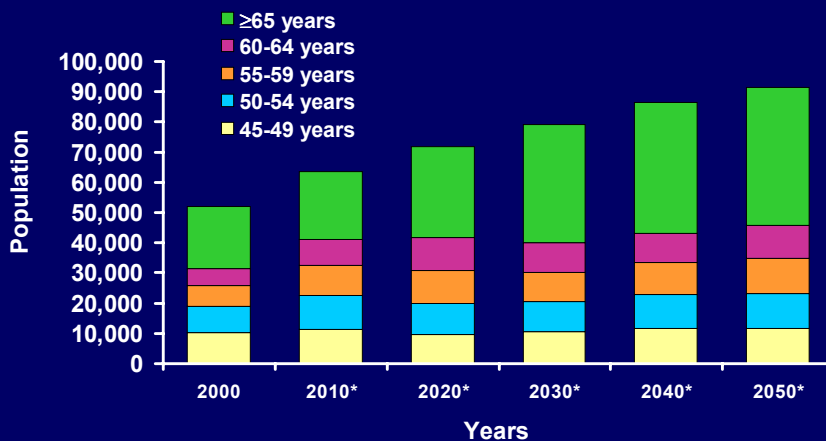


ΚΑΡΚΙΝΟΣ

ΚΑΙ

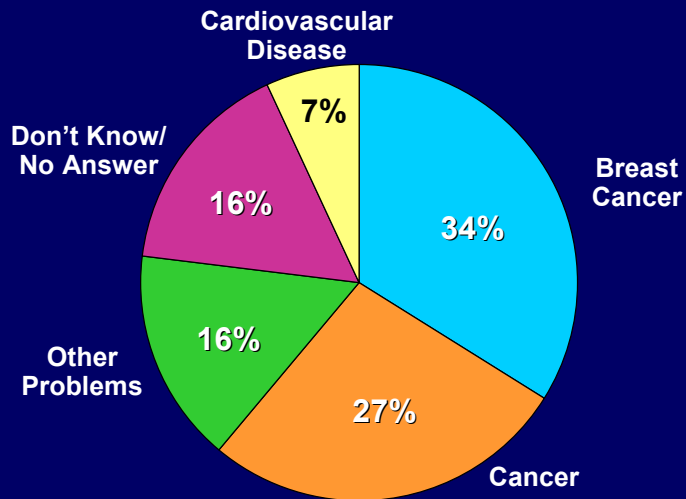
ΟΡΜΟΝΙΚΗ ΥΠΟΚΑΤΑΣΤΑΣΗ

Number of Postmenopausal Women in the US Is Continually Increasing



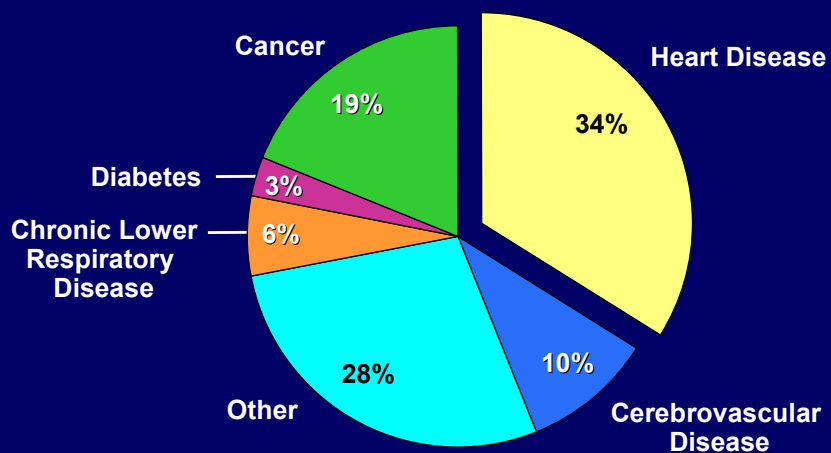
*Projected estimate.
 US Census Bureau. *Statistical Abstract of the United States*. 2000;15.
 US Census Bureau. National population projections. Available at:
<http://www.census.gov/population/www/projections/natsum-T3.html>. Accessed 1/3/02.

Women's Perceptions of Their Greatest Health Problems



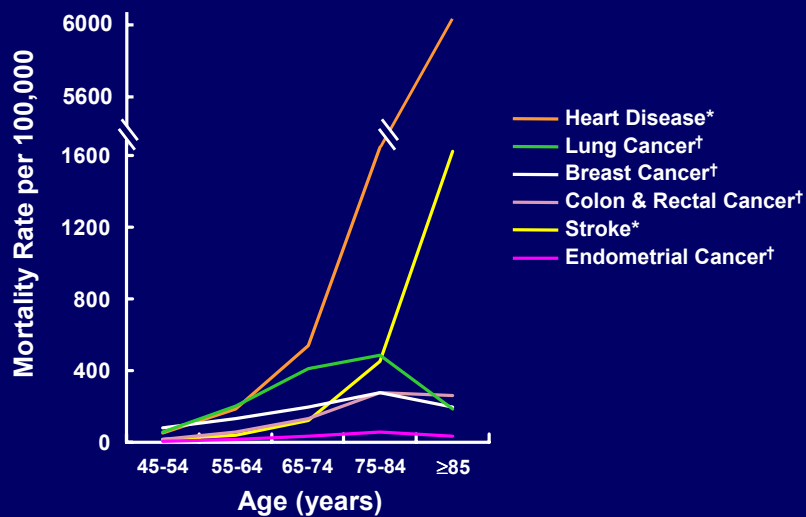
Adapted from Mosca L, et al. *Arch Fam Med.* 2000;9:506-15.

Causes of Death Among Women*



*Percentage of total deaths in 1999 among women aged 65 and older.
Anderson RN. *National Vital Statistics Reports.* 2001;49:1-13.

Mortality Rates in Women



*Mean of years 1995-1998; †1994-1998.

Eberhardt VMS, et al. *Health, United States, 2001*. National Center for Health Statistics, 2001:189,192.
Ries LAG, et al. *SEER Cancer Statistics Review, 1973-1998*. National Cancer Institute, 2001.

ΕΠΙΠΤΩΣΗ ΤΟΥ ΚΑΡΚΙΝΟΥ ΤΟΥ ΜΑΣΤΟΥ

- ≈ 170000 γυναίκες τον χρόνο διαγιγνώσκονται στις ΗΠΑ
- 1:8 γυναίκες θα νοσήσει από Ca μαστού

ΠΑΡΑΓΟΝΤΕΣ ΚΙΝΔΥΝΟΥ (I)

Σχετικός Κίνδυνος

<2

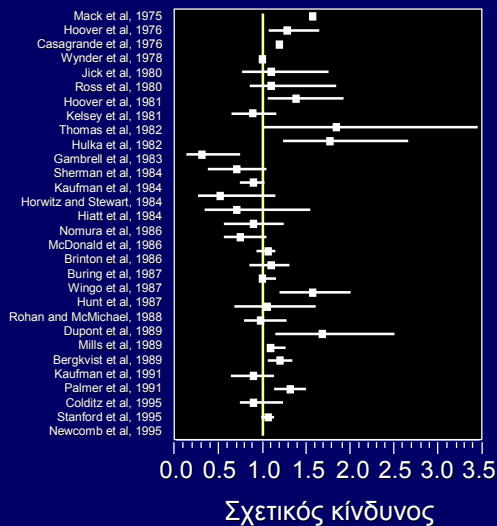
- πρόιμη εμμηναρχή
- μεγάλη ηλικία εμμηνόπαυσης
- ατεκνία
- παχυσαρκία
- παραγωγική καλοήθης νόσος μαστού
- κατανάλωση αλκοόλ

ΠΑΡΑΓΟΝΤΕΣ ΚΙΝΔΥΝΟΥ (II)

Σχετικός Κίνδυνος 2-4

- ηλικία πρώτου τοκετού >35
- έκθεση σε ακτινοβολία

ΣΧΕΤΙΚΟΣ ΚΙΝΔΥΝΟΣ ΑΝΑΠΤΙΞΗΣ ΚΑΡΚΙΝΟΥ ΤΟΥ ΜΑΣΤΟΥ ΜΕ ΤΗ ΘΟΥΥ

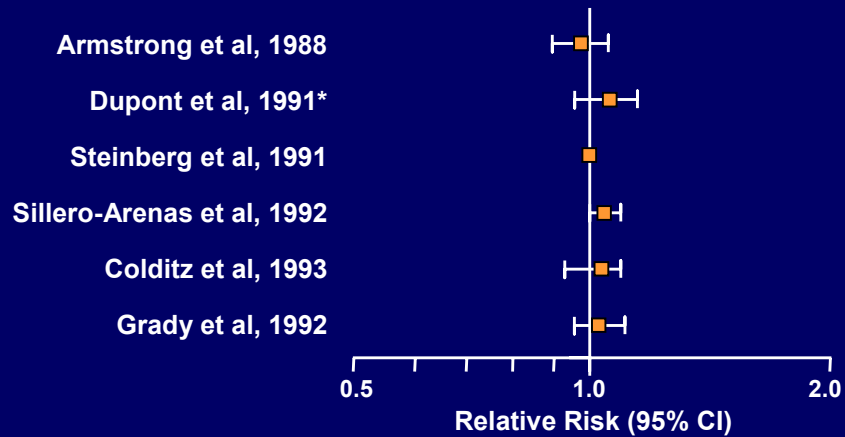


Review of Studies Published from 1975-2000: Lack of Consistent Results

- ◆ ERT and Breast Cancer Risk (45 studies)
 - 82% of studies reported risk estimates **not significantly different from 1.0**
 - 13% of studies reported risk estimates >1.0 but none >2.0
 - 2% of studies reported risk estimates <1.0
- ◆ HRT and Breast Cancer Risk (20 studies)
 - 80% of studies reported risk estimates **not significantly different from 1.0**
 - 10% of studies reported risk estimates >1.0
 - 10% of studies reported risk estimates <1.0

Bush TL, et al. *Obstet Gynecol.* 2001;98:498-508.

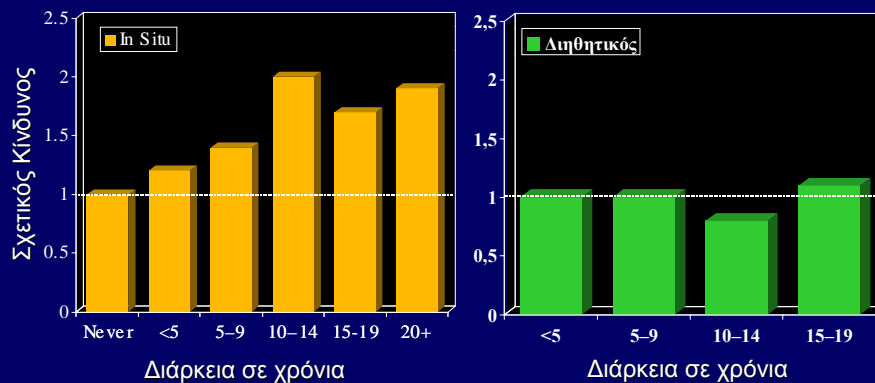
Ever Use of HRT and Breast Cancer Risk *Meta-Analyses*



*Women who took 0.425 mg or less of conjugated estrogens.

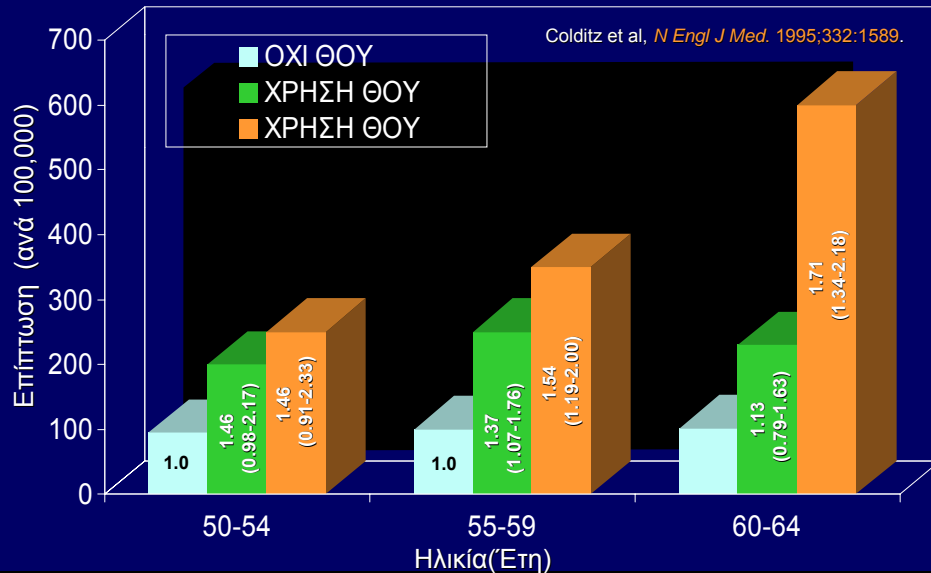
ΣΧΕΤΙΚΟΣ ΚΙΝΔΥΝΟΣ ΚΑΡΚΙΝΟΥ ΤΟΥ ΜΑΣΤΟΥ

Διάρκεια χρήσης Οιστρογόνων



Schairer et al, *Cancer Causes Control*. 1994;5:491.

ΕΠΙΠΤΩΣΗ ΚΑΙ ΣΧΕΤΙΚΟΣ ΚΙΝΔΥΝΟΣ ΚΑΡΚΙΝΟΣ ΤΟΥ ΜΑΣΤΟΥ



Collaborative Group Reanalysis

- ◆ 52,705 women with breast cancer
- ◆ 108,411 women without breast cancer
- ◆ 51 studies, 21 countries
- ◆ Main analysis based on
 - 53,865 postmenopausal women with known age at menopause; 17,830 (33%) HRT users
 - 17,949 cases / 35,916 controls

Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet.* 1997;350:1047-59.

Risk of Breast Cancer With HRT

<i>HRT Use</i>	<i>RR</i>
Ever use	1.14*
Current use	1.21*
Past use	1.07

* $P < .01$.

Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1997;350:1047-59.

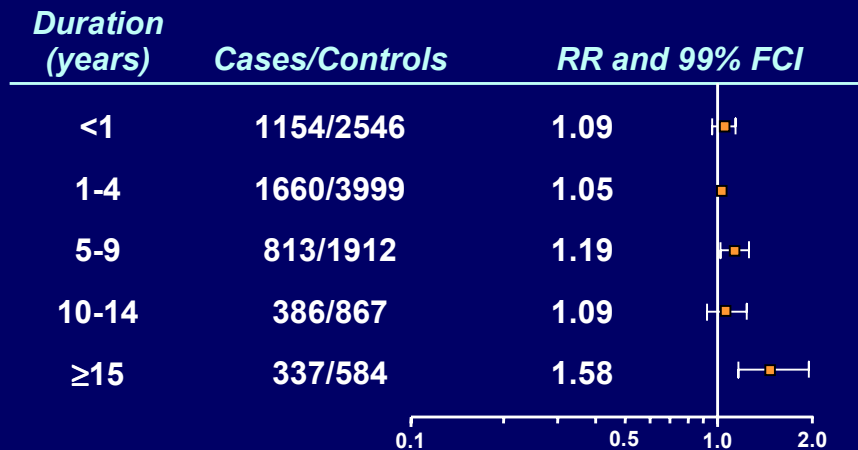
Collaborative Reanalysis: Clinical Implications

<i>Duration of HRT</i>	<i>Estimated Number Of Excess Breast Cancers/1000 Women*</i>	<i>Proportion of Users Affected</i>
5 years	2	0.2%
10 years	6	0.6%
15 years	12	1.2%

*Based on 2.3% increase in risk with each year of use.

Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1997;350:1047-59.

Odds of Breast Cancer by Duration of HRT Use



Increase in risk per year = 1.023; FCI = floated confidence interval.

Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1997;350:1047-59.

Type of HRT Regimen and Breast Cancer Risk

Hormone Use	No. of Cases	RR (95% CI)
No use of hormones	761	1.0
Estrogen only	805	1.1 (1.0-1.3)
Estrogen-progestin (subset analysis)	101	1.3 (1.0-1.6)

- ◆ Retrospective data on hormone use collected by questionnaire
- ◆ Total number of women = 46,355
- ◆ Cases of breast cancer = 2082
- ◆ Only 12 women in the study took progestin >15 days/month

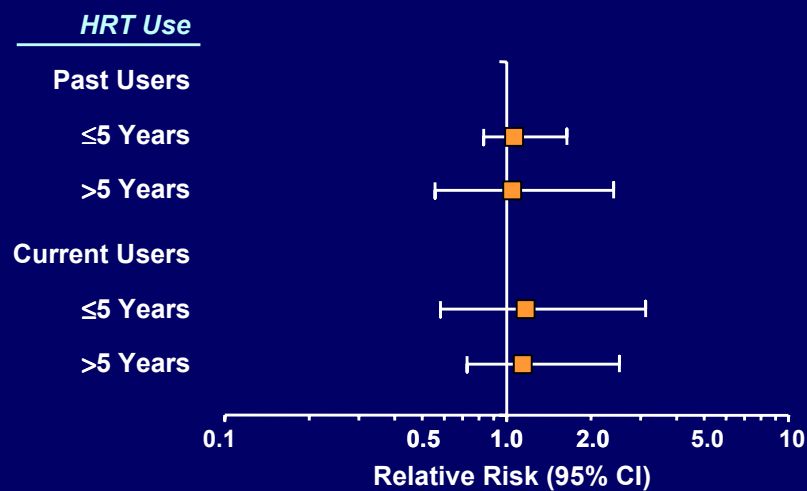
Schairer C, et al. *JAMA*. 2000;283:485-91.

HRT and Breast Cancer Risk

<i>HRT Use</i>	<i>No. of Cases</i>	<i>RR (95% CI)</i>
ERT (current)	243	1.1 (1.0-1.3)
HRT (current)	77	1.4 (1.1-1.9)
<4 years	26	1.1 (0.8-1.7)
≥4 years	22	1.5 (1.0-2.4)
Lean, ≥4 yrs. use	26	2.0 (1.3-3.0)
Not lean, ≥4 yrs. use	13	1.3 (0.7-2.4)

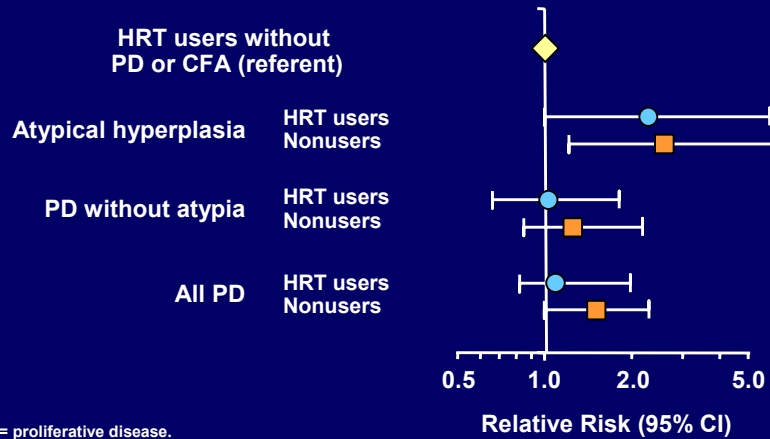
Total number of cases = 2082.
 Schairer C, et al. *JAMA*. 2000;283:485-91.

Breast Cancer Risk With HRT Use in Women With a Family History



Sellers TA, et al. *Ann Intern Med*. 1997;127:973-80.

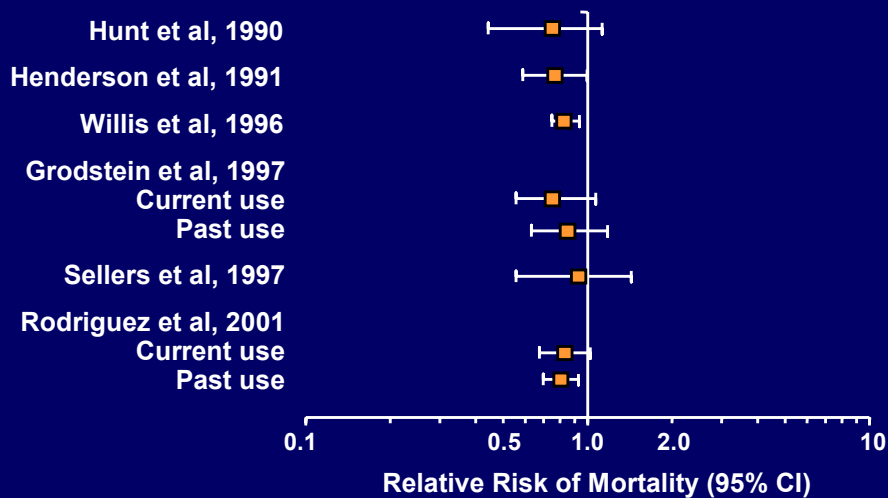
HRT Use and Breast Cancer in Women With a History of Benign Breast Disease



PD = proliferative disease.
CFA = complex fibroadenoma.

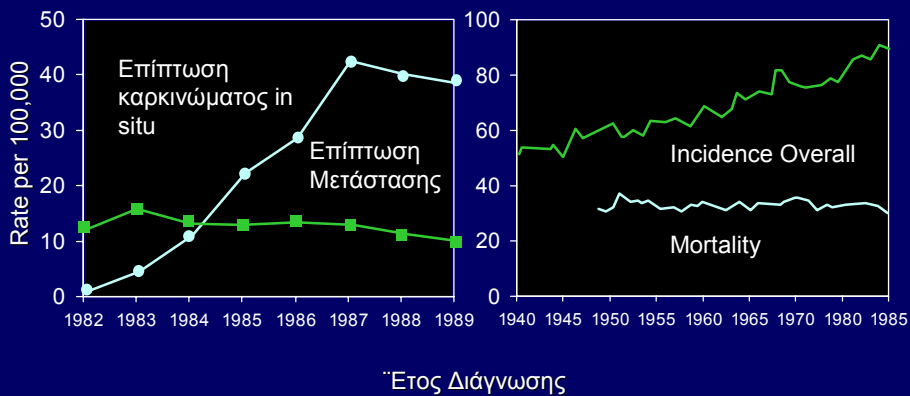
Dupont WD, et al. *Cancer*. 1999;85:1277-83.

Results for Breast Cancer Mortality With ERT/HRT Use Show Consistency



Η ΑΛΛΑΓΗ ΜΟΡΦΗΣ ΤΟΥ ΚΑΡΚΙΝΟΥ ΤΟΥ ΜΑΣΤΟΥ

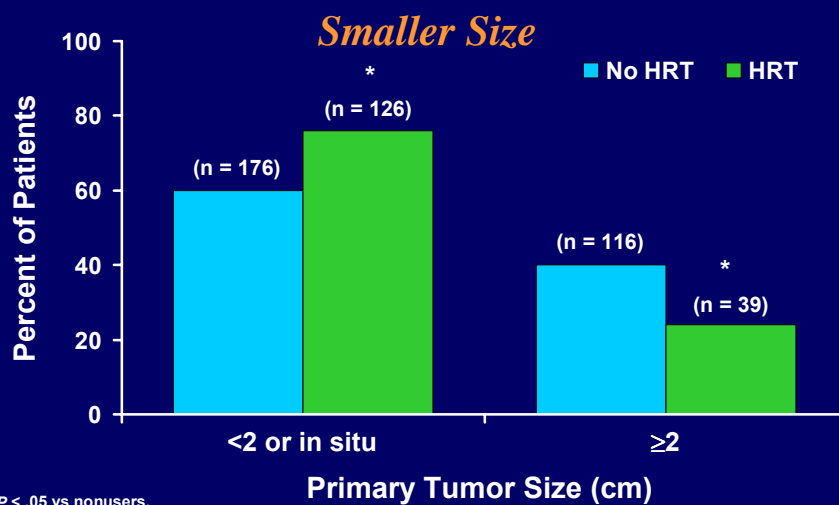
Age-Adjusted Incidence and Mortality



Έτος Διάγνωσης

Miller et al, *N Engl J Med.* 1992;327:1756.
Harris et al, *N Engl J Med.* 1992;327:319.

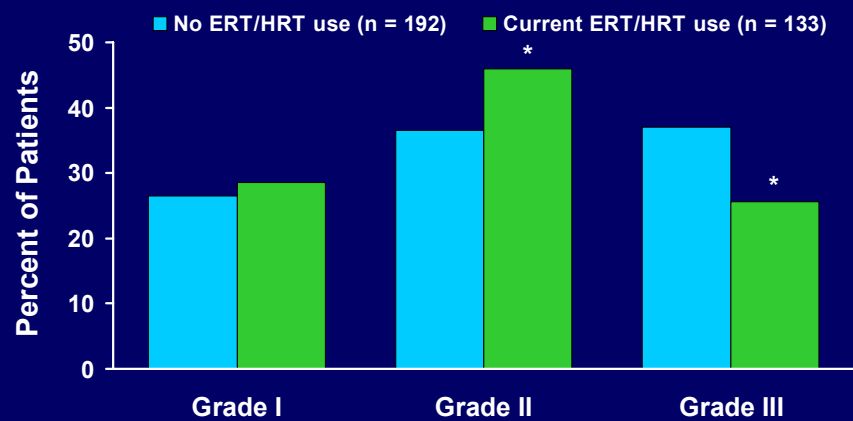
Tumors in ERT/HRT Users Are Biologically Less Aggressive



Holli K, et al. *J Clin Oncol.* 1998;16:3115-20.

Tumors in ERT/HRT Users Are Biologically Less Aggressive

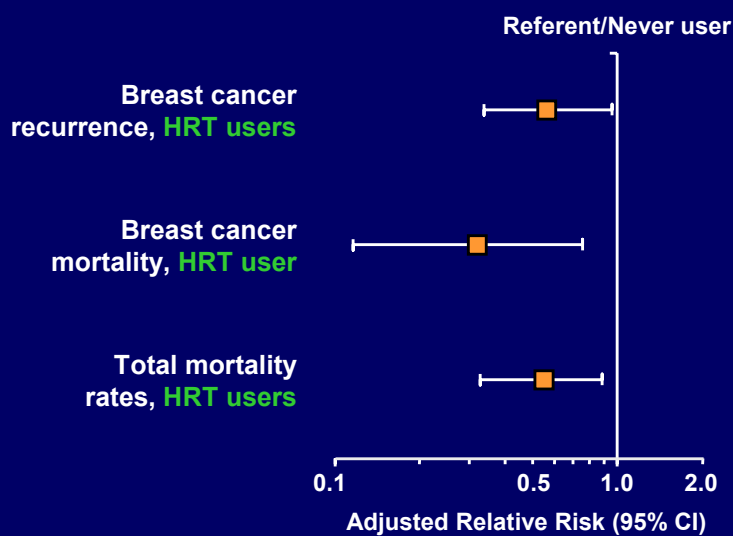
Lower Grade



*P < .05 vs nonusers.

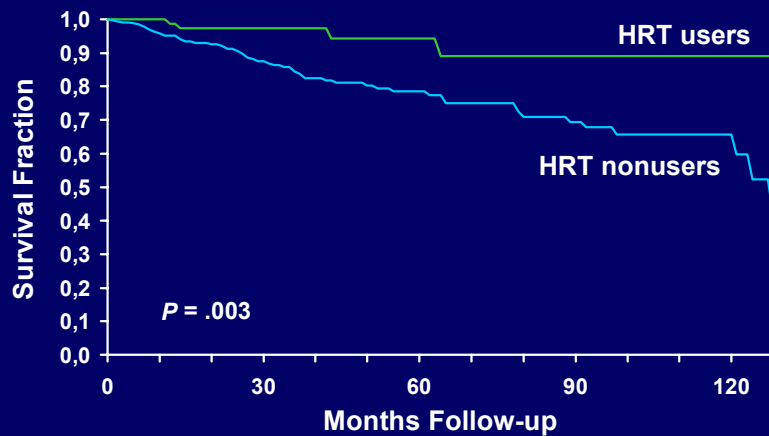
Billimora MM, et al. *An Surg Oncol.* 1999;6:200-7.

Recurrence and Mortality in Relation to HRT Use After Diagnosis of Breast Cancer



O'Meara ES, et al. *J Natl Cancer Inst.* 2001;93:754-61.

Survival Rates for Breast Cancer Patients *HRT Users Compared to Nonusers*



DiSaia PJ, et al. *Am J Clin Oncol.* 2000;23:541-5.

Women's Health Initiative (WHI)

© 2002, Wyeth Pharmaceuticals, Philadelphia, PA 19101

July 2002

101663-01

Women's Health Initiative (WHI) Study Design of Clinical Trial

- ◆ Large-scale, NIH-sponsored, randomized, **multi-center study** of estrogen (ERT) and combination estrogen plus progestin (HRT)
- ◆ Purpose: assess long-term risk/benefit ratio of ERT and combination HRT in disease prevention
- ◆ Primary endpoints: prevention of **cardiovascular disease** and the incidence of **breast cancer**
- ◆ Enrolled 27,000 women aged 50-79 years (**mean age, ~63 years**) between 1993 and 1998; scheduled to conclude in 2005

The Women's Health Initiative Study Group. *Control Clin Trials*. 1998;19:61-109.

WHI Baseline Characteristics

Characteristic	HRT n = 8,506	Placebo n = 8,102
Age at screening, yrs*	63.2 (7.1)	63.3 (7.1)
Prior hormone use, %	26.1	25.6
Body mass index, kg/m ² *	28.5 (5.8)	28.5 (5.9)
Never smokers, %	49.6	50.0
Diabetes, %	4.4	4.4
Hypertension, %	35.7	36.4
Statin use at baseline, %	6.9	6.8
Family Hx breast cancer, %	16.0	15.3
History of MI,† %	1.6	1.9
History of CABG/PTCA,† %	1.1	1.5‡

*Values are means (SD); †Overall incidence of prior cardiovascular disease = 7.7%; ‡P = .04 vs HRT.

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI

HRT Component of WHI Clinical Trial

- ◆ Average duration of follow-up = 5.2 years
- ◆ Regimens: CEE 0.625 mg/d + MPA 2.5 mg/d (n = 8,506) or placebo (n = 8,102)
- ◆ Primary outcome: coronary heart disease (nonfatal MI and CHD death)
- ◆ **Primary adverse outcome: invasive breast cancer**
- ◆ Global index: a summary measure of the overall balance of risks and benefits

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Findings

- ◆ The HRT component of the study was **stopped** early because the health risks outweighed the benefits after **5.2 years** of follow-up
- ◆ The study showed a statistically significant increase in risk of CVD, strokes, venous thromboembolisms (VTEs)/PEs
- ◆ After **4 years** of therapy an **increase of invasive breast cancer** was noted

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Results

Relative Risk of Combination HRT

Health Event	Relative Risk vs Placebo at 5.2 Years
Heart attack	1.29
Stroke	1.41
Breast cancer	1.26
VTE	2.11
Colorectal cancer	0.63
Hip fracture	0.66

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Results: Invasive Breast Cancer Summary by Year

Year	HRT n (%)	Placebo n (%)	Hazard Ratio*
1	11 (0.13)	17 (0.21)	0.62
2	26 (0.31)	30 (0.38)	0.83
3	28 (0.34)	23 (0.29)	1.16
4	40 (0.50)	22 (0.29)	1.73
5	34 (0.57)	12 (0.22)	2.64
6+	27 (0.53)	20 (0.47)	1.12

n = number of patients; (%) = annualized % calculated from average exposure over ~60 months.
*z score for trend across all years = 2.56; test for trend based on Cox proportional hazard model with time-dependent treatment effects.

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

HAZARD RATIO ΣΕ ΓΥΝΑΙΚΕΣ ΠΟΥ ΠΗΡΑΝ ΘΟΥ

Χωρίς προηγούμενη λήψη ΘΟΥ: 1,06 (0,81-1,38)

Με προηγούμενη λήψη ΘΟΥ:

- <5 χρόνια 2,13 (1,15-3,94)
- 5-10 χρόνια 4,61 (1,01-21,02)
- >10 χρόνια 1,81 (0,60-5,43)

ΚΑΡΚΙΝΟΣ ΕΝΔΟΜΗΤΡΙΟΥ

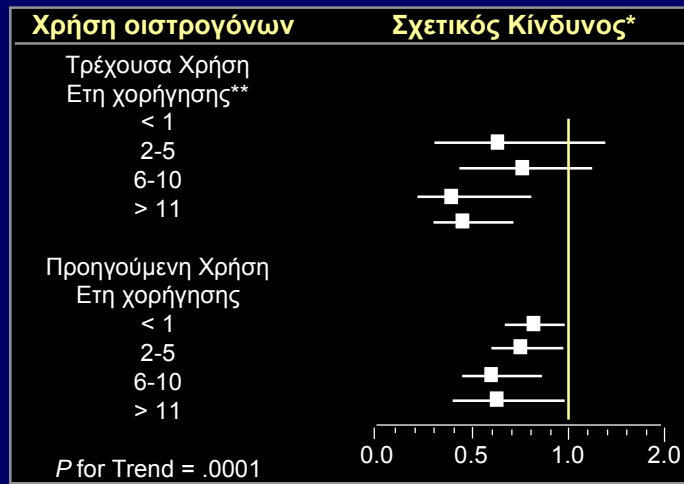
Σχετικός Κίνδυνος που συνδέεται με τη ΘΟΥ
(Γυναίκες με άθικτη μήτρα)

	Σχετ. Κινδ.	95% CI
Όχι ΘΟΥ	1.0	–
Οιστρογόνα μόνο	5.0	1.6-5.9
Οιστρ.+Προγεσταγόνο	0.9	0.7-1.2

Persson et al, *Int J Cancer*. 1996;67:327.

ΘΟΥ ΚΑΙ ΚΑΡΚΙΝΟΣ ΤΟΥ ΕΝΤΕΡΟΥ

Θνησιμότητα σε σχέση με τη διάρκεια της χρήσης



*RR Estimates Adjusted for Age and Race
 **Includes 50 Non-Case Subjects with Unclassified Years of Estrogen Use
 Calle et al, *J Natl Cancer Inst.* 1995;87:517.