigation

Ovarian Suppression With Triptorelin During Adjuvant Breast Cancer Chemotherapy and Long-term Ovarian Function, Pregnancies, and Disease-Free Survival

A Randomized Clinical Trial

Matteo Lambertini, MD; Luca Boni, MD; Andrea Michelotti, MD; Teresa Gamucci, MD; Tiziana Scotto, MD; Stefania Gori, MD; Monica Giordano, MD; Ornella Garrone, MD; Alessia Levaggi, MD; Francesca Poggio, MD; Sara Giraudi, MD; Claudia Bighin, MD; Carlo Vecchio, MD; Mario Roberto Sertoli, MD; Paolo Pronzato, MD; Lucia Del Mastro, MD; for the GIM Study Group

Figure 2. Cumulative Incidence Estimate of Menstrual Resumption in the Treatment Groups



No. at risk

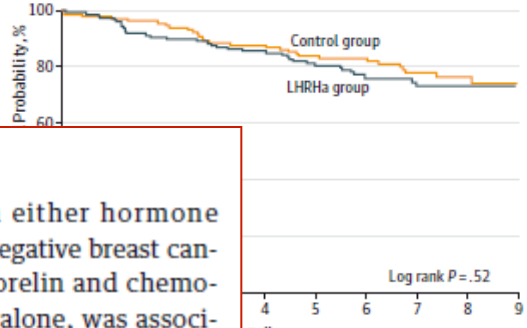
Control group	133	82	61
LHRHa group	148	73	49

LHRHa indicates luteinizing hormone-r

domized

148 Randomiz chemothe
146 Rece tripto

Figure 3. Disease-Free Survival in the Treatment Groups



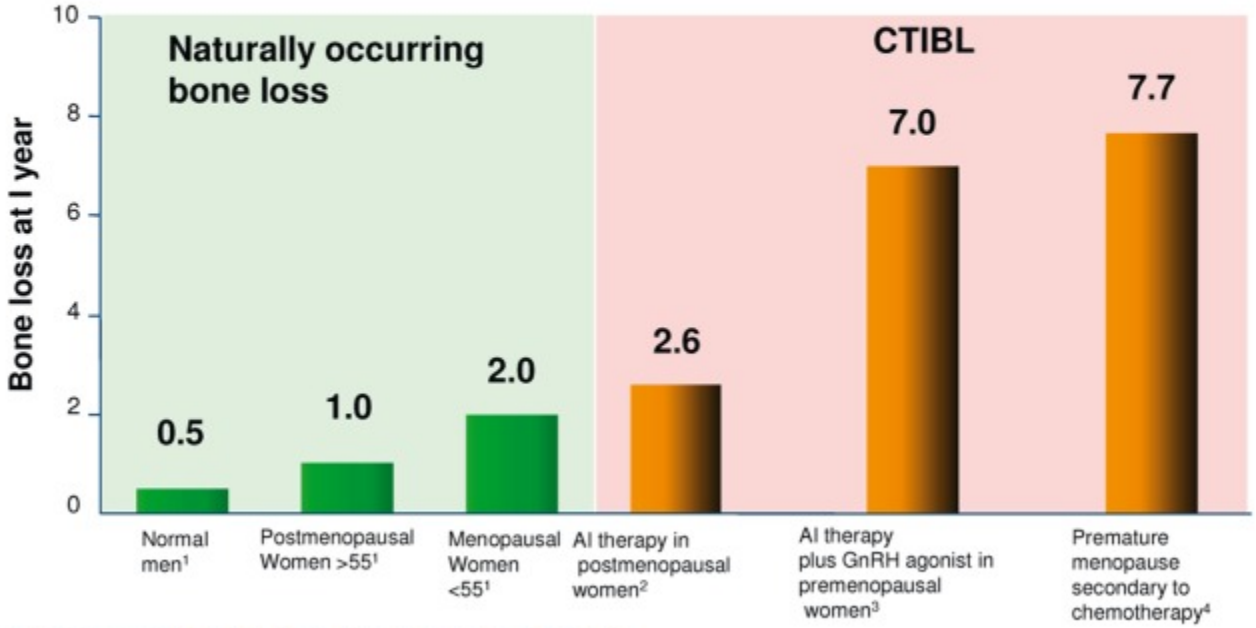
	112	106	93	63	35	5
	122	108	90	56	34	8

asing hormone analogues.

Conclusions

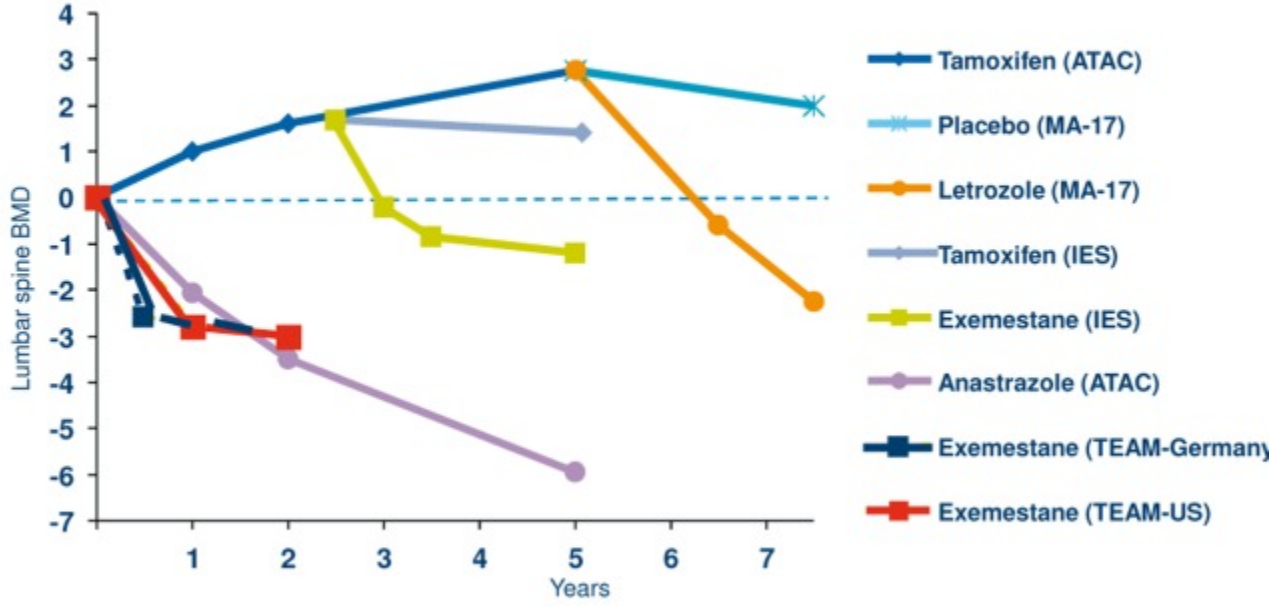
Among premenopausal women with either hormone receptor-positive or hormone receptor-negative breast cancer, concurrent administration of triptorelin and chemotherapy, compared with chemotherapy alone, was associated with higher long-term probability of ovarian function recovery, without a statistically significant difference in pregnancy rate. There was no statistically significant difference in DFS for women assigned to triptorelin and those assigned to chemotherapy alone, although study power was limited.

Normal and Cancer Treatment Related Bone Loss Rates



1. Kanis JA. *Osteoporosis*.1997:22-55. : Eastell R et al. *J Bone Mineral Res.* 2002.
2. Gnant M. *San Antonio Breast Cancer Symposium*, 2002. : Shapiro CL et al. *J Clin Oncol.* 2001;19:3306-3311.

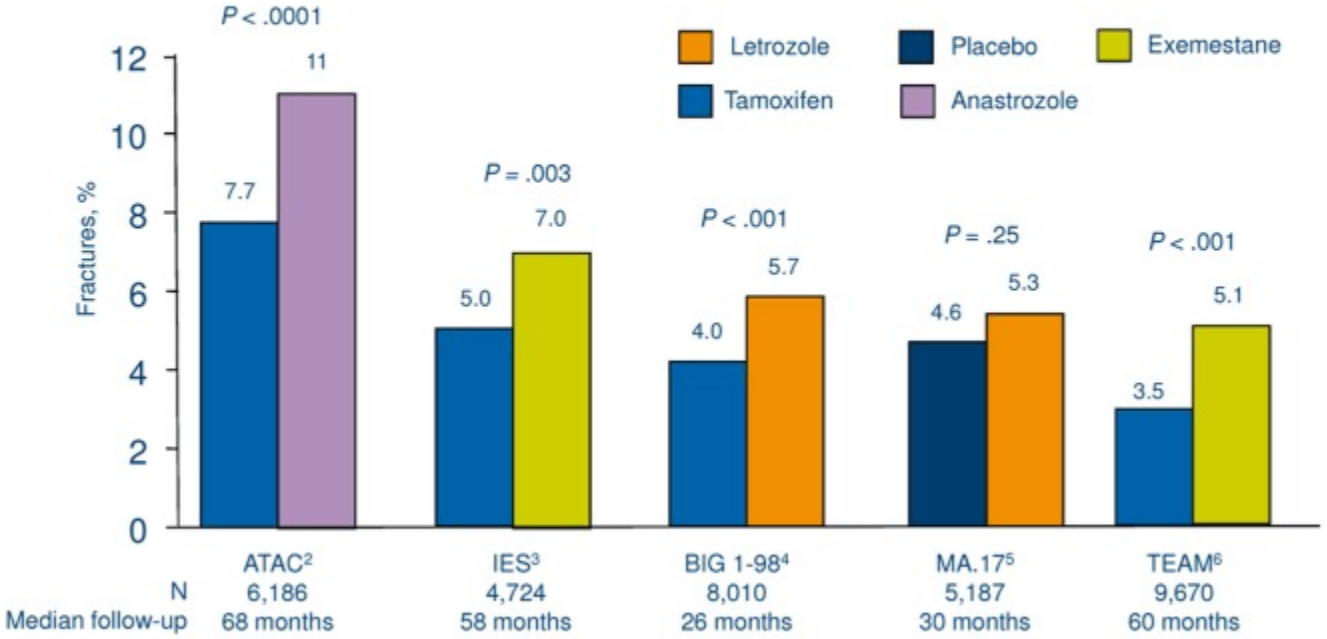
Influence of AI on spine BMD



ATAC[1] Anastrozole vs tamoxifen upfront,; IES[2] Exemestane vs tamoxifen following switch after 2-3 years tamoxifen; MA-17[3] Letrozole vs placebo following switch after 5 years on tamoxifen,; TEAM[4] Exemestane vs tamoxifen for 2-3 years (before switching from TAM to EXE vs. EXE for 5 years)

1. Howell A, et al. Lancet 2005;365:60–2; 2. Coleman RE, et al. Lancet Oncol 2007;8:119–27; 3. Goss PE, et al. J Natl Cancer Inst 2005;97:1262–71; 4. Hadji P, et al. Presented at 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, USA; December 10-14, 2008; Abstract 1143.

Influence of AI on fracture and osteoporosis risk



1. Adapted from Hadji P, et al. US Oncological Disease 2007;1:18–21; 2. Howell A, et al. Lancet 2005;365:60–2; 3. Coleman RE, et al. Lancet Oncol 2007;8:119–27; 4. Thurlimann B, et al. N Engl J Med 2005;353:2747–57; 5. Goss PE, et al. J Natl Cancer Inst 2005;97:1262–71; 6. Jones SE, et al. Presented at: SABCS 2008. Abstract 15.

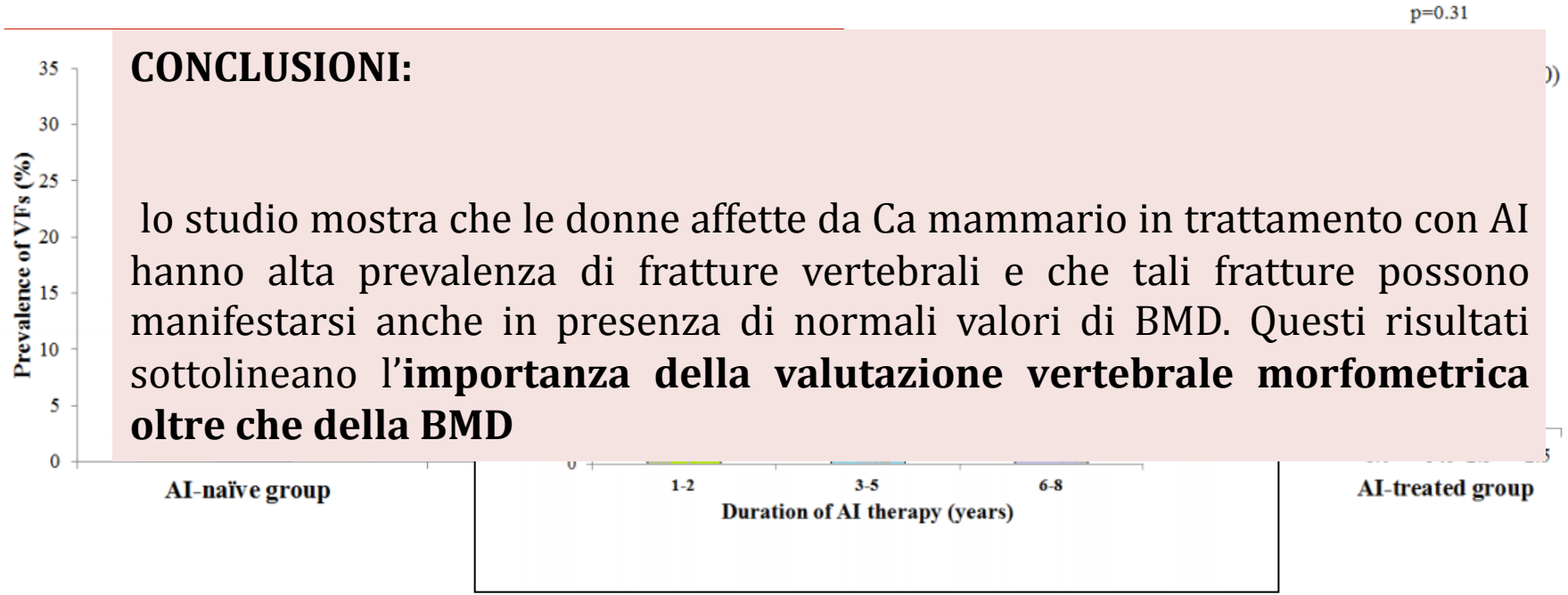
Bone. 2017 Apr;97:147-152. doi: 10.1016/j.bone.2017.01.013. Epub 2017 Jan 16.

Morphometric vertebral fractures in breast cancer patients treated with adjuvant aromatase inhibitor therapy: A cross-sectional study.

Pedersini R[1], Monteverdi S[1], Mazziotti G[2], Amoroso V[3], Roca E[4], Maffezzoni F[5], Vassalli L[1], Rodella F[1], Formenti AM[5], Frara S[6], Maroldi R[7], Berruti A[4], Simoncini E[8], Giustina A[6].

CONCLUSIONI:

lo studio mostra che le donne affette da Ca mammario in trattamento con AI hanno alta prevalenza di fratture vertebrali e che tali fratture possono manifestarsi anche in presenza di normali valori di BMD. Questi risultati sottolineano l'**importanza della valutazione vertebrale morfometrica oltre che della BMD**



Prevenzione della perdita di BMD durante la terapia con IA

Antiresorptive agent (trial)	*N*	BMD study, *n*[a]	Dosing	Treatment duration, years	Follow-up, months	Mean BMD change from baseline, %	
						LS	TH
Zoledronic acid (ZO-FAST) [28]	1065	1065	4 mg i.v. q6mo	5	36[b]	+4.39	+1.9
Zoledronic acid (Z-FAST) [39]	602	602	4 mg i.v. q6mo	5	61	+6.19	+2.57
Zoledronic acid (E-ZO-FAST) [40]	527	527	4 mg i.v. q6mo	5	36	+5.98	NR
Zoledronic acid (N03CC) [41]	558	395	4 mg i.v. q6mo	5	24	+4.94	+1.22
Denosumab (HALT-BC) [42]	252	252	60 mg s.c. q6mo	2	24	+6.2[c]	+3.7[c]
Risedronate (SABRE) [43]	154	111	35 mg p.o./week	2	24	+2.2	+1.8
Risedronate [44]	87	87	35 mg p.o./week	2	24	+0.4	+0.9
Clodronate [45]	61	61	1600 mg p.o./day	3	60	−1.0	−0.1
Risedronate (ARBI) [46]	213	70	35 mg p.o./week	2	24	+5.7	+1.6
Risedronate (IBIS-II) [47]	613	59	35 mg p.o./week	5	12	+0.32	+0.67
Ibandronate (ARIBON) [48]	131	50	150 mg p.o./month	2	24	+2.98	+0.6
Risedronate [49]	118	11	35 mg p.o./week	1	12	+4.1	+1.8

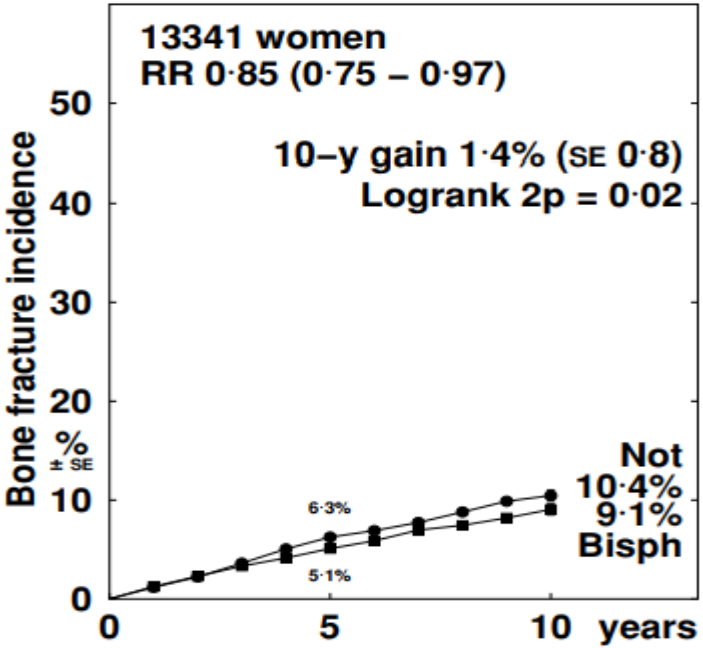
- Minor evidenza di riduzione del rischio fratturativo
- Evidenza generale di impatto positivo su BMD.

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)†

THE LANCET

BONE FRACTURE INCIDENCE



Bone fracture incidence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	1·06 (309 / 29021)	0·88 (106 / 12112)	0·40 (7 / 1767)
Not	1·27 (371 / 29143)	0·89 (108 / 12200)	0·43 (8 / 1852)
Rate ratio, from (O–E) / V	0·82 SE 0·07 –32·5 / 164·7	0·97 SE 0·14 –1·7 / 51·4	0·75 SE 0·47 –1·0 / 3·5

Informazioni sulle fratture disponibili solo in 13341 (71%) delle 18766 donne.

Fratture:

-Bifosfonati: 422/6649 (6.3%)

-Controlli: 487/6692 (7.3%)

(RR 0.85, 95% CI 0.75–0.97; 2p = 0.02)

Rischio di frattura a 5 anni:

-Bifosfonati: 5.1%

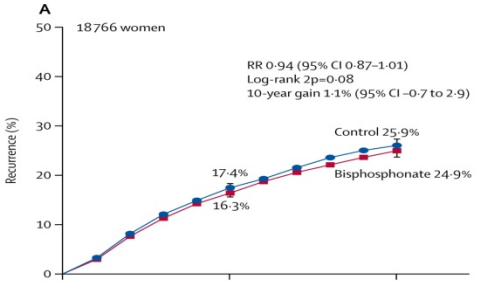
-Controlli: 6.3%

Effetto limitato nel primo anno, maggiore fra il 2° e 4° anno, piccolo beneficio aggiuntivo dopo il 5° anno

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

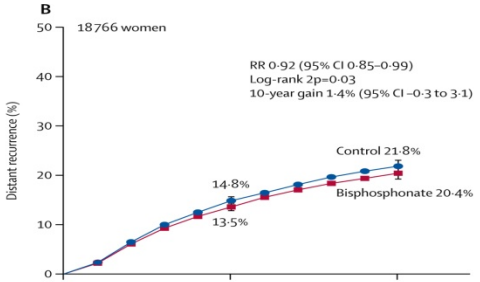
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)†

THE LANCET



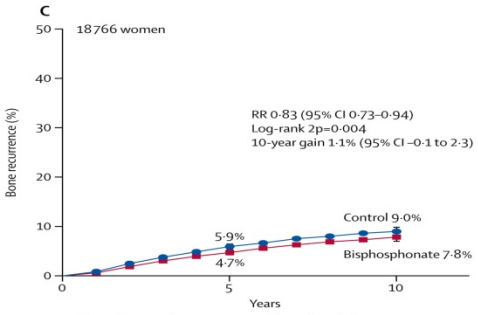
Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	3·63 (1415/38 979)	2·34 (308/13 171)	0·87 (15/1724)
Control	3·85 (1384/35 984)	2·36 (314/13 322)	0·95 (17/1790)
Rate ratio (95% CI)	0·93 (0·85–1·01)	0·98 (0·81–1·14)	0·72 (CI 0·01–1·43)
from (O–E)/V	–41·9/593·7	–3·1/139·4	–1·8/5·5



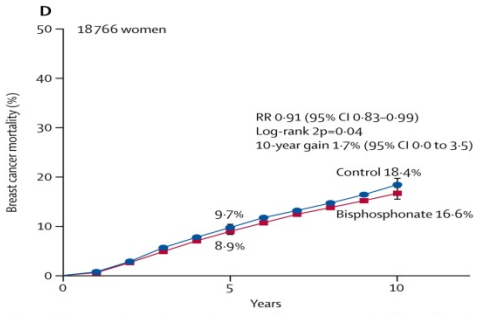
Distant recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	2·97 (1173/39 559)	1·84 (253/13 746)	0·67 (13/1932)
Control	3·20 (1170/36 571)	1·82 (253/13 931)	1·08 (21/1941)
Rate ratio (95% CI)	0·91 (0·83–0·99)	0·99 (0·81–1·18)	0·47 (0·21–1·03)
from (O–E)/V	–47·5/499·9	–0·7/114·3	–4·5/5·9



Bone recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	0·99 (391/39 559)	0·76 (104/13 746)	0·10 (2/1932)
Control	1·21 (441/36 571)	0·71 (99/13 031)	0·10 (2/1941)
Rate ratio (95% CI)	0·79 (0·66–0·92)	1·02 (0·73–1·31)	0·61 (0·08–2·25)
from (O–E)/V	–45·0/189·5	0·8/46·8	–0·4/0·9



Death rates (%/year: total rate minus rate in women without recurrences) and log-rank statisti

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	1·83 (1·70–1·97)	1·81 (1·59–2·03)	1·21 (0·72–1·69)
Control	1·98 (1·84–2·12)	1·97 (1·75–2·20)	1·69 (1·12–2·25)
Rate ratio (95% CI)	0·91 (0·81–1·01)	0·92 (0·75–1·10)	0·66 (0·18–1·15)
from (O–E)/V	–30·5/321·7	–9·5/121·0	–4·5/10·9

Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial

Michael Gnant, Georg Pfeiler, Peter C Dubsky, Michael Hubalek, Richard Greil, Raimund Jakesz, Viktor Wette, Marija Balic, Ferdinand Haslbauer, Elisabeth Melbinger, Vesna Bjelic-Radisic, Silvia Artner-Matuschek, Florian Fitzal, Christian Marth, Paul Sevelda, Brigitte Mlineritsch, Günther G Steger, Diether Manfreda, Ruth Exner, Daniel Egle, Jonas Bergh, Franz Kainberger, Susan Talbot, Douglas Warner, Christian Fesl, Christian F Singer, on behalf of the Austrian Breast and Colorectal Cancer Study Group*

- ✓ Antiresorptive agents (e.g. bisphosphonates, denosumab) have been used to successfully prevent and treat cancer treatment-induced bone loss in patients with breast cancer
- ✓ Denosumab has previously been shown to reduce the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis
- ✓ ABCSG-18: a prospective, double-blind, placebo-controlled, phase 3 trial to investigate the effects of adjuvant denosumab on fractures and other bone health parameters, and on safety outcomes, in postmenopausal patients with hormone receptor-positive, early-stage breast cancer receiving AI treatment[5]

Primary endpoint

Time to first clinical fracture

Secondary endpoints

Percentage change in total lumbar spine, total hip and femoral neck BMD from baseline to Month 36

Incidence of new vertebral fractures at Month 36

Incidence of new or worsening of pre-existing vertebral fractures at Month 36

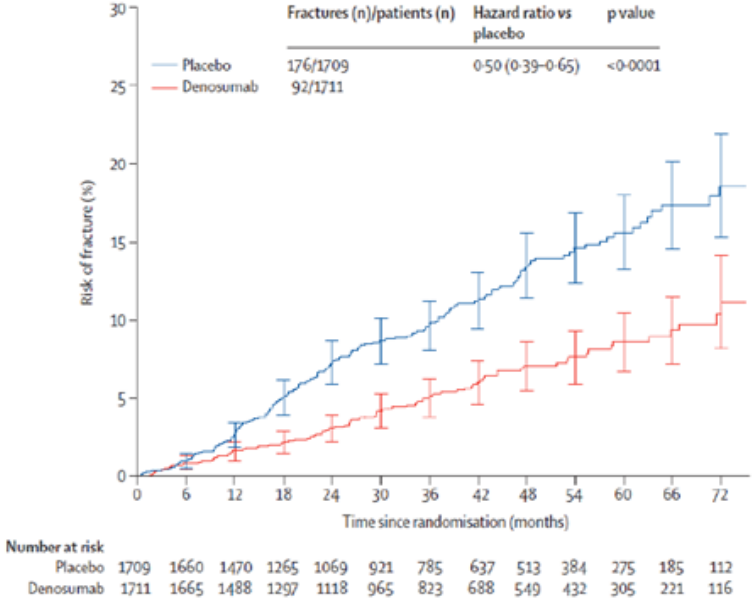
DFS

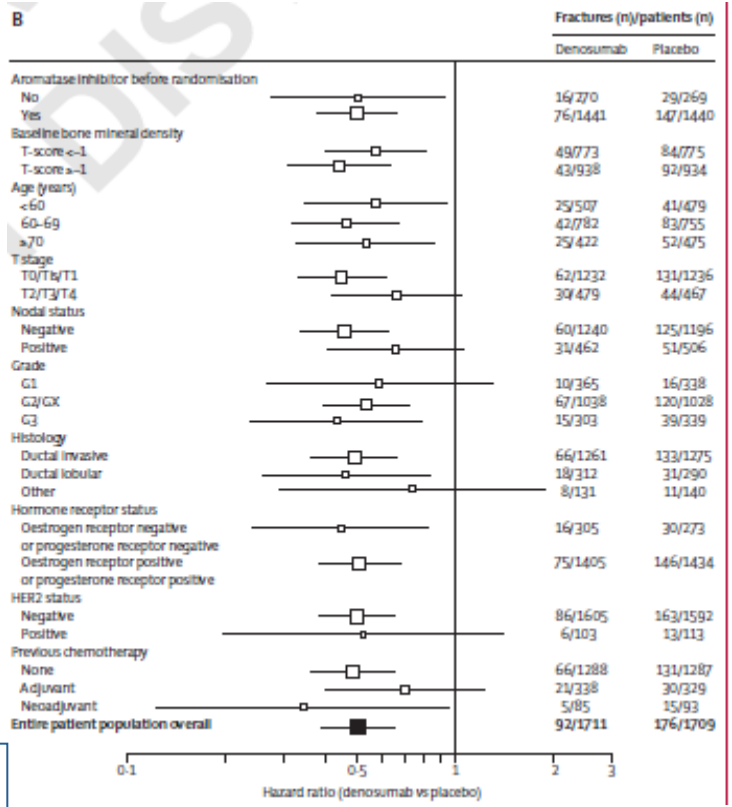
BMFS

OS

RISULTATI DELLO STUDIO CONDOTTO DA GNANT

Esordio della prima frattura significativamente ritardato rispetto al placebo

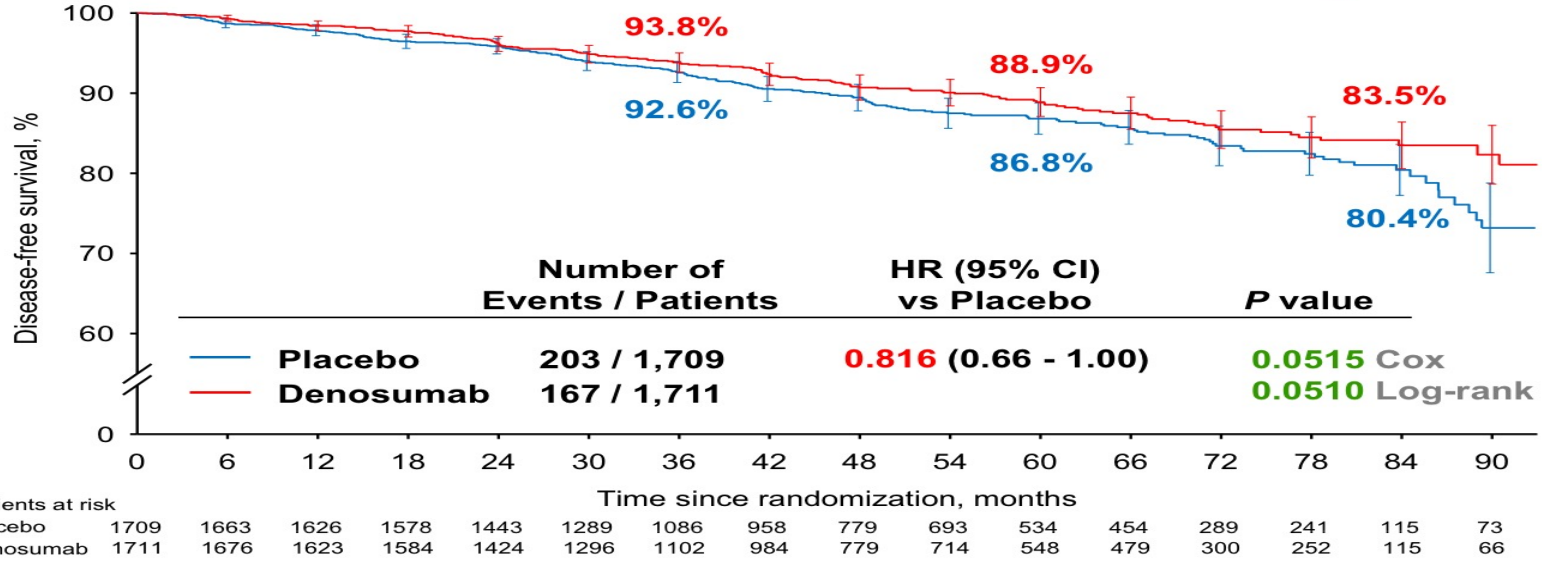




Riduzione significativa dell'incidenza delle fratture nella popolazione con denosumab rispetto al controllo

San Antonio Breast Cancer Symposium, December 8-12, 2015

ABCSG-18 Results of the DFS ITT Analysis



Patients at risk

Placebo	1709	1663	1626	1578	1443	1289	1086	958	779	693	534	454	289	241	115	73
Denosumab	1711	1676	1623	1584	1424	1296	1102	984	779	714	548	479	300	252	115	66

stratified by hospital type, use of prior aromatase inhibitor, and baseline lumbar spine bone mineral density

Diversamente dai bp, l'utilizzo di denosumab può essere preso in considerazione senza necessità di aggiustamento della dose anche in presenza di una grave riduzione della funzione renale. Denosumab è generalmente ben tollerato. Il favorevole profilo di sicurezza favorisce un'adeguata aderenza al trattamento. Gli studi disponibili in merito suggeriscono una migliore aderenza al trattamento con denosumab rispetto ad altre alternative terapeutiche per l'osteoporosi, in particolare i bisfosfonati, probabilmente attribuibile, oltre che alla buona tollerabilità del farmaco, anche a frequenza e via di somministrazione.

SHORT REPORT

JBMR®

Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases

Athanasios D Anastasilakis,[1] Stergios A Polyzos,[2] Polyzois Makras,[3] Berengere Aubry-Rozier,[4] Stella Kaouri,[5] and Olivier Lamy[4]

SHORT REPORT

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112 fratture vertebrali verificatesi in 24 donne in età post-menopausale in un lasso di tempo compreso tra 2 e 10 mesi dopo 8 -16 mesi dall'ultima iniezione

Dopo la sospensione di denosumab si assiste ad un incremento repentino degli indici di *turnover* osseo e a un altrettanto rapido decremento della BMD (-6.6% alla colonna lombare e -5.3% al femore totale entro i primi 12 mesi di interruzione), che tende a tornare ai livelli precedenti il trattamento. Il meccanismo alla base di questo **fenomeno di rimbalzo del riassorbimento osseo** non è completamente chiarito, ma potrebbe essere riconducibile a un elevato rapporto RANKL/osteoprotegerina o a un *pool* estremamente numeroso di precursori osteoclastici, che si attivano simultaneamente dopo la scomparsa di denosumab dal circolo. Qualora si ritenga comunque opportuno sospendere il trattamento, una strategia appropriata potrebbe essere quella di somministrare, a partire da 6 mesi dall'ultima iniezione, un altro farmaco anti-riassorbitivo per evitare il rimbalzo. In questo contesto, quindi, i bisfosfonati potrebbero avere un ruolo fondamentale

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 21, 2016 VOL. 375 NO. 3

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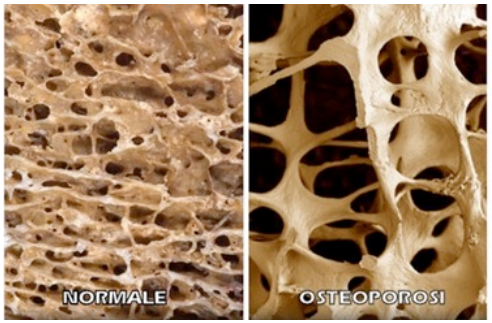
Table 3. Adverse Events.*

Event	Letrozole (N = 959)	Placebo (N = 954)	P Value
	number (percent)		
Toxic effect during receipt of trial regimen			
Bone fracture‡	133 (14)	88 (9)	0.001
Spine	17 (2)	9 (1)	0.12
Wrist	27 (3)	16 (2)	0.09
Pelvis	1 (<1)	7 (1)	0.08
Hip	7 (1)	6 (1)	0.79
Femur	9 (1)	4 (<1)	0.17
Tibia	5 (1)	4 (<1)	0.74
Ankle	19 (2)	11 (1)	0.14
Other	68 (7)	48 (5)	0.06
New-onset osteoporosis	109 (11)	54 (6)	<0.001

È necessaria la figura dell'Endocrinologo nelle Breast Units ?




GRAZIE