

# Rischi e benefici dei contraccettivi orali: Valutazione critica



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Lodi, 2009

By virtue of their ability to prevent pregnancy  
OCs have revolutionized reproductive  
choices for women

OCs provide a unique opportunity for a  
woman to prevent pregnancy and obtain  
health benefits by using a single medication

Some concerns about possible adverse  
effects persist

## **Hormonal contraceptives could provide health benefits for women in four ways:**

- By providing highly effective contraception**
- By preventing some gynaecological and medical conditions (cycle-related noncontraceptive benefits)**
- By treating some gynaecological symptoms**
- By preventing some non-gynecological conditions**

# Gynecological noncontraceptive benefits of OCs

- Cycle-related:

- Irregular cycles → Scheduled bleeding episodes

- Dysmenorrhea → Less painful periods

- Less PMS and PMDD symptoms (depending on progestin-type)

# The improvement of of gynecological conditions with estro-progestin preparations

- Menorrhagia
- Endometriosis
- Fibroids
- Adenomyosis
- Endometrial hyperplasia
- PID
- Ovarian cysts

# Sanguinamenti uterini eccessivi

## Estroprogestinici

Prima scelta nell'urgenza

↓ 43% perdita ematica (Fraser 1991)

▶ Determinano una rapida emostasi attraverso lo stimolo alla crescita endometriale ed il blocco del bleeding arteriolare

↓ perdita ematica (%)

- |                               |             |
|-------------------------------|-------------|
| • LNG-IUS                     | 90 %        |
| • Danazolo                    | 60 %        |
| • <b>Contraccettivi orali</b> | <b>50 %</b> |
| • Ac. Tranexamico             | 50 %        |
| • FANS                        | 25-35 %     |
| • Progestinici orali          | 12 %        |

Efficacia del 24-88% in presenza di coagulopatie ma pochi dati in relazione al grado di difetto dell'emostasi

# Ovarian cysts and OCs-Protection?

Comment: Effect not on all cysts  
Time related

↓ 78% (95% CI 47%-93%) corpus luteum cysts (in the six months preceding diagnosis)

Vessey M, 1987

↓ 49% (95% CI 20%-70%) follicular cysts (in the six months preceding diagnosis)

Vessey M, 1987

28 (95% CI 16 to 35) operations for functional ovarian cysts avoided every 100,000 women who take oral contraceptives each year.

The protective effects of OCs reported with high-dose monophasic pills may be attenuated with the newer pills with lower hormonal potency?

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<b>Overall Current OC use</b>	<b>O.R 0.72</b>
OCs with 35 mcg of EE	O.R 0.69
OCs with lower doses of EE	O.R 0.79
Multiphasic OCs	O.R 0.76
<b>Sterilization</b>	<b>O.R 1.70</b>

Progestogen-only oral contraception increased frequency of functional ovarian cysts

Functional cysts with maximum diameters ranging between 30 and 58 mm in 12/21 women

# Oral Contraceptives Offer **No Benefit for Treating** Functional Ovarian Cysts



## Oral contraceptives for functional ovarian cysts

Grimes DA, Jones LB., Lopez LM, Schulz KF

4 studi controllati=277 women

- Combined oral contraceptives appear to be of no benefit for treating functional ovarian cysts
- Treatment with combined oral contraceptives did not hasten resolution of functional ovarian cysts in any trial. This held true for cysts that occurred spontaneously as well as those that developed after ovulation induction.

# Endometriosis

## Oral contraceptives

No improvement of endometriosis

*During OCs implants may become temporarily atrophic. Implants are reactivated when treatment stops*

Evers JHL et al, 2006

Improvement of symptoms

OCs → Symptoms relief: ↓ dysmenorrhea and pelvis pain

Vercellini P et al, 1993

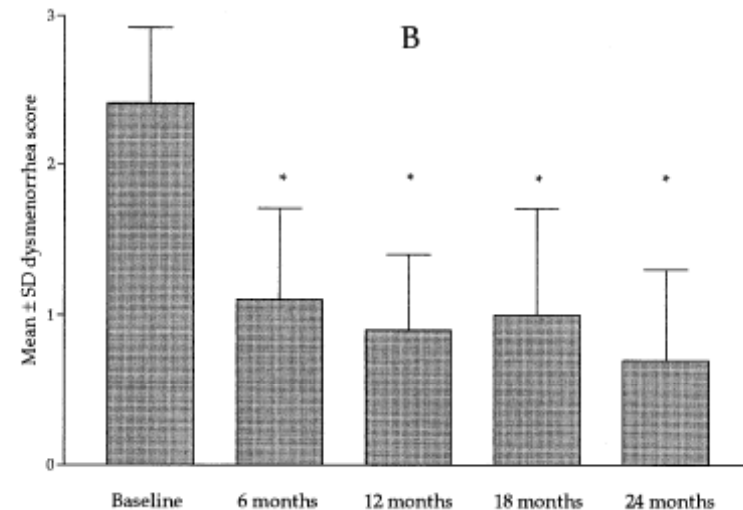
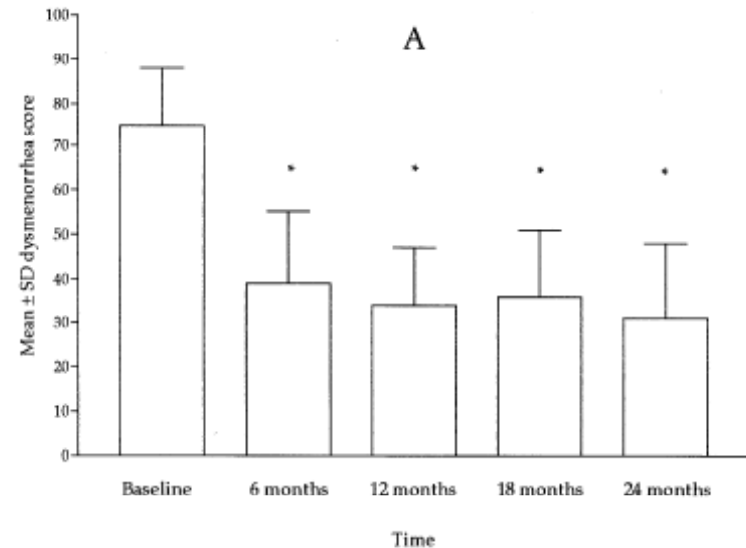
Better results on pelvic pain and dysmenorrhea with OCs in continuous regimen

Vercellini P et al, 2003

Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen

P. Vercellini, et al  
Fertil Steril 2003

Variations of intensity of dysmenorrhea after switch from cyclic to continuous oral contraceptive use. (A), Visual analog scale scores. (B), Verbal rating scale scores. Values are mean  $\pm$  SD. \* $P < .001$  compared with corresponding baseline value, paired  $t$  test.



# Adenomyosis

## Oral contraceptives

No improvement

*It is unclear whether the cyclical or continuous use of OCs reduces the symptoms.*

Evers JHL et al, 2006

Exacerbation of lesions in one case report

Falk RJ et al, 1989

Improvement in pain and ↓ of blood loss with IUS-LNG

Farquhar C et al, 2006

# PID

## Oral contraceptives

Unclear results

50% ↓ of hospitalization

Henry-Suchet J. et al, 1997

No ↓ of gonococcal and chlamydial infections

↑ rate of chlamydial infection and asymptomatic endometritis

Baeten JM et al, 2001


*OCs reduce the severity of inflammation and mask the diagnosis of PID?*

The PID Evaluation and Clinical Health: no hormonal preparation was related to a lower incidence in upper genital tract disease in women with PID, but symptoms less severe

Ness RB et al, 2001

## Fewer uterine fibroids in OC users?

Few data

17% reduction in risk with each 5 years of OC use.  
Significant  for use up to six 6 months before diagnosis.  
Ross RK et al, 1988

No interaction regarding risk of fibroids between OC use : RR 1.1 (95% CI 0.8-1.5).  
Parazzini et al 1992


Lower risk of fibroids during OCs use. Time related effect

Ever vs never users	O.R.	1.1 (95% CI 0.8-1.3).
Current users vs never users	O.R.	0.3 (95% CI 0.2-0.)
Ex-users vs never users	O.R.	1.1 (95% CI 0.9-1.4).
OC for 4-6 yrs vs never users	O.R.	0.8 (95% CI 0.5-1.2)
OC for >7 yrs vs never users	O.R.	0.5 (95% CI 0.3-0.9 ( P = 0.03).

Chiaffarino F et al, 1999

## Uterine fibroids and low dose OCs

Reduction in the duration of menstrual flow, with resultant improvement in hematocrit, without reducing uterine size.

No Change in uterine myomas volume but  in the duration of menstrual flow after 2 yrs 20 mcg EE OCs use.( N.58)

 Uterine myoma volume in control group. (N. 61)

Orsini G et al, 2002

Very low dose OCs protect against an increase in volume?

No change in uterine size after 12 months of OC use (N. 55) and in OC nonusers (n.32).

 in menstrual flow and  in hematocrit in OC users

Friedman AJ, Thomas PP, 2002

OCs and cancer



## Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study

Philip C Hannaford, Sivasubramaniam Selvaraj, Alison M Elliott, Valerie Angus, Lisa Iversen, Amanda J Lee,

OCs was not associated with an overall increased risk of cancer; indeed it may even produce a net public health gain

Dataset contained about 339 000 woman years of observation for never users and 744 000 woman years for ever users

	Ever users	Never users	Relative Risk
	Observed rate (No of women)	Observed rate (No of women)	
Any Cancer	282.53 (936)	318.67 (715)	0.97 (0.88 to 1.06)

BMJ 2007;335:651 (29 September),

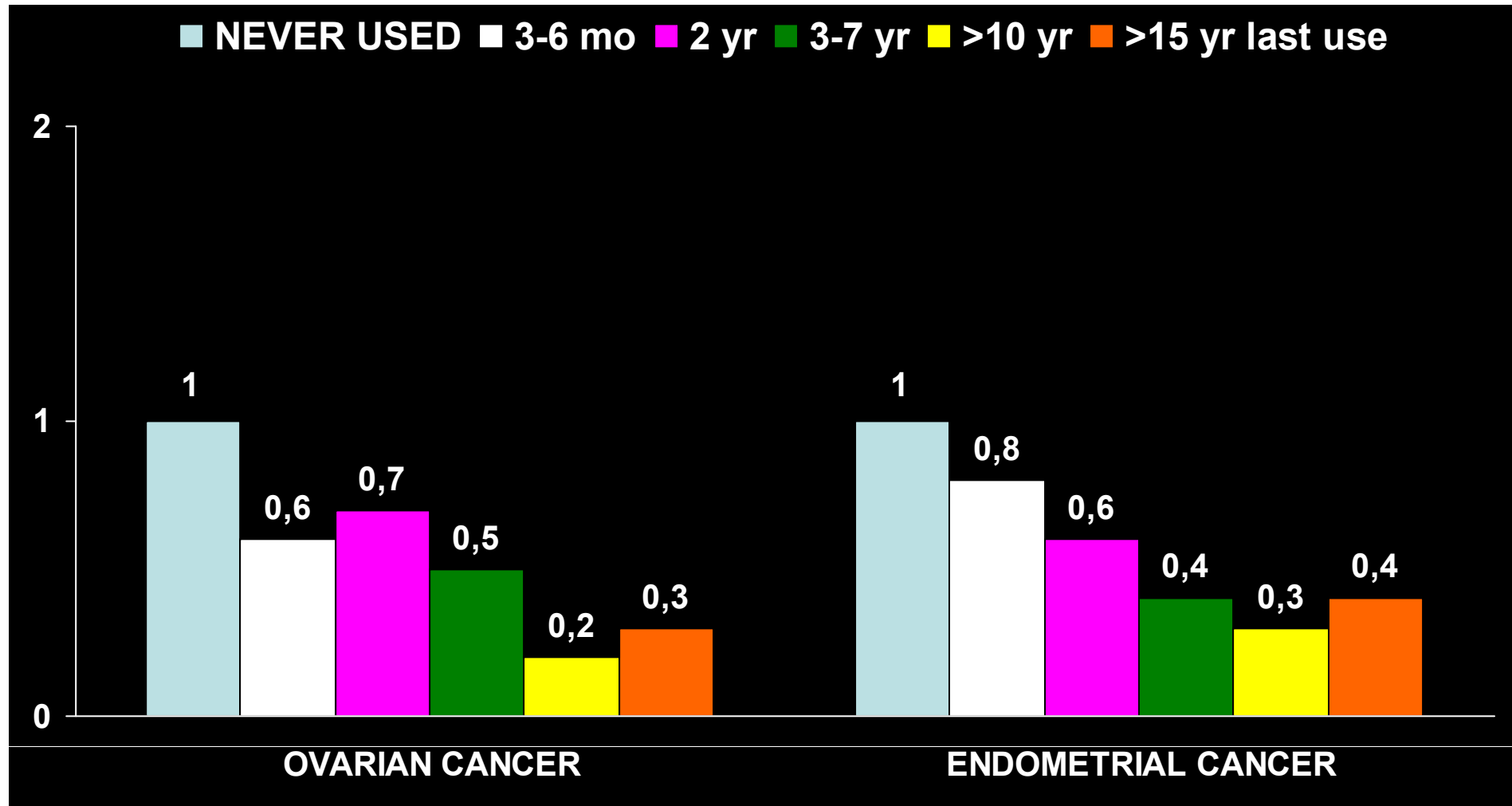
# Risk of cancer among oral contraceptive users

Malignancies	Ever Users	Never users	Relative risk(95% CI)
Large Bowel or rectum	188	135	0.72 (0.58-0.90)
Gallbladder or liver	14	13	0.55 (0.26-1.17)
Lung	206	91	1.05 (0.82-1.35)
Melanoma	96	50	0.92(0.65-1.29)
Breast	891	448	0.98 (0.87-1.10)
Invasive cervix	118	36	1.33 (0.92-1.94)
Uterine body	81	75	0.58(0.42-0.79)
Ovary	96	93	0.54(0.4-0.71)
Central NS or pituitary	34	15	1.34(0.73-2.47)
<b>Any Cancer</b>	<b>2485</b>	<b>1392</b>	<b>0.88 (0.83-0.94)</b>

Cohort data from the Royal College of General Practitioner's oral contraception study

BMJ 2007;335:651

# RELATIVE RISK OF CANCER BY DURATION OF OCs USE



# Cancer Protection with Ultra Low-Dose OCs?

- 30  $\mu\text{g}$  are protective as OCs with a higher EE dose

 No long-term epidemiologic data on OCs <25  $\mu\text{g}$  EE

- 20  $\mu\text{g}$  EE were not analyzed separately from the other low dose pills
- If protective effect is due to prevention of “incessant ovulation,” or to a reduced exposure of the endometrium to “unopposed” estrogen, low-dose OCs are likely protective

# Meta-analysis of Breast Cancer Studies

Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1996; 347: 1713-1727

Pooled analysis of 54 studies with more than cases 53,297 and 100,000 controls found:

- **Current users (RR 1.24)** or recent past users (within 1 to 4 years) (RR 1.16) were diagnosed with breast cancer slightly more often

**The increase of the risk before age 20 only**

No effect after 10 years

- Using OCs before a term pregnancy did not increase risk relative to starting OCs after delivering a child

# Meta-analysis of Breast Cancer Studies (2)

- **No effect of family history:** Women with a family history of breast cancer had the same risk whether or not they used OCs
- **No effect of duration of use**
- No specific hormone dose was associated with elevated risk of breast cancer

Breast cancers less advanced than those in never-users (for spread of disease beyond the breast, RR= 0.88; 95% CI, 0.81–0.95)

# Oral Contraceptives: Breast Cancer

- NICHD Women's CARE Study
  - More than 9200 women 35-64 years old
  - Case/control: • 77% of cancer patients/79% of controls used oral contraceptives
- Current users (RR 1.0, 0.8-1.3) and prior users (RR 0.9, CI .8-1.0) **had no** increased incidence of breast cancer diagnosis

Oral contraceptives used **before age 20** or before first birth ***did not increase the risk of breast cancer***

# Oral Contraceptives: Breast Cancer Conclusions

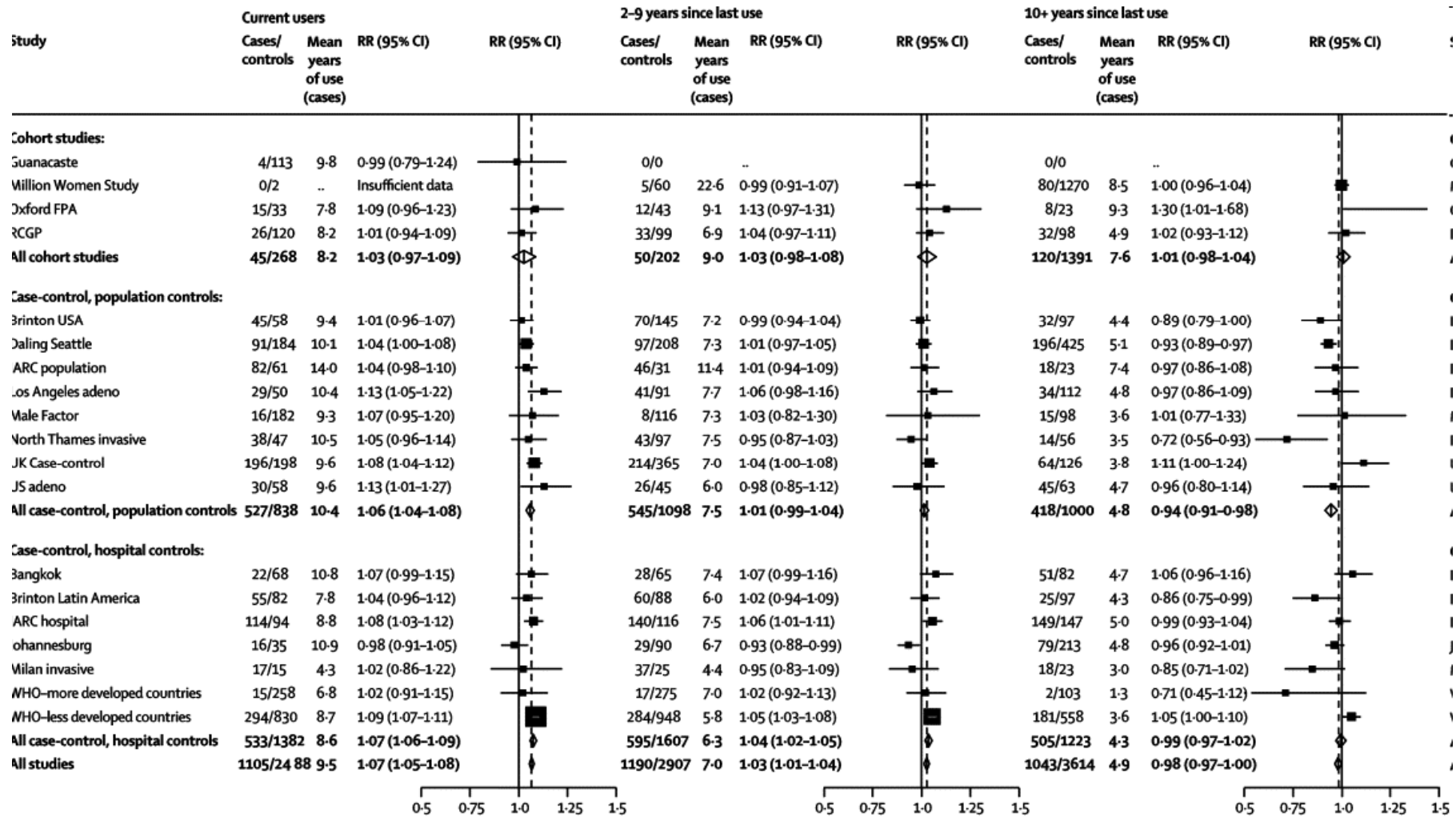
- Recent data are not strongly suggestive of an increased risk of breast cancer in women using oral contraceptives

The slightly elevated risk seen in both current OC users and those who had stopped use within 10 years **may not be due to the contraceptive itself.**

**Evidence are not consistent with the usual process of carcinogenesis.** Cancer usually is more likely to occur with increased duration and/or degree of exposure to a carcinogen.

Neither hormonal concentration nor duration of use affected the outcomes.

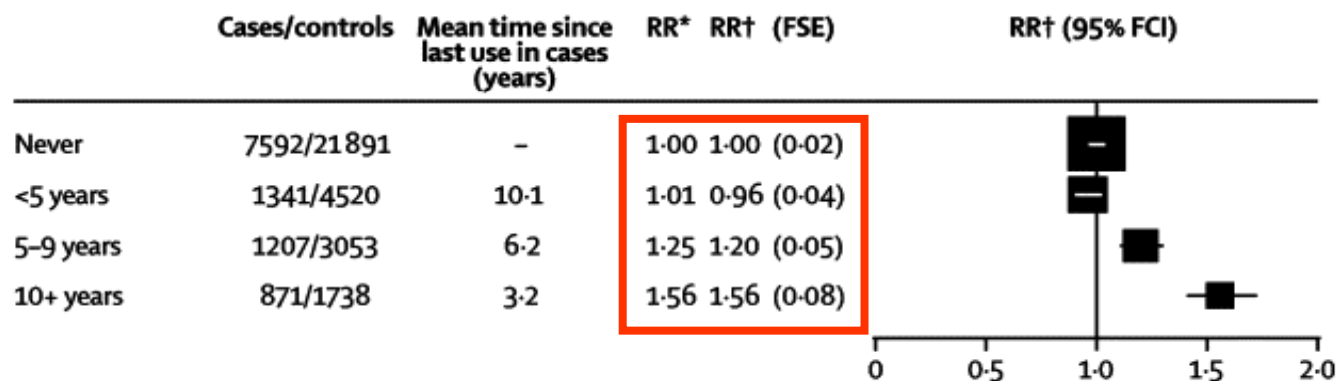
# Relative risk of invasive cervical cancer per year of use of combined oral contraceptives, by study



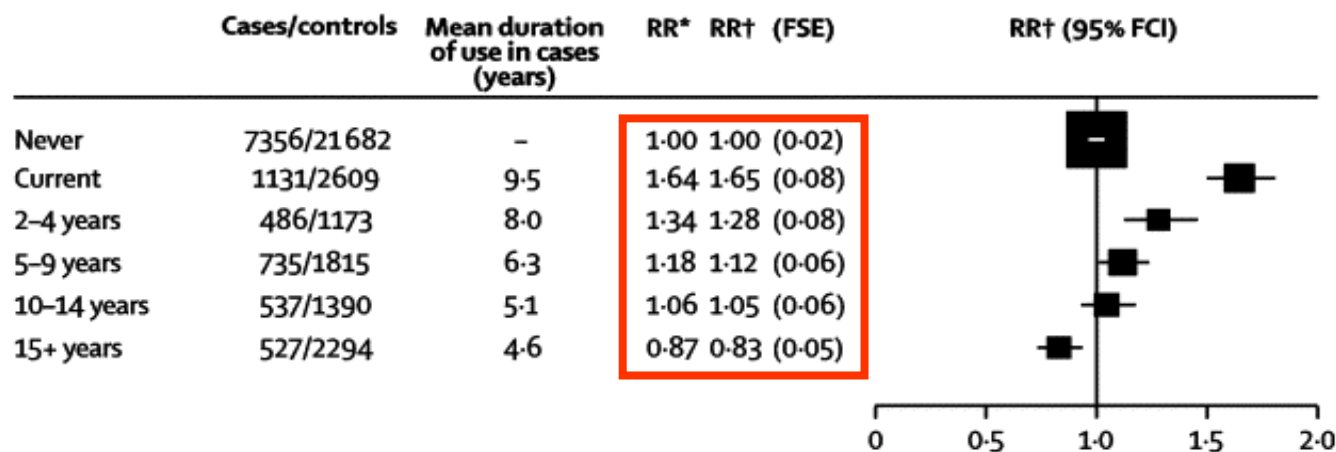
Test for heterogeneity for current users: between all studies,  $\chi^2_{11}=23.7$ ,  $p=0.1$ ; between study designs,  $\chi^2_2=3.1$ ,  $p=0.2$   
 Test for heterogeneity for 2-9 years since last use: between all studies,  $\chi^2_{11}=28.8$ ,  $p=0.04$ ; between study designs,  $\chi^2_2=2.3$ ,  $p=0.3$   
 Test for heterogeneity for 10+ years since last use: between all studies,  $\chi^2_{11}=44.9$ ,  $p=0.0003$ ; between study designs,  $\chi^2_2=8.7$ ;  $p=0.01$

## Relative risk (RR) of invasive cervical cancer in relation to duration of use and time since last use of combined oral contraceptives

### A By duration of use of combined oral contraceptives



### B By time since last use of combined oral contraceptives



Test for trend within users: by duration  $\chi^2_1=60.0$ ,  $p<0.0001$ ; by time since last use  $\chi^2_1=85.8$ ,  $p<0.0001$

RR\*=relative risk stratified only by age at diagnosis and study or study centre. RR†=relative risk, floated standard error (FSE), and 95% floated confidence interval (FCI) stratified by age, study or study centre, age at first intercourse, lifetime number of sexual partners, number of full-term pregnancies, smoking, and screening status.

Estimated cumulative incidence rate (per 1000 women) of invasive cervical cancer at age 50 in relation to oral contraceptive use from age 20

Less developed countries

More developed countries

	Never users	OCs users	Never users	OCs users
5 years	7.3	7.5	3.8	4.0
10 years		8.3		4.5

Lancet 2007

# Cervical Dysplasia/Carcinoma and Oral Contraceptives

- *Prior epidemiologic studies show increased risk for oral contraceptive users*

- Long-standing debate whether the increased incidence of cervical cancer is due to lifestyle differences or hormonal therapy

- OC users have more risk factors for HPV:

- More partners; more cigarette smoking

- Barrier contraceptives may protect

## Effect of potential confounding factors on the relative risk invasive cervical cancer

	RR (95%CI) per year of use of OCs	$\chi^2$
Age+study	1.064(1.050-1.077	95.1
+age at first intercourse	1.053 (1.039-1.068)	57.0
+sexual partners	1.057(1.043-1.071)	67.9
+age at first birth	1.064(1.050-1.079)	80.0
+parity	1.073(1.058-1.088)	99.4
+smoking	1.068(1.054-1.083)	97.0
+condom use	1.061(1.048-1.074)	83.1
+screening	1.062(1.049-1.0729	
Age.study+age at first intercourse+sexual partners+parity+smoking +screening	1.052(1.037-1.068)	48.2

# Systematic Review in 2003: Oral Contraceptives and Cervical Cancer

	5-9 years of OC use Relative Risk	➤10 years of OC use Relative Risk
Overall	1.3	2.2
HPV (+)	1.9	2.5
HPV (-)	0.9	1.3
SquamCA	1.5	2
AdenoCA	1.7	2.8

Smith, JS et al. *Lancet* 2003 Apr5;361:1159-67

Odds ratios for adenocarcinoma of cervix associated with ever use of oral contraceptives, by ever/never use of barrier methods of contraception

Ever used barrier contraception (diaphragm or condom)	Ever used oral contraceptives	
	No	Yes
No		
OR* (95% CI)	1.0	<b>5.1</b> (1.6–15.7)
Cases/controls	5/29	77/108
Yes		
OR* (95% CI)	3.2 (0.8/12.0)	<b>3.7</b> (1.2–11.4)
Cases/controls	14/45	99/204 (P=0.03)

\* Adjusted for education, annual household income, number of sexual partners before age 20, number of known episodes of genital warts, months of diaphragm use, and weight gain from age 18 to time of case's diagnosis.

From: Ursin: Obstet Gynecol Surv, Volume 50(5).May 1995.381-384

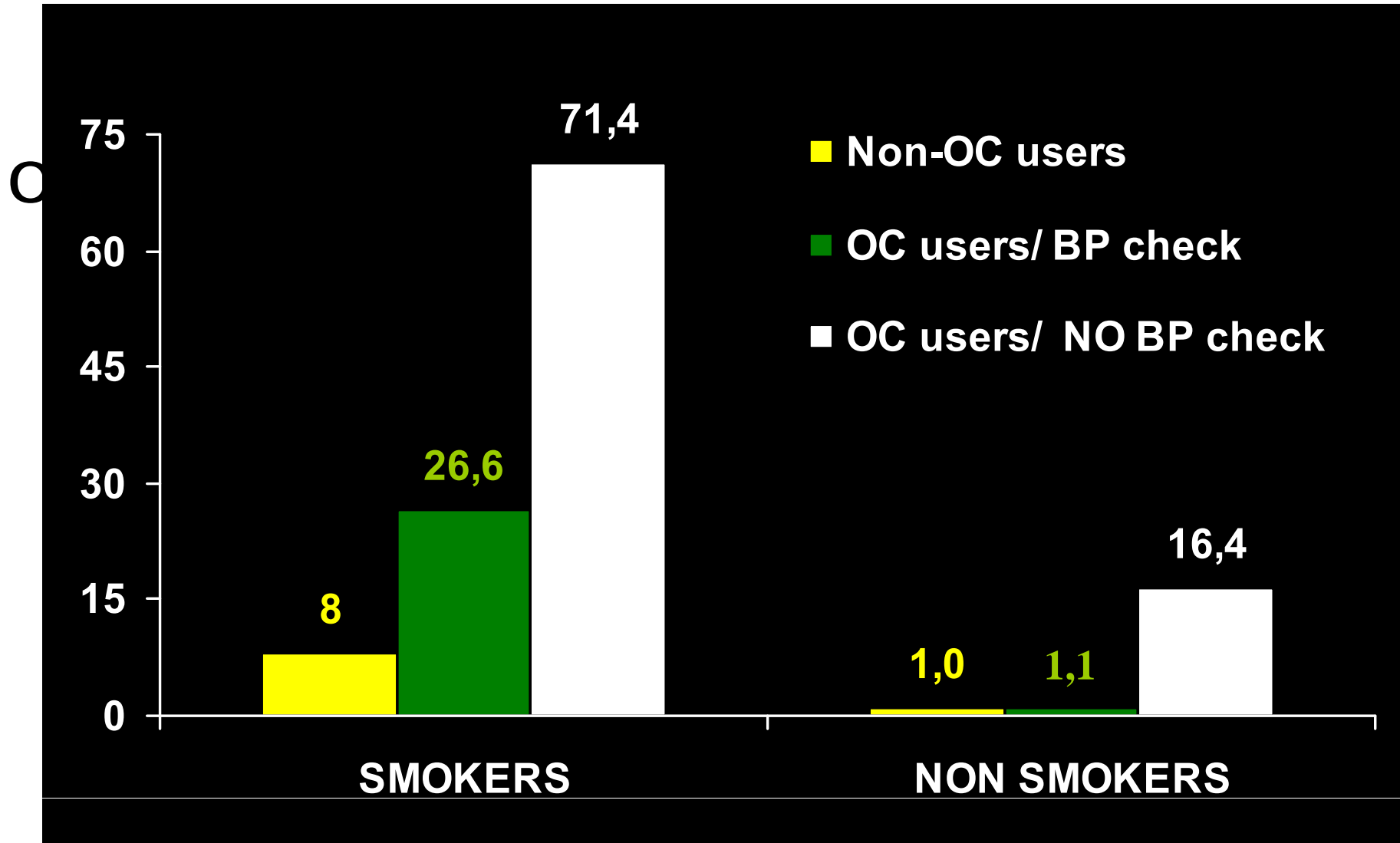
# **Cervical Cancer Counselling**

- Screen women on oral contraceptives annually to check for dysplasia**
- Encourage smoking cessation and barrier STD protection in pill users to optimize their health**

# OCs: Effect of EE dose on CVD events

	Relative Risk		Expected events(n/100,000 women-yr)		
	$\geq 50 \mu\text{g}$	$30 \mu\text{g}$	Non users	$\geq 50 \mu\text{g}$	$30 \mu\text{g}$
MI	4.7	1.6	2,4	11,2	3.8
Ischemic stroke	2.9	1.8	2	5.8	3.6
VTE	4.8	3.4	4,8	23	16

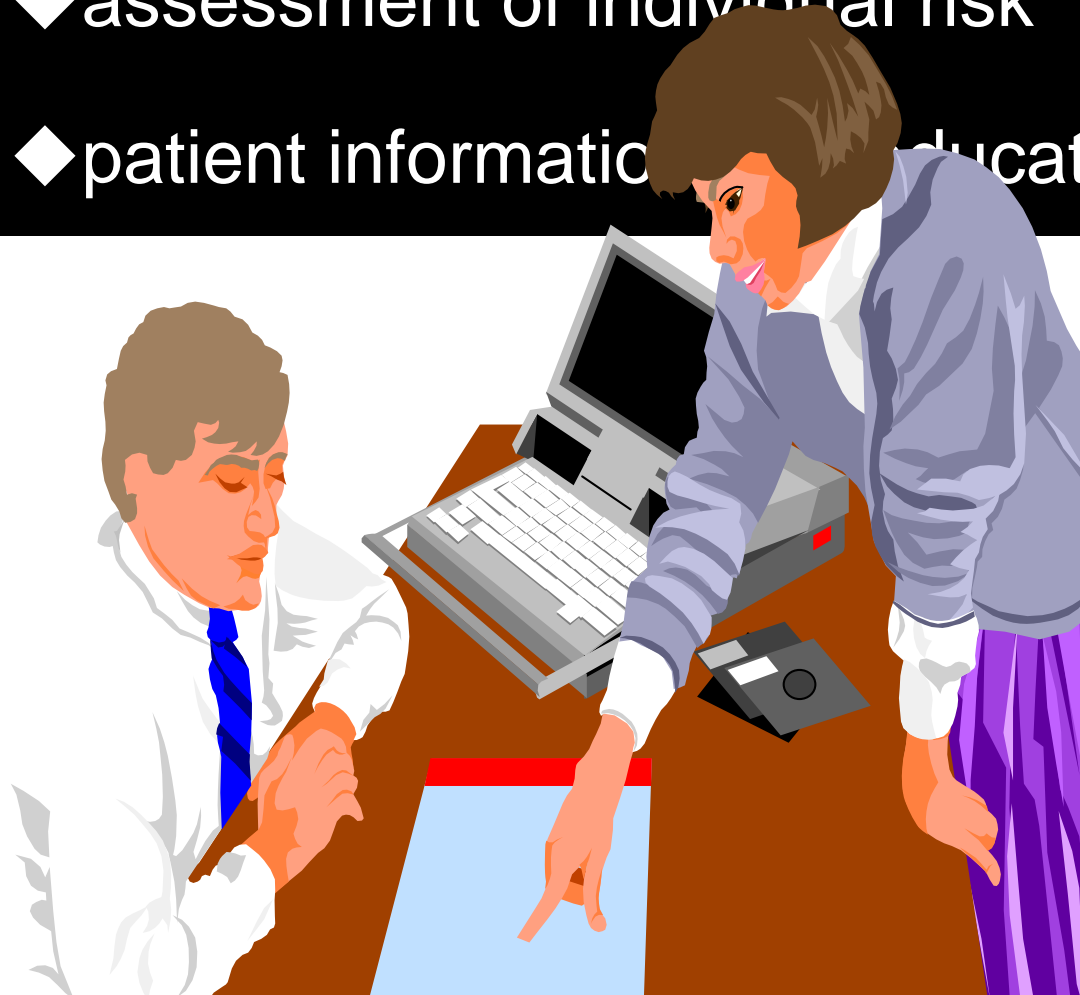
# Risk of IMA during OCs: Effect of Smoking and Blood Pressure check



LANCET, 1997

# STRATEGIES FOR WOMEN HEALTH CARE

- ◆ assessment of individual risk
- ◆ patient information education



## CONSIDERING INDIVIDUAL

- ◆ NEEDS
- ◆ WISHES
- ◆ PREFERENCES

## **Per assicurare una contraccezione sicura è necessario :**

- **Identificare soggetti con fattori di rischio**
- **Identificare la presenza di condizioni mediche o trattamenti che richiedono una particolare cautela o che rappresentano una controindicazione**
- **Verificare che la P.A. sia normale**
- **In assenza di indicazione clinica, non è necessario eseguire indagini biochimiche**
-