



# **Hormone und Krebs – von der Pubertät bis zu den Wechseljahren**

**C Tempfer**

Universitätsklinik für Frauenheilkunde

- ◆ **Hormonelle Kontrazeptiva**
- ◆ **IUD - Gestagene**
- ◆ **Hormonersatztherapie**
- ◆ **Tibolon**

- ◆ Brustkrebs (CGHFBC 1996)
  - 54 Studien; 25 Länder; n=53 297 (BC) vs. 100 239 (kein BC)
  - current use RR 1.24 (1.15-1.33)
  - erhöhtes Risiko bis 10 Jahre nach Absetzen
  - kein erhöhtes Risiko >10 a (RR 1.01 [0.96-1.05])

- ◆ populationsbasierte Fallkontrollstudie  
(White 2004)
- ◆ 747 cases 1983-1990; 961 controls
  - **early use <5 yrs menar. 1.3 (1.0-1.8)**
  - **high progestin potency 1.5 (1.1-2.1)**

## ◆ Ovarialkarzinom und Ovulation

# Ovulation – *Eierstockkrebs*



## ◆ Legehennen (*Gallus domesticus*)

- Spezies meisten Ovulationen
  - 300/a; 1 d zw. Ovulation - Oviposition
  - Spezies höchstes OvCa-Risiko
  - 400 Legehennen (Barnes 2002)
  - 16 Monate Beobachtung 43%

- ◆ Ovarialkarzinom nach OC (Bosetti 2002)
  - 6 Studien; n=2 768 cases, 6 247 controls
  - sign. reduziertes Risiko OR 0.66 (0.56-0.79)
  - >5a stärkere Reduktion OR 0.50 (0.33-0.76)
  - kein Verlust der Protektion >20a nach Absetzen
  - sign. reduz. Risiko auch bei belasteter FA, BRCA-Trägerinnen

- ◆ Myokardinfarkt (Khader 2003)
  - Metaanalyse; 23 Studien
  - current use OR 2.48 (1.9-3.2)
  - past use OR 1.15 (0.98-1.35)
- ◆ Zervixkarzinom (Deligeoroglu 2003)
  - past use OR 2.5 (1.1-6.1)
- ◆ Subarachnoidalbltg. (Johnston 1998)
  - Metaanalyse; 11 Studien

- ◆ Langzeiteffekte über 25 Jahre (Beral et al. 1999)
  - n=46 000; 63% OC; 1599 Todesfälle
    - Ovarialkarzinom OR 0.2 (0.1-0.8) **3 vs. 12**
    - Zervixkarzinom OR 2.5 (1.1-6.1) **17 vs. 7**
    - zerebrovaskuläre Mort. OR 1.9 (1.2-3.1) **44 vs. 29**
  - nach >10 a kein Effekt auf Mortalität

13.04.2007



## **Mirena<sup>®</sup> – Wichtige Änderungen der Produktinformationen und Einführung eines Einverständnisverfahrens**

Im Rahmen eines Stufenplanverfahrens und in Abstimmung mit anderen Arzneimittelbehörden in der EU wurde die Aufnahme zusätzlicher Risikoangaben in die Produktinformationen von Mirena<sup>®</sup> angeordnet. Mirena<sup>®</sup> ist eine Intrauterinspirale, die lokal kontinuierlich Levonorgestrel freisetzt. Dadurch

# LNG-IUD

In Bezug auf ein mögliches Brustkrebsrisiko wird jetzt darauf hingewiesen, dass bei Anwenderinnen von Gestagen-only-Kontrazeptiva (z.B. Mirena<sup>®</sup>) ein Brustkrebsrisiko besteht, das möglicherweise in der gleichen Größenordnung liegt wie das bei Anwenderinnen kombinierter oraler Kontrazeptiva. Weiterhin stellt das Vorliegen von Geschlechtshormon-abhängigen Tumoren nun auch für Mirena<sup>®</sup> eine absolute Kontraindikation dar.

In Bezug auf Uterusperforationen wird in einem Warnhinweis darauf hingewiesen, dass das Risiko einer Insertions-assoziierten Uterusperforation bei stillenden Frauen, bei Frauen mit fixierten Lageanomalien des Uterus sowie bei postpartaler Insertion erhöht sein kann. Deshalb sollte in Betracht gezogen werden, eine Insertion erst nach der 12. postpartalen Woche durchzuführen.

Weiterhin besteht in Deutschland zukünftig die Notwendigkeit, die ausführliche Aufklärung der Patientin vor der Einlage von Mirena<sup>®</sup> und ihr Einverständnis schriftlich zu dokumentieren (Einverständnisverfahren). Damit soll sichergestellt werden, dass alle Frauen vor der Einlage von

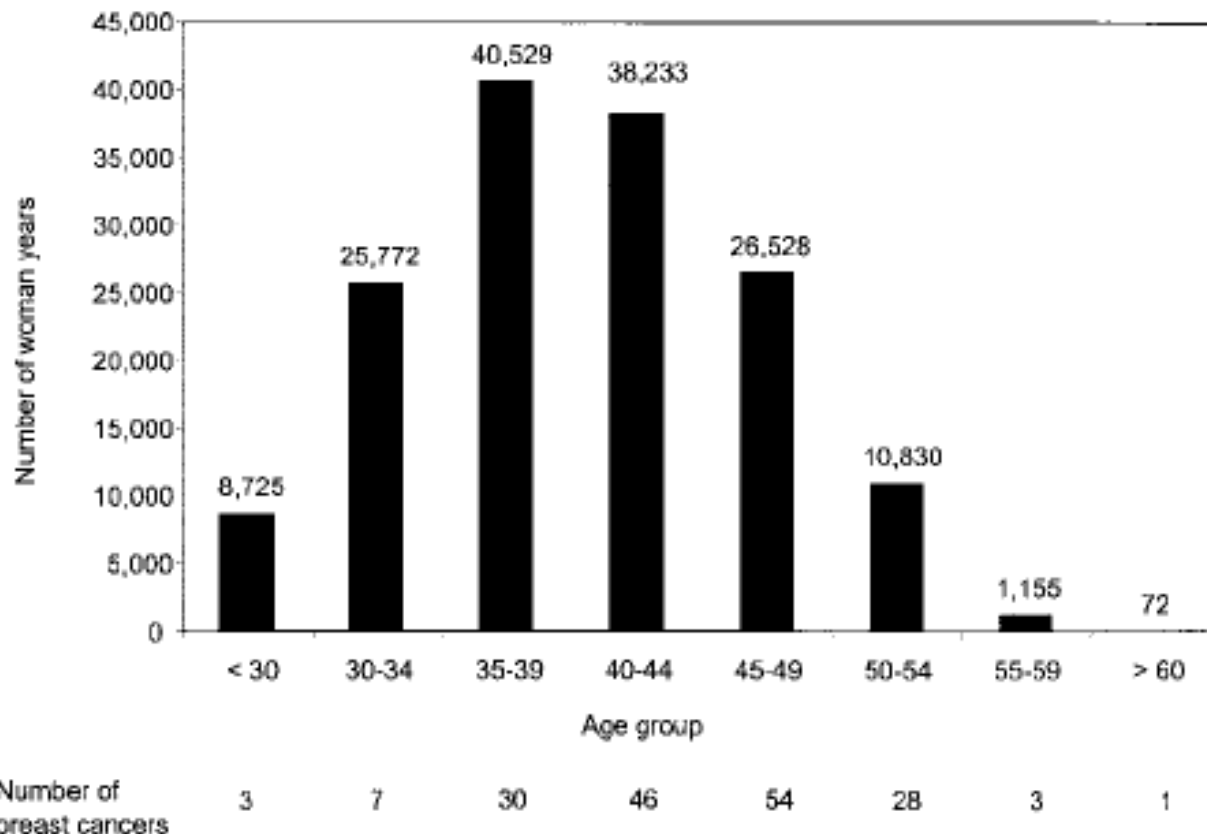
- ◆ **Norplant® – subdermal, LNG**
  - 5-Jahre Kohortenstudie; n=78 000 Frauenjahre (Meirik 2001)
  - kein Unterschied Prävalenz Brustkrebs
- ◆ **Fallkontrollstudie – LNG-implant oder Gestagen i.m.**
  - kein erhöhtes Brustkrebsrisiko (Strom 2004)

# LNG-IUD

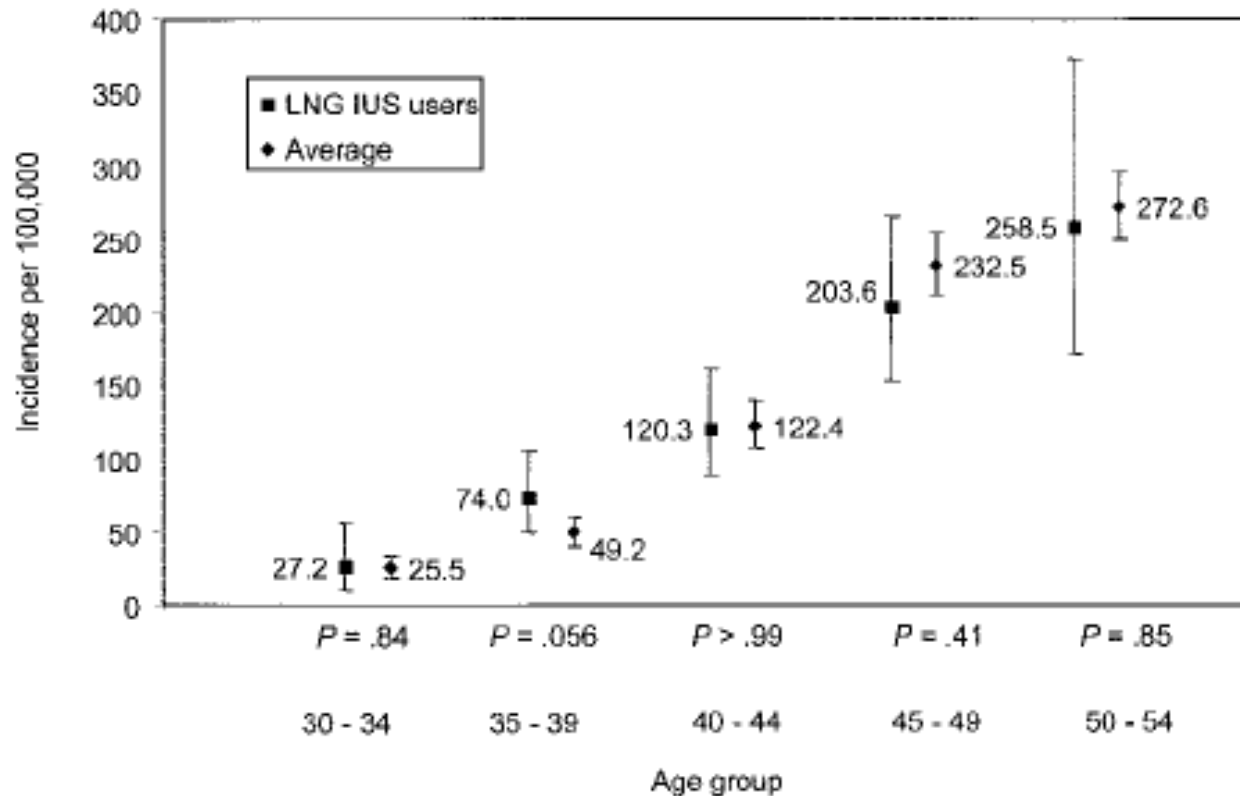
## Use of the Levonorgestrel-Releasing Intrauterine System and Breast Cancer

*Taina Backman, Ilkka Raurama, Kimmo Jaakkola, Pirjo Iuk, Kaja Vaahera, Aino Launonen,*

◆ **Sti**



**Fig. 1.** Distribution of woman-years and breast cancer diagnoses by age group.



**Fig. 2.** Incidence of breast cancer per 100,000 woman-years by age group in levonorgestrel-releasing intrauterine system users and the overall Finnish female population (average). The  $P$  values refer to the Fisher exact test. LNG IUS, levonorgestrel-releasing intrauterine system.

- ◆ 2 Cochrane-Analysen (Lethaby 2000; French 2004)
- ◆ hormonally impregnated IUD
  - **contraception, heavy menstrual bleeding**
- ◆ Zusammenfassung aller kontrollierter Studien
- ◆ 21 RCTs/5 RCTs
  - **In keiner der Studien erhöhtes Brustkrebsrisiko als sAE**

- ◆ **retrospektive Fallkontroll-Studie**
- ◆ **6 Spitäler; Belgien** (Trinh 2008)
- ◆ **n=76 N. mammae+LNG-IUD**
- ◆ **n=120 matched**
  - Alter, Tumorcharakteristika, Behandlungsmodalität

# LNG-IU

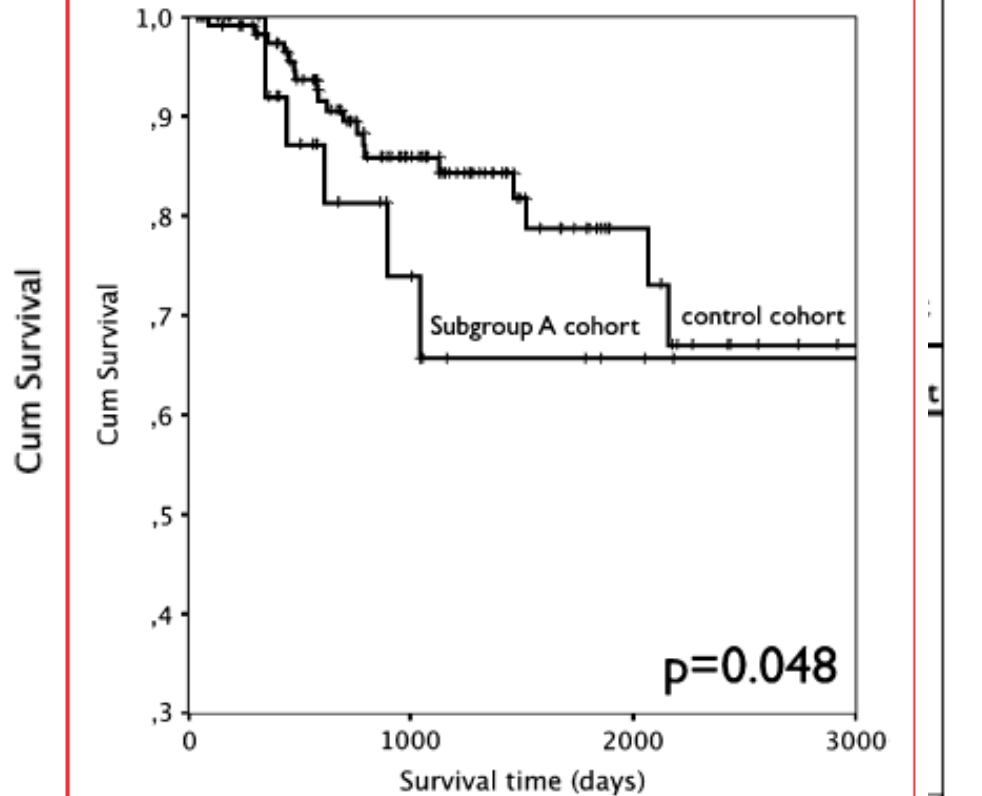
- ◆ Rezidi (20/12)
- ◆ Subg
  - at t
  - after

FIGURE 1

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FIGURE 2

Kaplan-Meier survival curve: LNG IUS breast cancer patients who had a LNG IUS at time of diagnosis and continued using it (subgroup A) vs. control cohort.



Trinh. LNG IUS in breast cancer patients. Fertil Steril 2007.

Trinh. LNG IUS in breast cancer patients. Fertil Steril 2007.

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**Case-control Studies**

Shu et al., 1991	China
Rosenblatt et al., 1996	Multi-country
Hill et al., 1997	United States
Sturgeon et al., 1997	United States
Tao et al., 2006	China
Castellsague et al., 1993	United States
Salazar-Martinez et al., 1999	Mexico
Parazzini et al., 1994	Italy
Benshushan et al., 2002	Israel

**Pooled adjusted odds ratio**

**Cohort Studies**

Wernli et al., 2006	China
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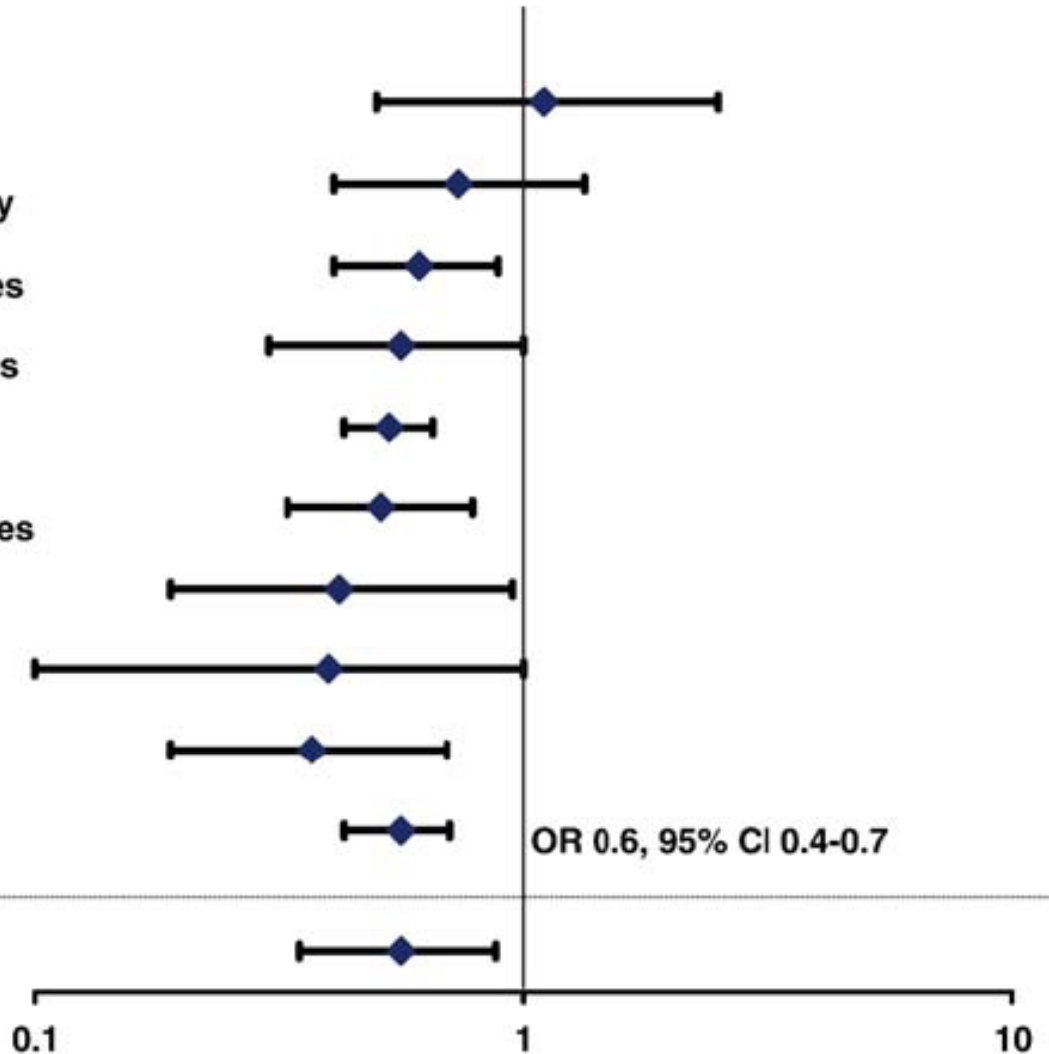
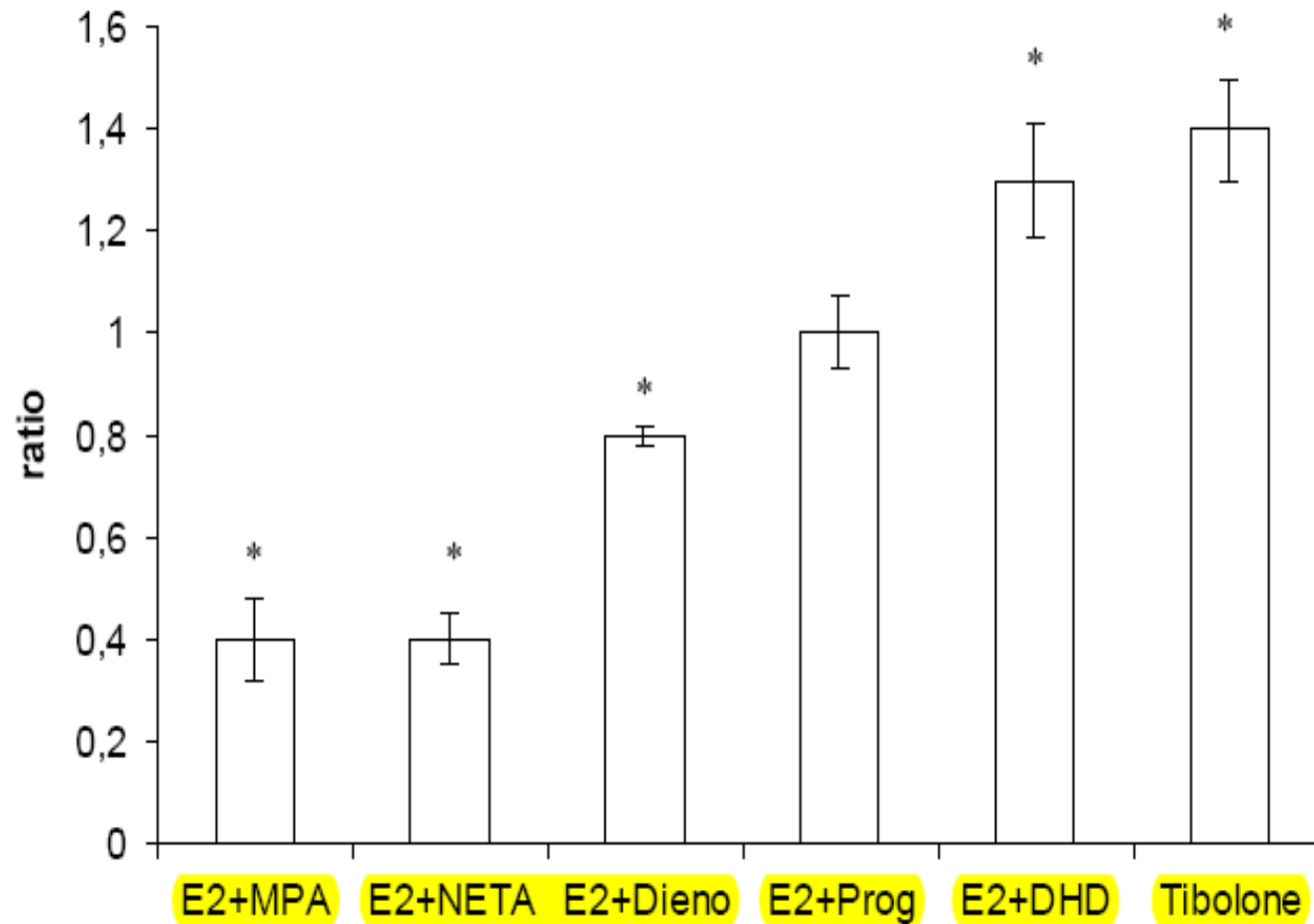


Fig. 1. Adjusted ORs and 95% CIs for the association between IUD use and endometrial cancer.



acetate; NETA, norethisterone acetate; E2, estradiol; Dieno, dienogest; DHD, dihydrodydrogesterone; and Prog, progesterone. A ratio >1 means induction of apoptosis. \* $P < 0.05$  vs. controls.



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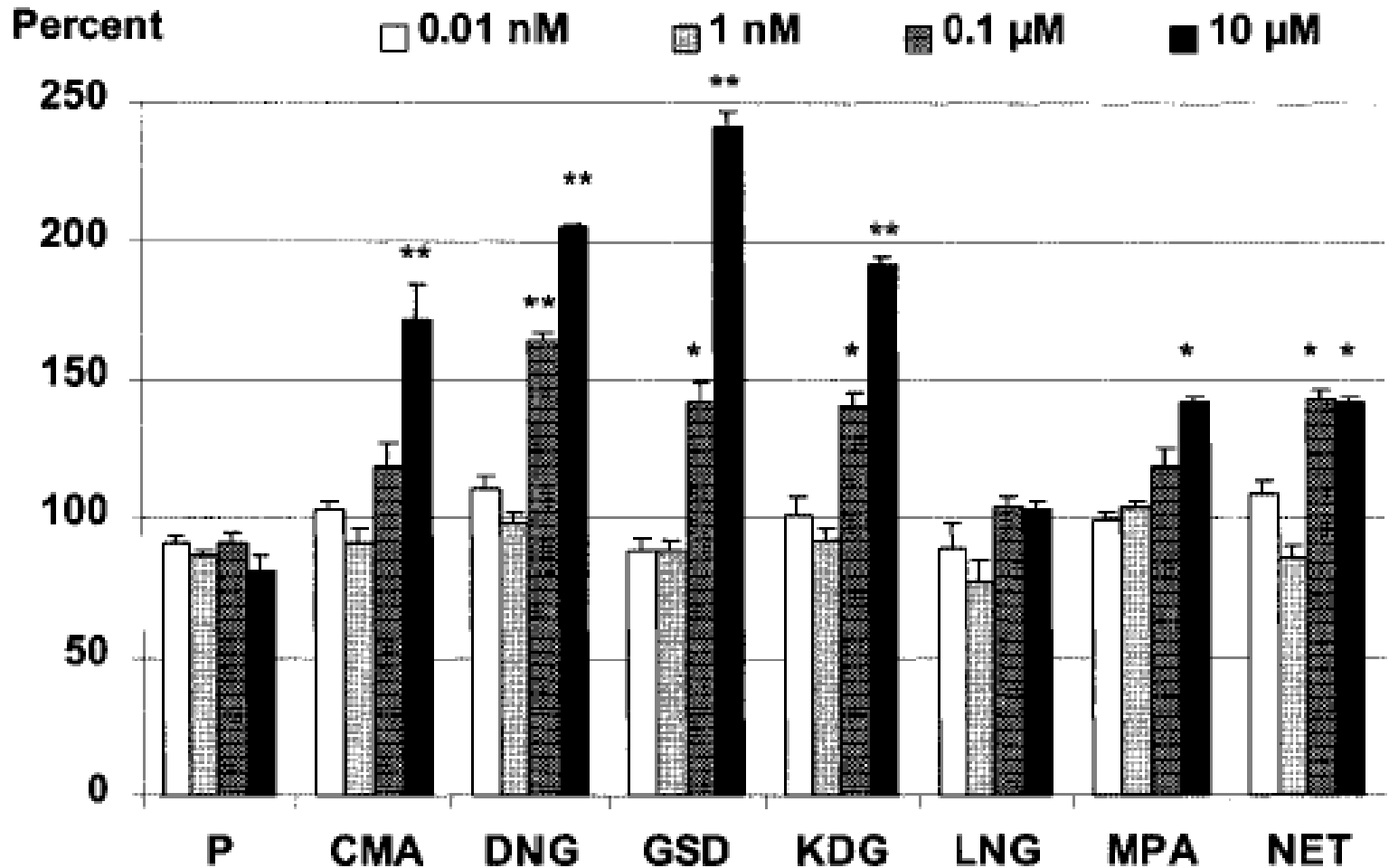
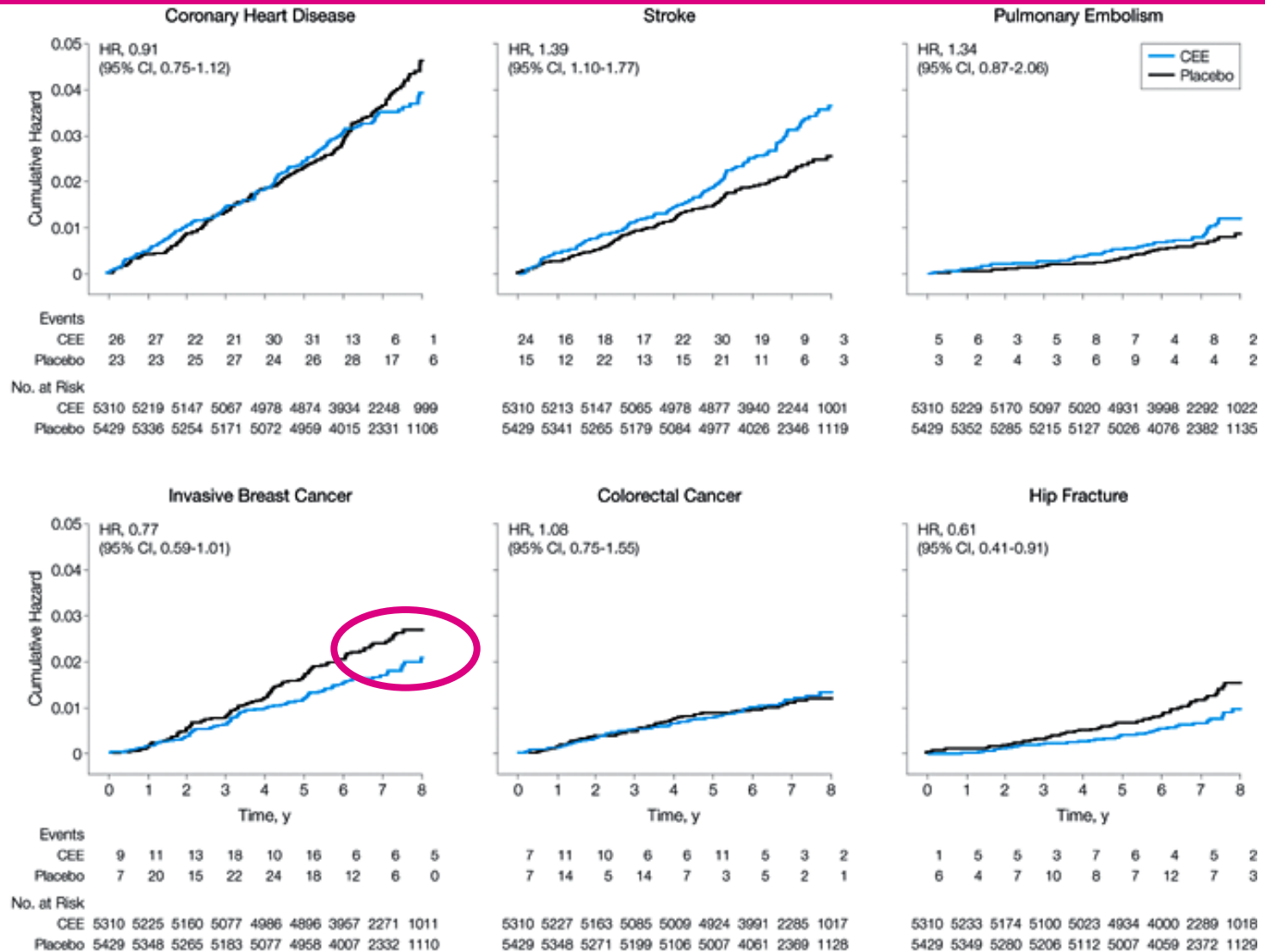
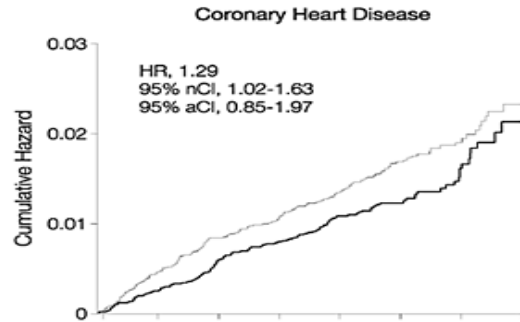


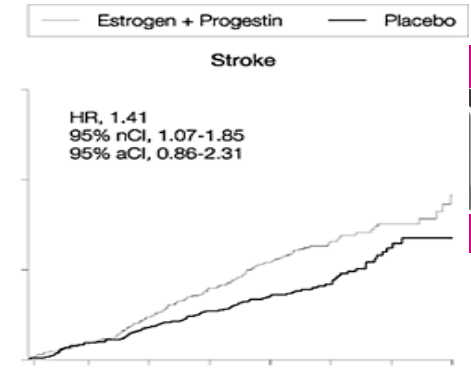
Fig. 1 Changes of serum-stimulated growth of MCF-7 cells after addition of progestins. P: progesterone, CMA: chlormadinone acetate, DNG: dienogest, GSD: gestodene, KDG: 3-ketodesogestrel, LNG: levonorgestrel, MPA: medroxyprogesterone acetate, NET: norethisterone (means  $\pm$  SD, \*  $p < 0.05$ , \*\*  $p < 0.01$  vs. control value = 100%).



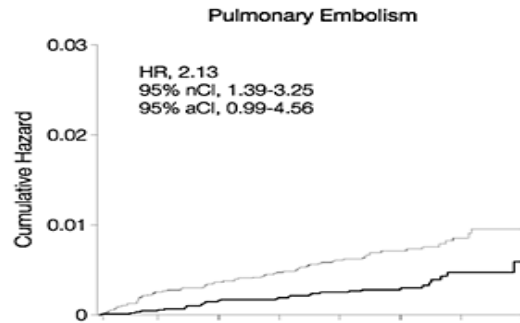


No. at Risk

Estrogen + Progestin	8506	8353	8248	8133	7004	4251	2085	814
Placebo	8102	7999	7899	7789	6639	3948	1756	523

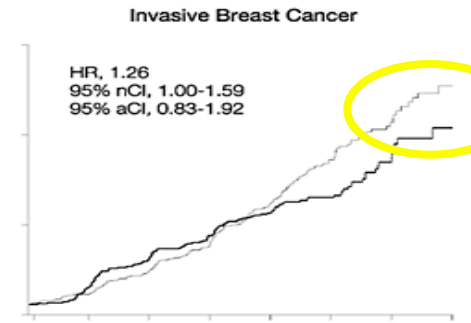


Estrogen + Progestin	8506	8375	8277	8155	7032	4272	2088	814
Placebo	8102	8005	7912	7804	6659	3960	1760	524

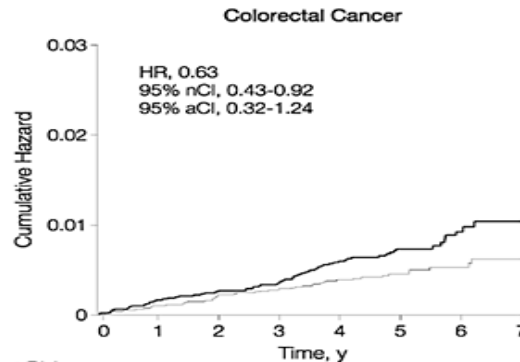


No. at Risk

Estrogen + Progestin	8506	8364	8280	8174	7054	4295	2108	820
Placebo	8102	8013	7924	7825	6679	3973	1770	526

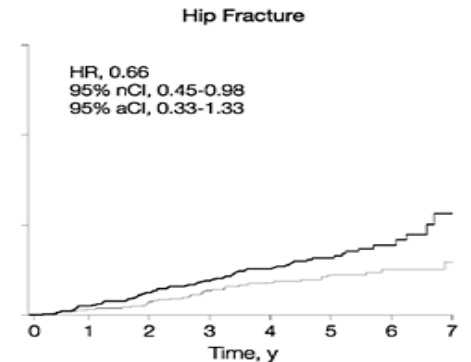


Estrogen + Progestin	8506	8378	8277	8150	7000	4234	2064	801
Placebo	8102	8001	7891	7772	6619	3922	1740	523



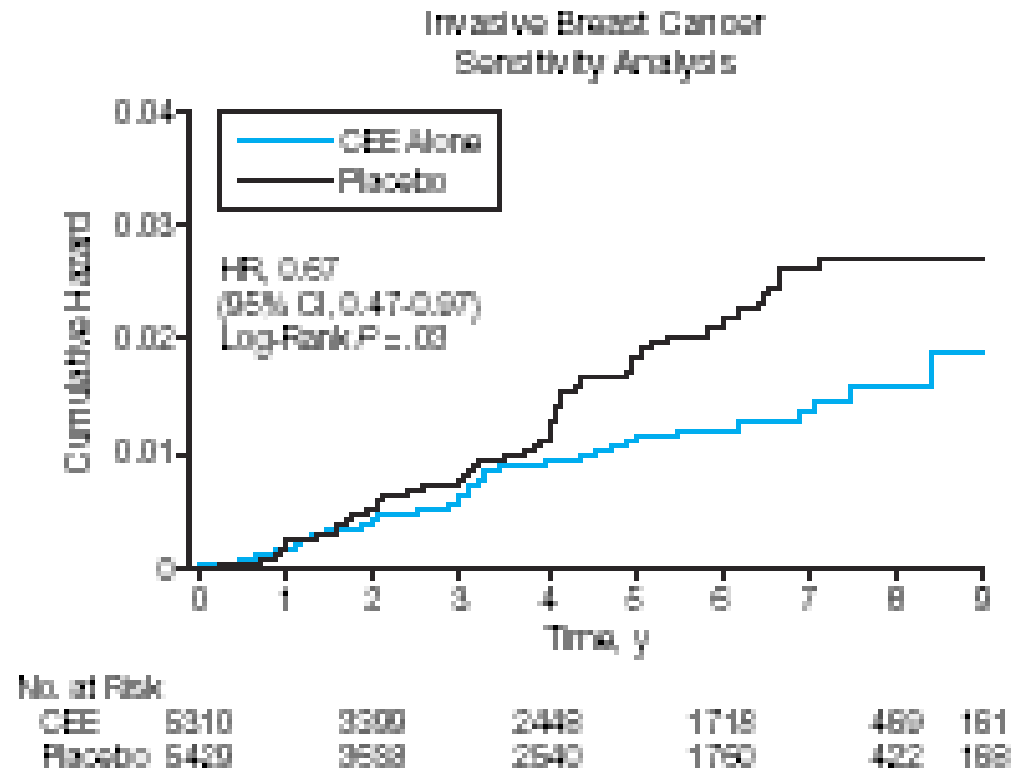
No. at Risk

Estrogen + Progestin	8506	8379	8297	8194	7073	4305	2111	825
Placebo	8102	8003	7916	7814	6660	3958	1756	522



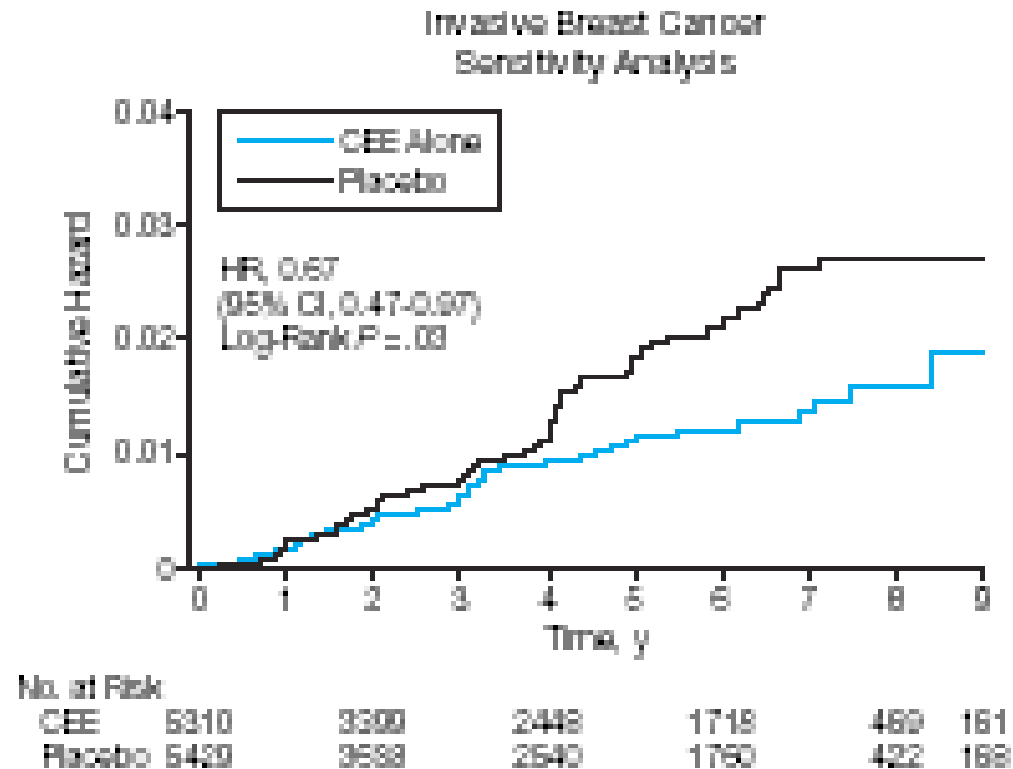
Estrogen + Progestin	8506	8382	8299	8190	7073	4305	2116	826
Placebo	8102	8009	7915	7807	6659	3958	1763	525

**Figure 2. Cumulative Hazard for Invasive Breast Cancer: Sensitivity Analysis**



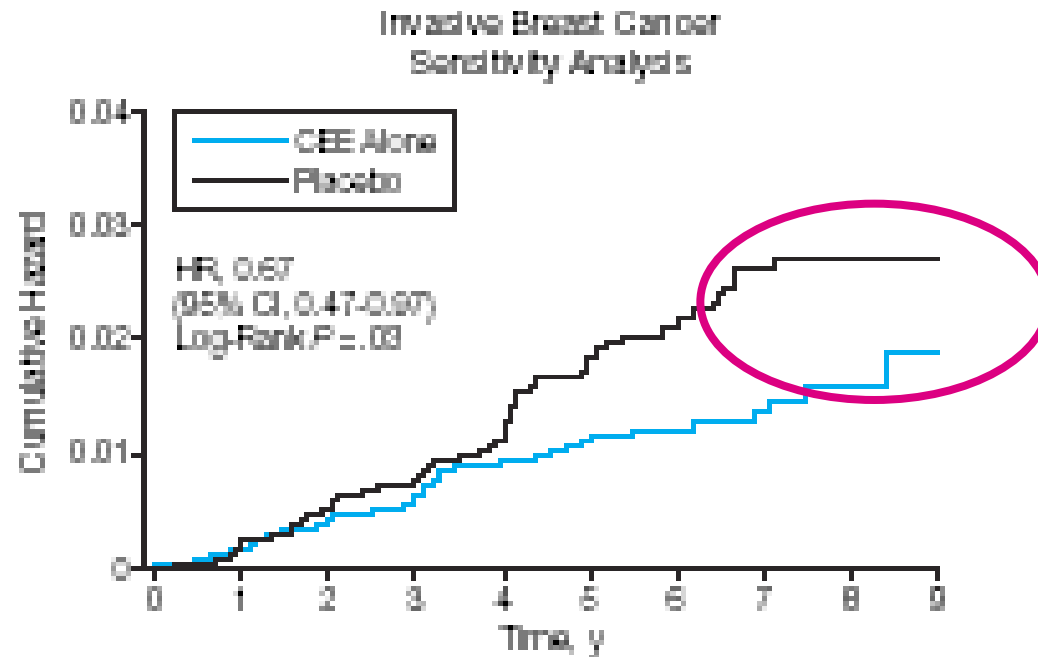
Participants with less than 80% adherence to study medications were censored 6 months after their first episode of nonadherence. CEE indicates conjugated equine estrogens; CI, confidence interval; HR, hazard ratio.

**Figure 2. Cumulative Hazard for Invasive Breast Cancer: Sensitivity Analysis**



Participants with less than 80% adherence to study medications were censored 6 months after their first episode of nonadherence. CEE indicates conjugated equine estrogens; CI, confidence interval; HR, hazard ratio.

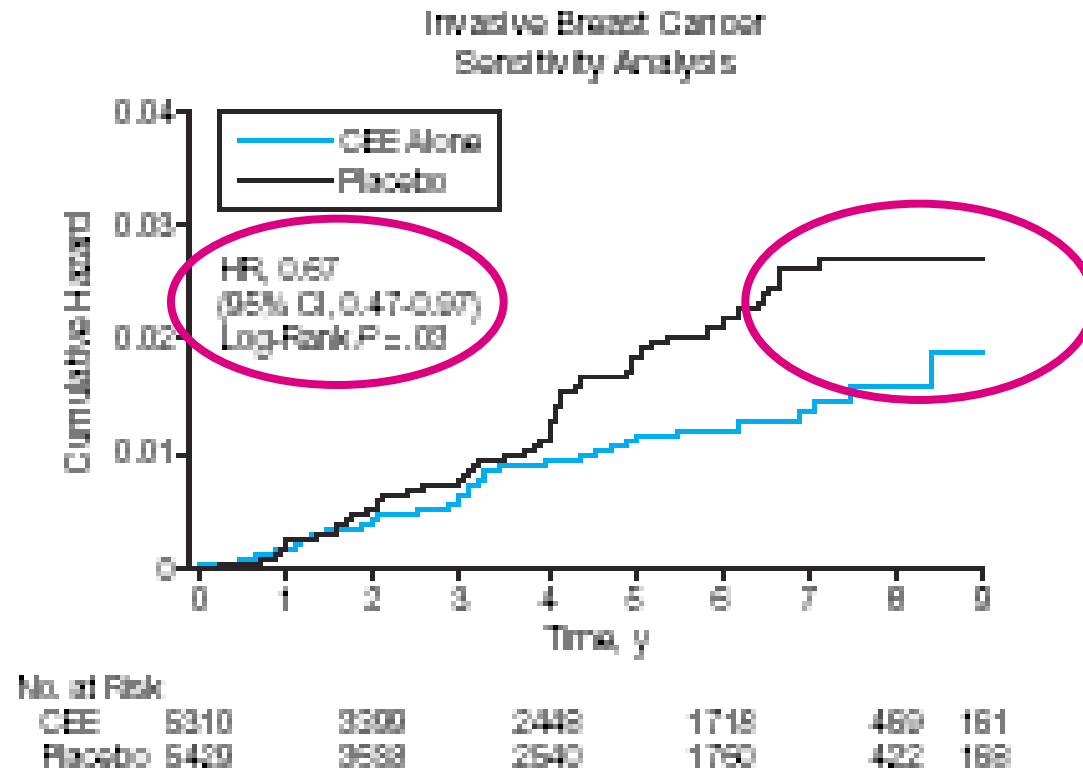
**Figure 2. Cumulative Hazard for Invasive Breast Cancer: Sensitivity Analysis**



No. at Risk	0	1	2	3	4	5	6	7	8	9
CEE	5310	3300	2448	1718	460	161				
Placebo	5429	3588	2540	1750	422	168				

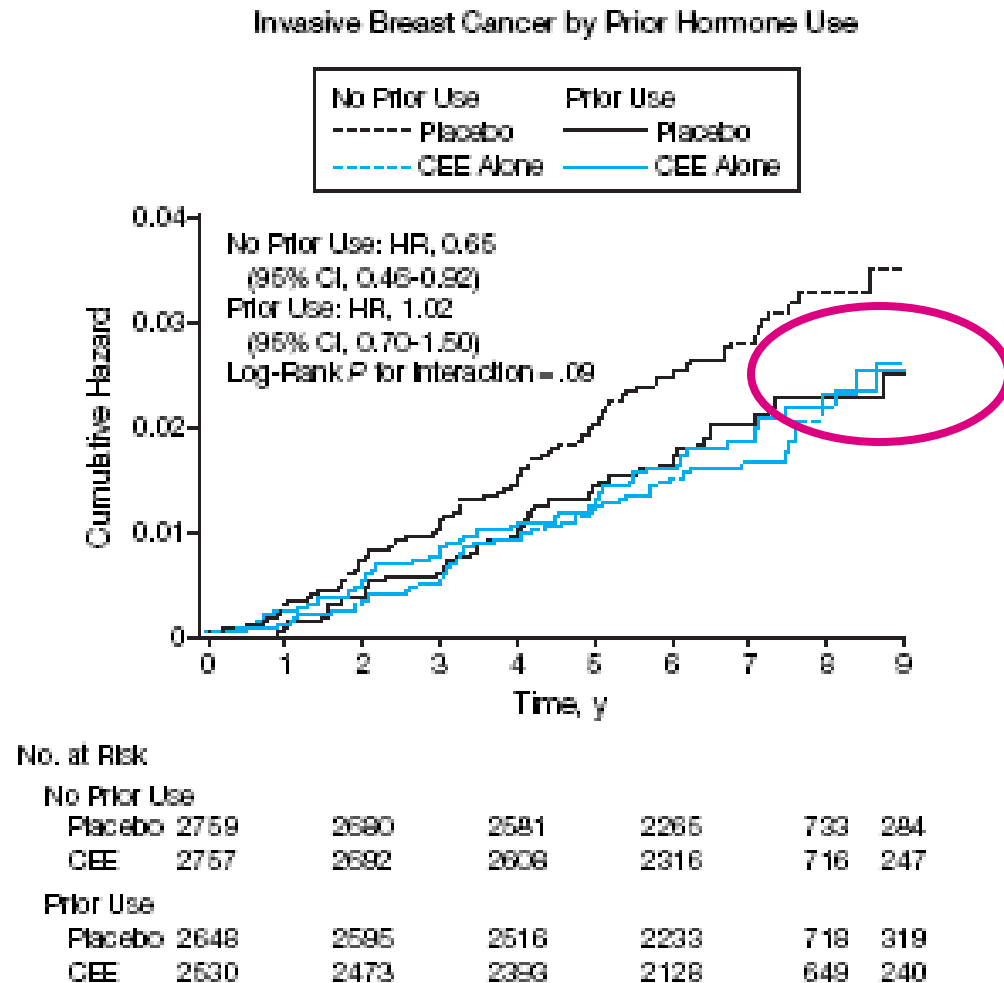
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**Figure 2. Cumulative Hazard for Invasive Breast Cancer: Sensitivity Analysis**



Participants with less than 80% adherence to study medications were censored 6 months after their first episode of nonadherence. CEE indicates conjugated equine estrogens; CI, confidence interval; HR, hazard ratio.

**Figure 4.** Cumulative Hazard for Invasive Breast Cancer by Prior Hormone Use and Randomization Assignment



CEE indicates conjugated equine estrogens; CI, confidence interval; HR, hazard ratio.

# Relationship Between Long Durations

**Table 2.** Use of Unopposed Estrogen Replacement Therapy (ERT) and Risk of Overall and Specific Histological Types of Invasive Breast Carcinoma\*

Regimen	Controls, No. (%) (n = 1007)	All Cases (n = 975)		IDC Cases (n = 656)		ILC Cases (n = 196)	
		No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
<b>Exclusive ERT User†</b>							
Never	339 (33.7)	284 (29.1)	Reference	199 (30.3)	Reference	47 (24.0)	Reference
Ever	397 (39.4)	360 (36.9)	1.0 (0.8-1.3)	240 (36.6)	1.0 (0.8-1.4)	75 (38.3)	1.3 (0.8-2.0)
6 mo-4.9 y	113 (11.2)	79 (8.1)	0.8 (0.6-1.2)	56 (8.5)	0.9 (0.6-1.3)	17 (8.7)	1.1 (0.6-2.0)
5-14.9 y	83 (8.2)	90 (9.2)	1.2 (0.8-1.7)	60 (9.1)	1.2 (0.8-1.8)	19 (9.7)	1.5 (0.8-2.9)
15-24.9 y	77 (7.6)	86 (8.8)	1.3 (0.9-1.9)	61 (9.3)	1.4 (0.9-2.2)	14 (7.1)	1.3 (0.6-2.6)
≥25 y	124 (12.3)	105 (10.8)	1.0 (0.7-1.4)	63 (9.6)	0.9 (0.6-1.3)	25 (12.8)	1.3 (0.7-2.4)
<b>Recency of ERT Use Among Exclusive ERT Users‡</b>							
Never	339 (33.7)	284 (29.1)	Reference	199 (30.3)	Reference	47 (24.0)	Reference
Former	123 (12.2)	119 (12.2)	1.1 (0.8-1.5)	83 (12.7)	1.1 (0.8-1.6)	22 (11.2)	1.2 (0.7-2.1)
Current	274 (27.2)	241 (24.7)	1.0 (0.7-1.3)	157 (23.9)	1.0 (0.7-1.3)	53 (27.0)	1.3 (0.8-2.2)
6 mo-4.9 y	42 (4.2)	18 (1.8)	0.5 (0.3-0.9)§	12 (1.8)	0.5 (0.3-1.0)	6 (3.1)	1.1 (0.4-2.9)
5-14.9 y	49 (4.9)	50 (5.1)	1.2 (0.8-2.0)	34 (5.2)	1.3 (0.8-2.1)	11 (5.6)	1.8 (0.8-3.9)
15-24.9 y	63 (6.3)	72 (7.4)	1.4 (0.9-2.2)	51 (7.8)	1.5 (1.0-2.4)	12 (6.1)	1.5 (0.7-3.2)
≥25 y	120 (11.9)	101 (10.4)	1.0 (0.7-1.5)	60 (9.1)	0.9 (0.6-1.4)	24 (12.2)	1.4 (0.7-2.7)

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Ever users of CHRT (includes CHRT users who also had used ERT) had a 1.7-fold (95% confidence interval [CI], 1.3-2.2) increased risk of breast cancer, including a 2.7-fold (95%

Breast Cancer Res Treat (2008) 107:103–111  
DOI 10.1007/s10549-007-9523-x

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EPIDEMIOLOGY

## **Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study**

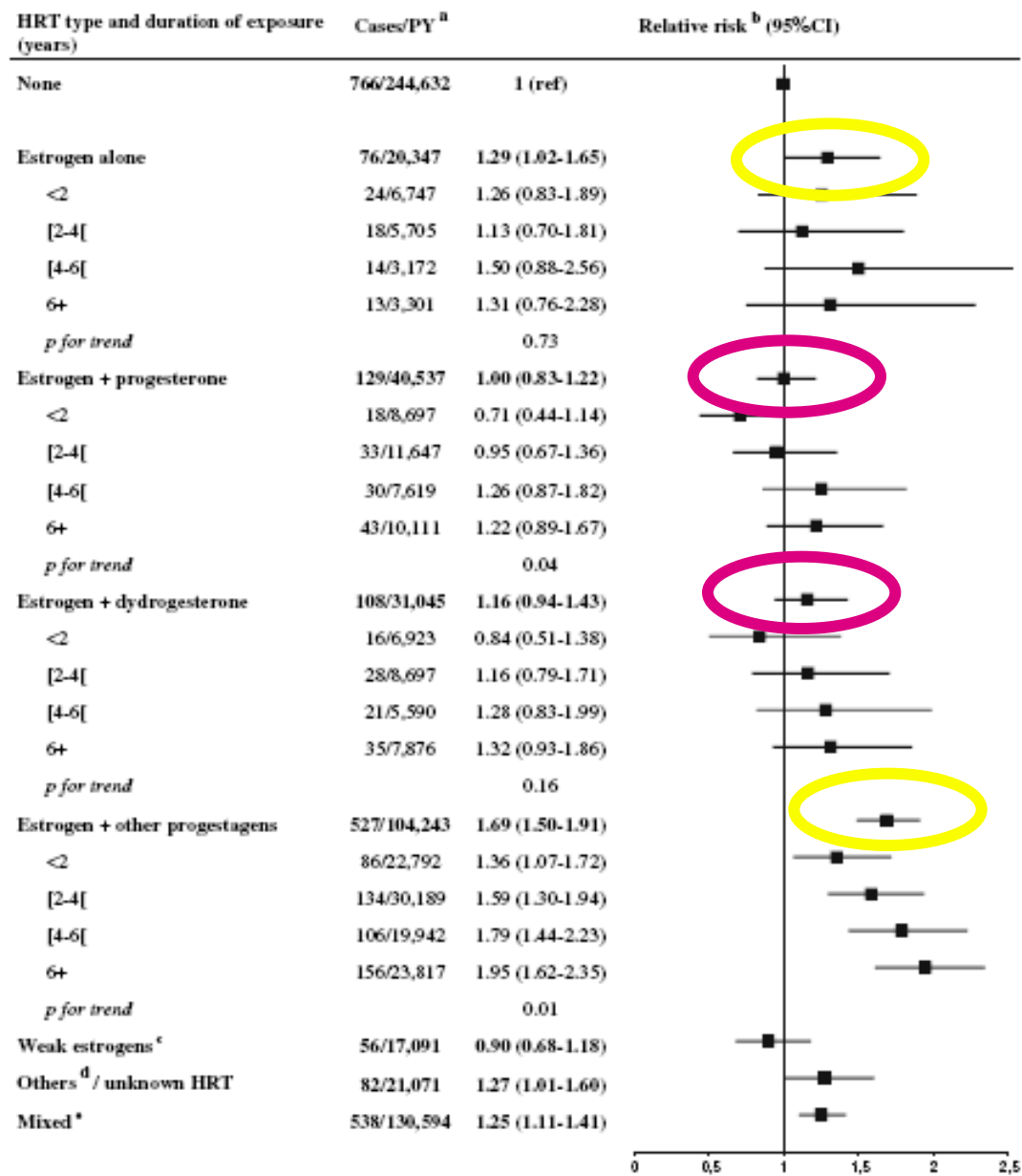
**Agnès Fournier · Franco Berrino ·  
Françoise Clavel-Chapelon**

- ◆ - prospektive Kohortenstudie
- ◆ - 1990; n= 80 377; mittl.  
Beobachtungsdauer 8.1a
- ◆ - HRT, ERT, Brustkrebs
- ◆ - 96% Brustkrebsfälle Histologie
- ◆ - Beginn ERT/HRT 52.4a
- ◆ - **ERT: 98% E2; diverse Gestagene**

**Table 2** Relative risks for invasive breast cancer according to route of estrogen administration and type of progestagen, compared with HRT never-use

	Oral Estrogen		Transdermal/ Percutaneous estrogen		P-values for homogeneity tests between routes of estrogen administration
	Cases/PY <sup>a</sup>	Relative risk <sup>b</sup> (95% CI)	Cases/PY <sup>a</sup>	Relative risk <sup>b</sup> (95% CI)	
Estrogen alone	13/3,598	1.32 (0.76–2.29)	56/14,826	1.28 (0.98–1.69)	0.93
Estrogen combined with:					
Progesterone		– <sup>c</sup>	121/35,513	1.08 (0.89–1.31)	–
Dydrogesterone	7/3,217	0.77 (0.36–1.62)	90/25,405	1.18 (0.95–1.48)	0.27
Medrogestone	91/1,031	2.77 (1.72–5.29)	28/3,598	2.02 (1.19–2.97)	0.12
Chlormadinone acetate	8/1,431	2.02 (1.00–4.06)	35/7,774	1.48 (1.05–2.09)	0.43
Cyproterone acetate	34/4,779	2.57 (1.81–3.65)		– <sup>c</sup>	–
Promegestone	13/2,814	1.62 (0.94–2.82)	69/14,910	1.52 (1.19–1.96)	0.84
Nomegestrol acetate	8/2,623	1.10 (0.55–2.21)	91/18,826	1.60 (1.28–2.01)	0.30
Norethisterone acetate	46/7,401	2.11 (1.56–2.86)		– <sup>c</sup>	–
Medroxyprogesterone acetate	29/7,035	1.48 (1.02–2.16)		– <sup>c</sup>	–
P-value for homogeneity among all progestagens		0.03		0.01	
P-value for homogeneity among progestagens other than progesterone and dydrogesterone		0.16		0.59	

**Table 3** Relative risks for invasive breast cancer by type of HRT and duration of exposure, compared with HRT never-use



# Breast Cancer Risk in Postmenopausal Women Using Estradiol–Progestogen Therapy

Table 2. Standardized Incidence Ratios of Invasive Breast Cancer in Women With the Use of Estradiol–Progestogen Therapy in Relation to Accurate Exposure Periods, or in Women With Accurate Exposure Data\*

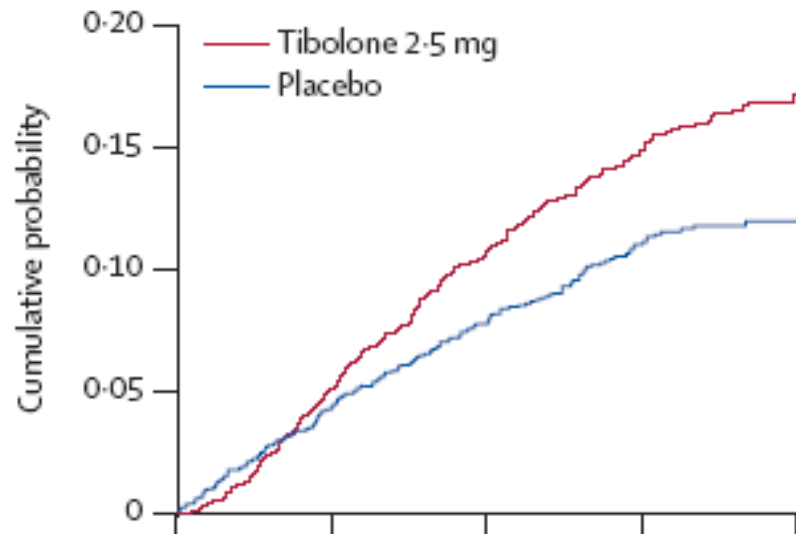
	N	Observed	Expected	SIR	95% CI
Accurate exposure					
6 mo to less than 3 y <sup>†</sup>	50,033	1024	976	1.05	0.97–1.11
3 y to less than 5 y <sup>†</sup>	30,583	547	418	1.31	1.20–1.42
5 y to less than 10 y <sup>†</sup>	32,466	472	273	1.72	1.58–1.89
10 y or more <sup>‡</sup>	23,131	299	146	2.07	1.84–2.30
Inaccurate exposure					
6 mo to less than 5 y <sup>‡</sup>	36,972	2,196	1,637	1.34	1.29–1.40
5 y to less than 10 y <sup>‡</sup>	48,366	1,673	969	1.73	1.65–1.81

**Table 4. Standardized Incidence Ratios of Invasive Breast Cancer Among Women Using Estrogen-Progestogen Therapy in 1994-2005, Grouped According to the Progestogen and Duration of Use\***

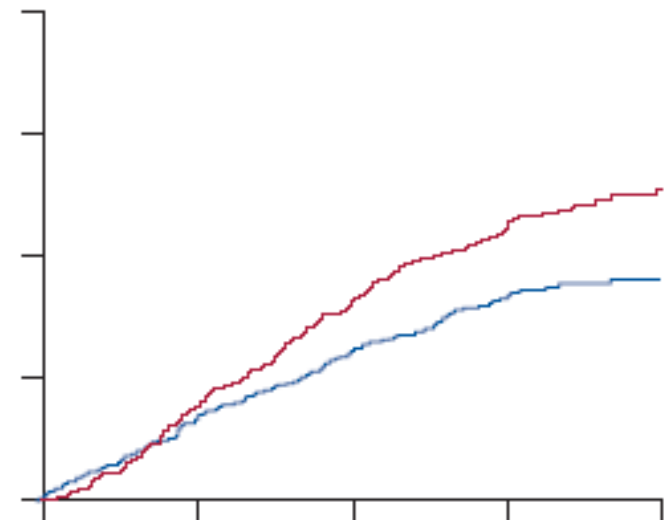
Progestin Type and Duration	N	Observed	Expected	SIR	95% CI
6 mo to less than 3 y <sup>†</sup>					
Norethisterone acetate	22,368	439	424	1.04	0.94–1.14
Medroxyprogesterone	13,438	336	324	1.04	0.93–1.15
Dydrogesterone	7,420	87	85	1.02	0.82–1.26
Other <sup>‡</sup>	7,213	149	134	1.11	0.94–1.30
3 y to less than 5 y <sup>†</sup>					
Norethisterone acetate	12,211	266	169	1.34	1.17–1.51
Medroxyprogesterone	8,648	166	130	1.27	1.09–1.48
Dydrogesterone	3,413	32	26	1.22	0.83–1.72
Other <sup>‡</sup>	4,357	61	55	1.12	0.85–1.43
5 y or more <sup>§</sup>					
Norethisterone acetate	24,093	670	330	2.03	1.88–2.18
Medroxyprogesterone	19,299	454	277	1.64	1.49–1.79
Dydrogesterone	1,014	8	7	1.13	0.49–2.22
Other <sup>‡</sup>	5,804	159	77	2.07	1.76–2.04
Mixed <sup>  </sup>	39,727	860	498	1.73	1.61–1.84
10 y or more <sup>§</sup>					
Norethisterone acetate	4,081	67	21	3.15	2.44–4.00
Medroxyprogesterone	2,049	16	8	1.90	1.07–3.07
Dydrogesterone	61	–	0.33	0.00	0.00–11.01
Other <sup>‡</sup>	289	6	2	2.79	1.02–6.07
Mixed <sup>  </sup>	6,492	70	30	2.33	1.82–2.94

# Tibolone

**A Overall (N=3098)**



**B Distant breast-cancer recurrence (N=3098)**



Number at risk

Tibolone 2.5 mg	1556	1420	1291	819	257
Placebo	1542	1391	1284	832	264

	1556	1423	1291	818	257
	1542	1393	1285	833	264

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Years

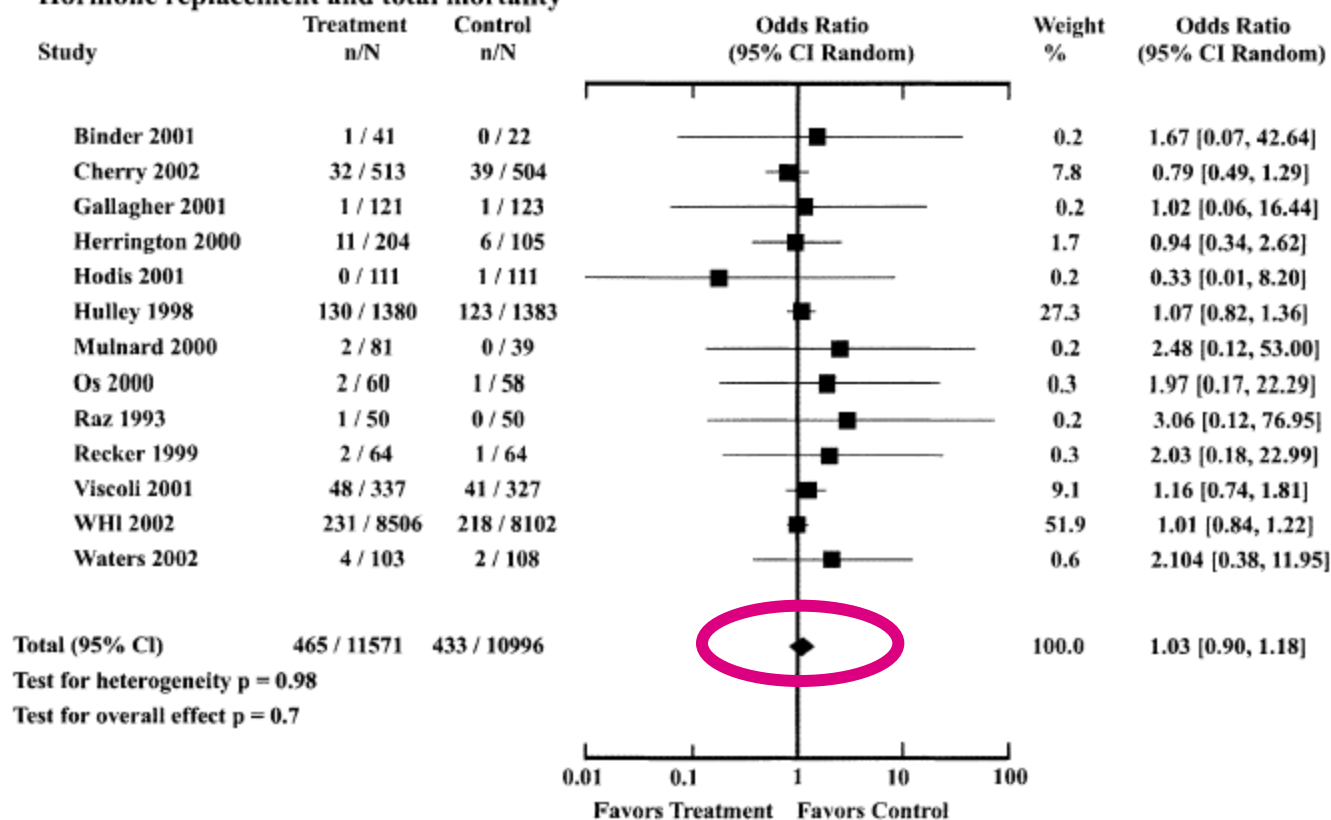
- ◆ **Growth School Age Girls** *Ahlgren et al. 2004*
  - n=117 415; Denmark
  - BC: n=3 340
  - high stature at 14 yrs, low BMI, early peak growth
  - independent risk factor of breast cancer
  - Russo et al.: hcG - proliferation

# Mortality Associated with Hormone Replacement Therapy in Younger and Older Women

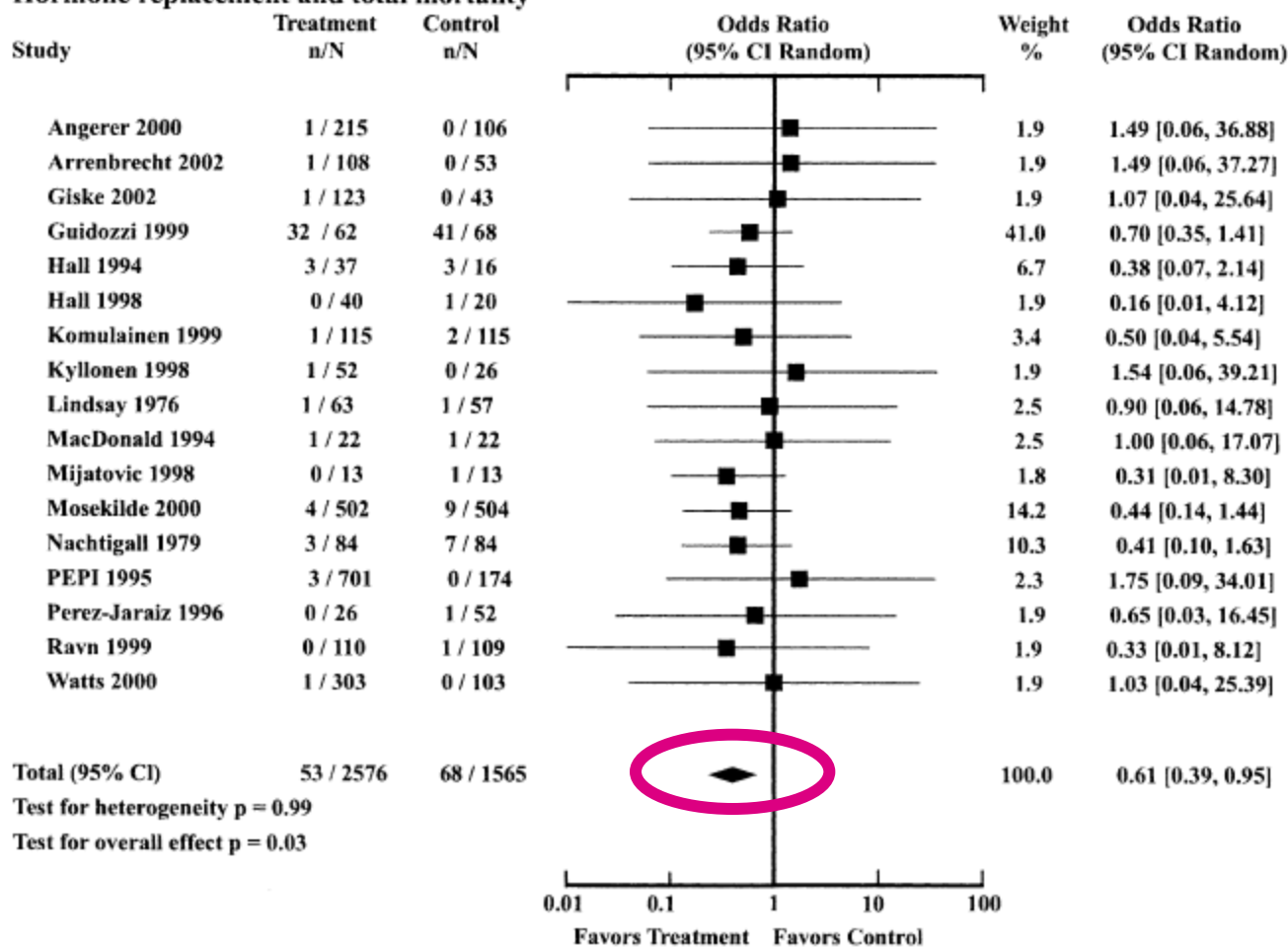
## A Meta-analysis

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Mean age > 60 years  
Hormone replacement and total mortality



Mean age < 60 years  
Hormone replacement and total mortality



## ◆ Hormone beeinflussen Krebsrisiko

- altersspezifisch, substanzspezifisch
- malignomspezifisch
- ERT vs. ccHRT
- Gestagene - synthet. Gestagene vs. Progesteron/Dydrogesteron
- Östrogene – E2 vs. CEE
- Tibolon