Il rischio oncologico nella contraccezione ormonale

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Homonal contraception = cancer benefits and few thrombotic / cardiovascular risks

Contraceptive and non-contraceptive benefits using COCs.

Contraceptive benefits means avoiding of	Reduction %
Pregnancy	>90
Deaths at birth	>90
Abortions (spontaneous/induced)	>90
Extrauterinal pregnancy	>90

Noncontraceptive benefits	Reduction %
Cycle disturbances	25–50
Dysmenorrhea	25–50
Anaemia	25
Acne, hirsutismus	10–50
Pelvic inflammation	50
Rheumatoid arthritis	50
Benign breast disease	25–50
Benign ovarial tumours	25
Ovarial follicle cysts	25
Ovarial carcinoma	50
Endometrium carcinoma	50
Colon/Rectal carcinoma	30

cardiovascolar

	COC	P/R	POP
Age			
<18 years	1	1	2
18–40 years	1	1	1
≥40 years	2	2	1
Obesity			
BMI ≥ 30	2	2	1
Smoking			
age < 35 years	2	1	1
age ≥ 35 years			
<15 cic	3	1	1
≥15 cic	4	4	1
Hypertension			
systolic 140–159 or diastolic 90–99 mmHg	3	3	1
systolic > 159 mmHg or diastolic > 99 mmHg	4	4	2
including vascular diseases	3/4	3/4	2
>2 cardiovascular risk factors	3/4	3/4	2

X. Ruan, A.O. Mueck / Maturitas 82 (2015) 266–270

Reduced incidence: colon, endometrium & ovary

-29% gynecologic cancers -12% overall cancers

Malignancies	ICD-8 code	Ever users: Observed rate (No of women)	Ever users: Standardised rate	Never users: Observed rate (No of women)	Never users: Standardised rate	Relative risk† (95% CI)
Main dataset*:						
Large bowel or rectum	153 and 154	24.65 (188)	26.01	38.56 (135)	36.10	0.72 (0.58 to 0.90)
Gallbladder or liver	155 and 156	1.83 (14)	1.99	3.70 (13)	3.62	0.55 (0.26 to 1.17)
Lung	162	26.97 (206)	27.12	25.94 (91)	25.77	1.05 (0.82 to 1.35)
Melanoma	172	12.58 (96)	12.86	14.28 (50)	13.99	0.92 (0.65 to 1.29)
Breast	174	117.79 (891)	121.53	129.31 (448)	124.20	0.98 (0.87 to 1.10)
Invasive cervix	180	15.48 (118)	14.94	10.28 (36)	11.19	1.33 (0.92 to 1.94)
Uterine body	182	10.61 (81)	11.30	21.41 (75)	19.53	0.58 (0.42 to 0.79)
Ovary	183	12.57 (96)	13.23	26.54 (93)	24.66	0.54 (0.40 to 0.71)
Central nervous system or pituitary	191, 1943	4.45 (34)	4.79	4.27 (15)	3.56	1.34 (0.73 to 2.47)
Site unknown	199	7.20 (55)	7.22	12.54 (44)	11.34	0.64 (0.43 to 0.95)
Other cancers		113.93 (863)	119.49	145.20 (504)	135.57	0.88 (0.79 to 0.98)
Main gynaecological	180, 182, 183	38.75 (295)	39.58	58.41 (204)	55.54	0.71 (0.60 to 0.85)
Any cancer	140-209	333.68 (2485)	344.91	410.20 (1392)	390.37	0.88 (0.83 to 0.94)

Hannaford BMJ. 2007; 335(7621): 651

Systematic Review on OC and breast, cervical, colorectal and endometrial K. More breast cancer??

In PubMed®, Embase®, and Cochrane Database of Systematic Reviews =>2000: 44 breast, 12 cervical, 11 colorectal, and 9 endometrial cancers studies.
All studies are observational= **no randomized controlled trials!**

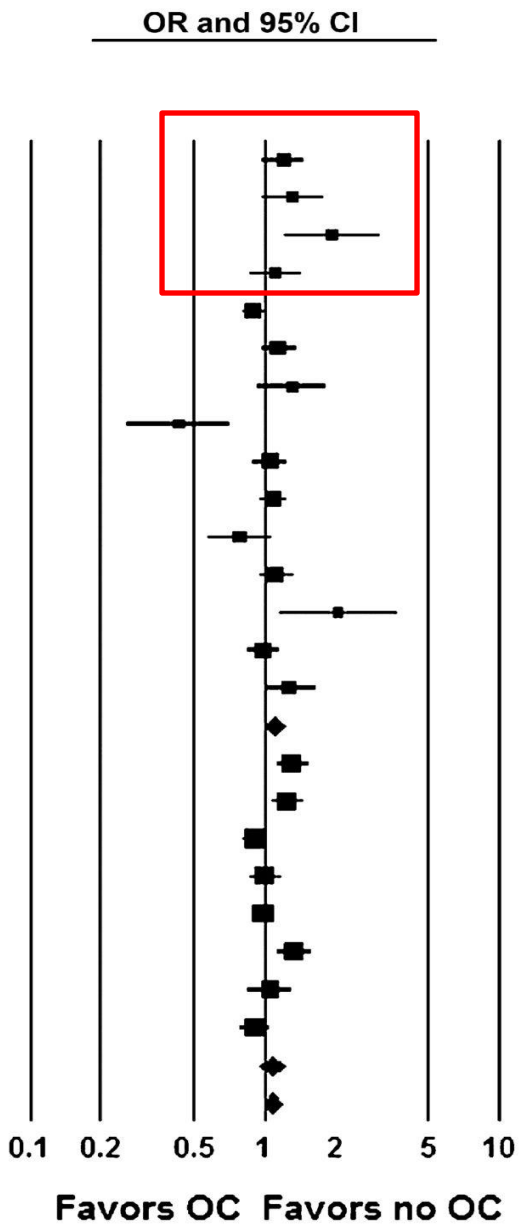
Breast cancer: OR=1.08, CI 1.00–1.17) Increase in estimated lifetime absolute risk of breast cancer 0.89% (NNH 113). The strength is moderate: some risk of bias. In only U.S.-based studies: OR 1.03; CI, 0.93 to 1.14.

No time-dependent relationship = no effect of duration of use. Time since last use: 0–5 years (OR = 1.21; CI, 1.04 to 1.41; then no more significant): results inconsistent (old studies). Higher risk associated with more recent use: promotion? Detection bias?

Gierisch Cancer Epidemiol Biomarkers Prev sept 2013.

Hormonal contraceptive use and breast cancer risk

Group by Type	Study	OR	Lower limit	Upper limit
Case–control	Shapiro, 2000	1.200	0.980	1.470
Case–control	Van Hoftin, 2000	1.310	0.959	1.789
Case–control	Gomes, 2001	1.930	1.194	3.120
Case–control	Moorman, 2001	1.110	0.858	1.436
Case–control	Marchbanks, 2002	0.900	0.801	1.011
Case–control	Althuis, 2003	1.140	0.958	1.357
Case–control	Suter, 2003	1.300	0.919	1.838
Case–control	Wrensch, 2003	0.430	0.258	0.716
Case–control	Shantakumar, 2007	1.050	0.890	1.239
Case–control	Sweeney, 2007	1.080	0.940	1.240
Case–control	Lee, 2008	0.780	0.569	1.069
Case–control	Phillips, 2009	1.110	0.937	1.315
Case–control	Lumachi, 2010	2.060	1.143	3.711
Case–control	Xu, 2011	0.980	0.833	1.154
Case–control	Urban, 2012	1.280	1.000	1.639
Case–control		1.088	0.986	1.201
Cohort	Kumle, 2002	1.300	1.111	1.521
Cohort	Dumeaux, 2003	1.250	1.070	1.460
Cohort	Dumeaux, 2005	0.910	0.807	1.026
Cohort	Vessey, 2006	1.000	0.852	1.173
Cohort	Hannaford, 2007	0.980	0.872	1.102
Cohort	Lund, 2007	1.330	1.111	1.592
Cohort	Dorjgochoo, 2009	1.050	0.841	1.311
Cohort	Rosenblatt, 2009	0.900	0.783	1.034
Cohort		1.072	0.955	1.203
Overall		1.081	1.003	1.165



OR, 1.08; 95% CI, 1.00–1.17 only U.S. studies (OR, 1.03; CI, 0.93–1.14).

Increase in estimated lifetime absolute risk of breast cancer is **0.89%** (**NNH, 113**) ??

Gierisch J M et al. Cancer Epidemiol Biomarkers Prev 2013;22:1931-1943

Cancer Epidemiology, Biomarkers & Prevention

BRCA: " The possible, whereas currently unconfirmed, small increase in the risk of breast cancer in OC users with BRCA1/2 mutations is strongly counterbalanced by the benefits in terms of ovarian cancer protection."

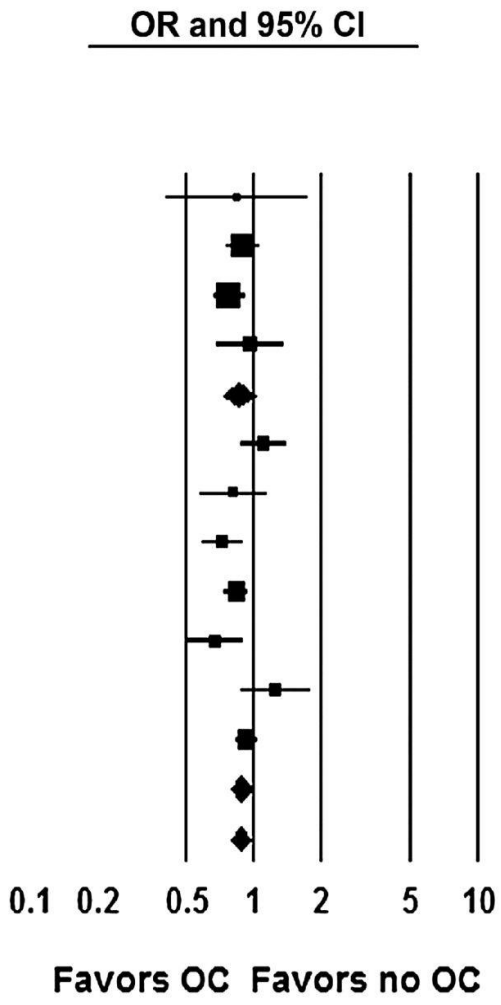
Table II Effect of OC use on breast cancer risk in BRCA mutation carriers.

Study	Mutation	Number	RR	CI 95%
Sweden (Jernstrom et al., 1999)	BRCA1/2	245	1.65	0.95–2.87
			Use <=20 years 2.10	1.02–2.62
			Before FFTP 1.63	1.32–3.33
Norway (Helmdal et al., 2002)	Familial	1423	0.90	0.68–1.18
	BRCA1	96	2.00	0.36–10.9
USA, Canada, Australia (Haile et al., 2006)	BRCA1	497/195cases	0.77	0.53–1.12
	BRCA2	307/128cases	Use >5 years 2.06	1.08–3.94
			Before FFTP 3.46	2.10–5.70
USA, Canada, Australia	BRCA1	47 cases	0.22	0.10-
(Milne et al., 2005)	BRCA2	36 cases	0.93	0.34–3.09
USA, Canada, Europe (Narod et al., 2002)	BRCA1	981 pairs	1.18	1.01–1.38
			Use <5 years NS	
			Use >5 years 1.33	1.11–1.60
	BRCA2	330 pairs	0.93	0.72–1.21
Europe (Brohet et al., 2007)	BRCA1	1181/597 cases	1.4	1.13–1.91
			Before FFTP + greater than 4 years: 1.49	1.05–2.11
	BRCA2	412/249 cases	1.49	0.8–2.70
			Before FFTP + greater than 4 years: 2.58	1.21–5.49
USA (Lee et al., 2008)	BRCA1/2	94 cases	NS	
USA (Figueiredo et al., 2010)	BRCA1	109 cases	2.38	0.72–7.83
	BRCA2	72 cases	0.82	0.21–3.13

Cibula Hum Rep Update 2010

oral contraceptive use and colorectal cancer incidence.

Group by Type	Study	OR	Lower limit	Upper limit
Case–control	Levi, 2003	0.830	0.403	1.711
Case–control	Nichols, 2005	0.890	0.749	1.058
Case–control	Campbell, 2007	0.770	0.651	0.911
Case–control	Long, 2010	0.950	0.672	1.344
Case–control		0.847	0.719	0.997
Cohort	Rosenblatt, 2004	1.090	0.864	1.376
Cohort	Vessey, 2006	0.800	0.568	1.126
Cohort	Hannaford, 2007	0.720	0.578	0.897
Cohort	Kabat, 2007	0.830	0.731	0.942
Cohort	Lin, 2007	0.670	0.502	0.894
Cohort	Dorjgochoo, 2009	1.240	0.867	1.774
Cohort	Tsilidis, 2010	0.920	0.830	1.020
Cohort		0.870	0.778	0.972
Overall		0.862	0.787	0.945



OR, 0.86; CI, 0.79–0.95).
Only US (OR, 0.83; CI, 0.69–1.01)

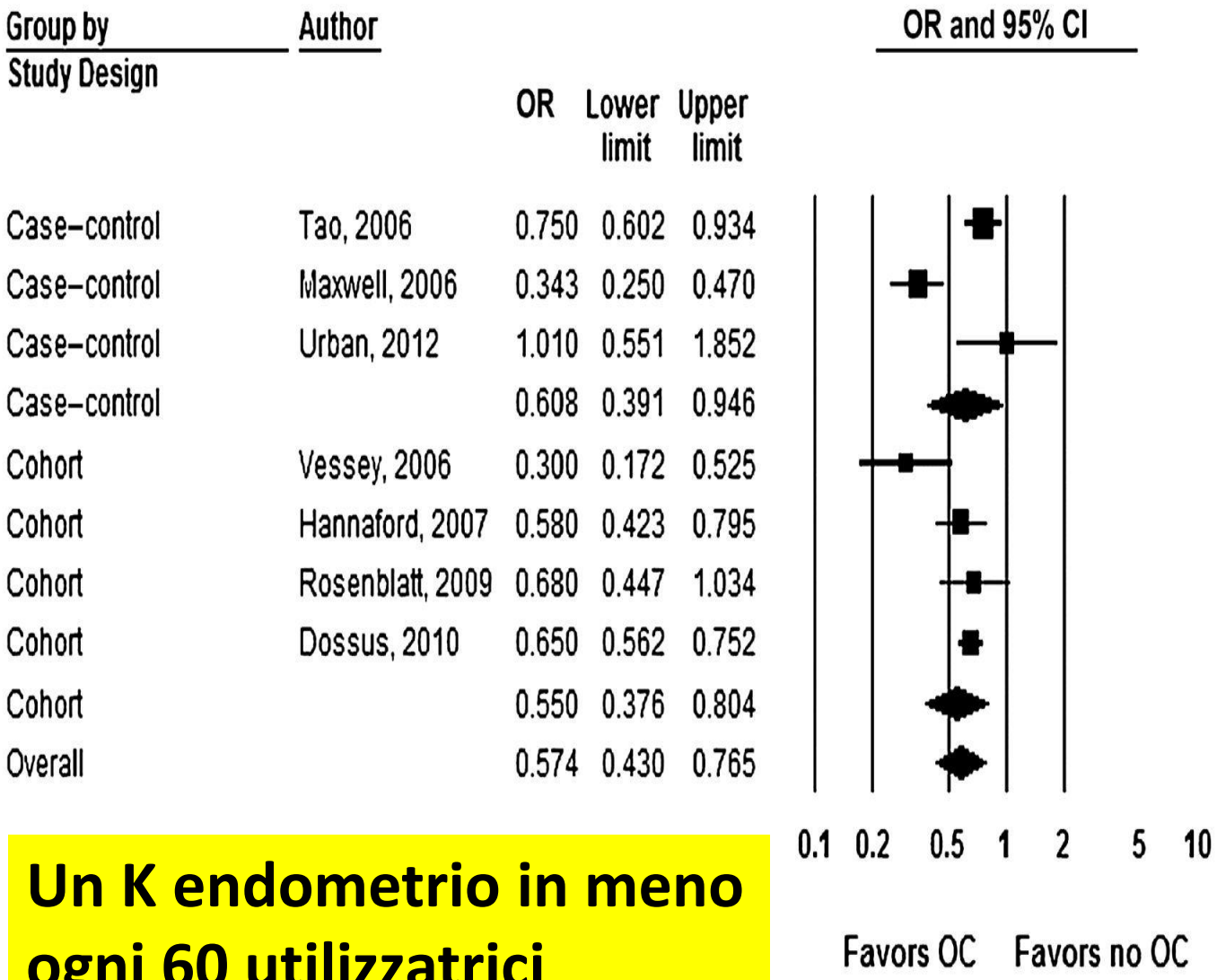
decrease in absolute risk of colorectal cancer is 0.76% (NNT 132).

Lynch syndrome can potentially find considerable benefit from COC use to reduce their increased risk for endometrial, colonic and ovarian epithelial K (Lu and Daniels 2013).

Gierisch J M et al. Cancer Epidemiol Biomarkers Prev 2013;22:1931-1943

Cancer Epidemiology, Biomarkers & Prevention

Oral contraceptive use and endometrial cancer incidence.



Un K endometrio in meno ogni 60 utilizzatrici

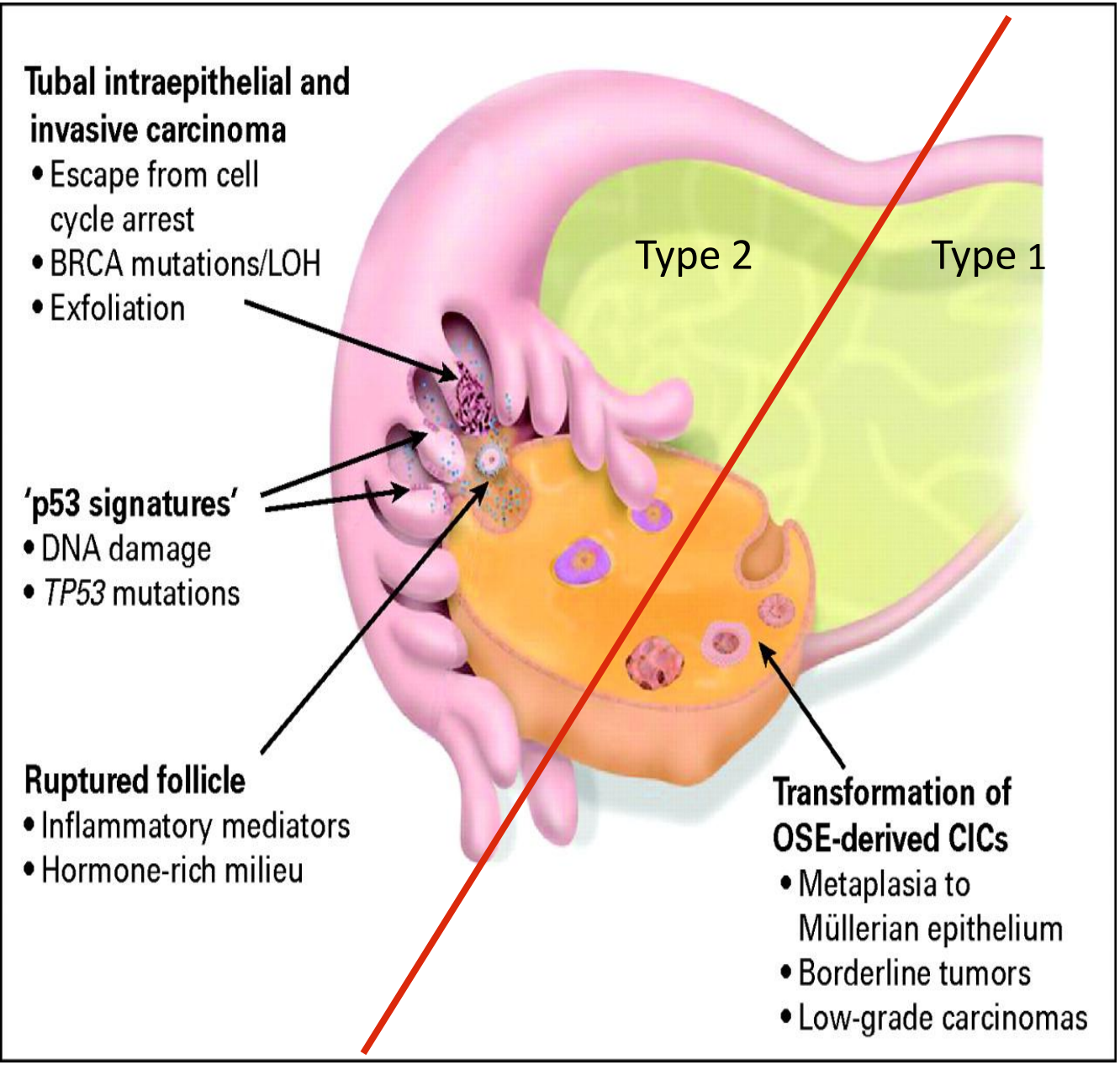
(OR, 0.57; CI, 0.43–0.77). Only US studies (OR, 0.34; CI, 0.25–0.47).

Decrease in absolute risk of endometrial cancer is **1.77% (NNT 60).**

Gierisch J M et al. Cancer Epidemiol Biomarkers Prev 2013;22:1931-1943

Cancer Epidemiology, Biomarkers & Prevention

An integrated model of high-grade serous carcinogenesis.



This model integrates the data about the stepwise development of serous carcinoma in the fimbria of the fallopian tube (FT) and in the ovarian surface epithelium (OSE) – derived cortical inclusion cysts (CICs). The hormone stimulation and the inflammatory mediators involved in ovulation are believed to have similar carcinogenic effect in both pathways.

Levanon K et al. JCO 2008;26:5284-5293

JOURNAL OF CLINICAL ONCOLOGY

Two ovarian cancer deaths every 1000 users for 10 years

- "never used oral contraceptives an estimated 1·2 % are diagnosed with ovarian cancer and 0·7 % die from the disease before the age of 75 years.
- For 10 years use of oral contraceptives the estimated cumulative incidence was 0·8 % and mortality was 0·5%"

Collaborative Group Lancet 2008; 371: 303–14

Tra coloro che hanno usato CO per 10 anni ogni 1000 donne 4 non avranno un cancro ovarico e 2 non ne moriranno.

(Beral Lancet, 2008)

Minus one ovarian cancer per 185 users for 5 years

Meta-analysis of 24 case-control and cohort studies
OR 0.73 (0.66–0.81); a significant duration–response relationship, with reduction in incidence of more than 50% >= 10 y.

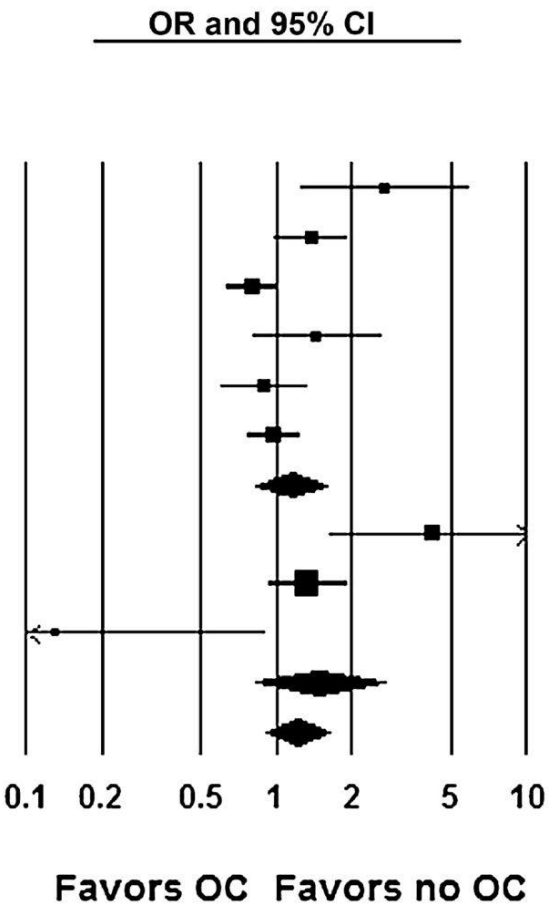
The lifetime reduction in ovarian cancer attributable to the use of OCPs is approximately 0.54%

Number-needed-to-treat of approximately 185 for a use period of 5 years.

Havrilesky Obstet Gynecol 2013

Oral contraceptive use and cervical cancer incidence??

Group by Type	Study	OR	Lower limit	Upper limit
Case–control	Madeleine, 2001	2.700	1.228	5.936
Case–control	Green, 2003	1.370	0.969	1.937
Case–control	Shapiro, 2003	0.800	0.632	1.013
Case–control	Vanakankovit, 2008	1.450	0.793	2.651
Case–control	Nojomi, 2008	0.900	0.600	1.350
Case–control	Urban, 2012	0.970	0.759	1.239
Case–control		1.141	0.828	1.573
Cohort	Vessey, 2006	4.200	1.632	10.811
Cohort	Hannaford, 2007	1.330	0.916	1.931
Cohort	Rosenblatt, 2009	0.130	0.019	0.901
Cohort		1.489	0.813	2.729
Overall		1.210	0.911	1.607



"Results were inconsistent… no time of use dependent
Studies did not control for factors that may influence risk"

Gierisch J M et al. Cancer Epidemiol Biomarkers Prev 2013;22:1931-1943

Cancer Epidemiology, Biomarkers & Prevention

Hormonal contraception= overall cancer risk is reduced (only if less than 8 y of use??)

compared with never users, women who used OC for short to medium-term lengths of time had a reduced risk of any cancer (up to 4 years: ARR 0.93, 95% CI: 0.82–1.06, 4–8 years use: ARR 0.85, 95% CI: 0.74–0.98), whereas **long-term users had a significantly increased risk (more than 8 years: ARR 1.22, 95% CI: 1.07–1.39). The increased risk in long-term users was mostly because of a higher risk of invasive uterine cervical cancer.**

Cibula Hum Rep Update 2010

Hormonal Contraceptives= less Cancer Death

Cause of death	Never users: Observed rate (No)	Never users: Standardised rate*	Ever users: Observed rate (No)	Ever users: Standardised rate*	Adjusted relative risk† (95% CI)
All cancers	205.29 (776)	194.55	160.16 (1312)	165.45	0.85 (0.78 to 0.93)
Large bowel and rectum	21.16 (80)	20.05	11.84 (97)	12.41	0.62 (0.46 to 0.83)
Gallbladder/liver	3.17 (12)	3.12	1.83 (15)	2.03	0.65 (0.30 to 1.39)
Lung	26.45 (100)	26.08	31.49 (258)	31.70	1.22 (0.96 to 1.53)
Melanoma	2.65 (10)	2.67	1.95 (16)	1.95	0.73 (0.33 to 1.61)
Breast	44.44 (168)	43.91	38.09 (312)	39.41	0.90 (0.74 to 1.08)
Invasive cervix	3.70 (14)	4.02	5.62 (46)	5.38	1.34 (0.74 to 2.44)
Uterine body	5.03 (19)	4.47	1.59 (13)	1.94	0.43 (0.21 to 0.88)
Ovary	19.84 (75)	18.04	9.16 (75)	9.47	0.53 (0.38 to 0.72)
Main gynaecological	28.57 (108)	26.51	16.36 (134)	16.80	0.63 (0.49 to 0.82)
CNS-pituitary	5.03 (19)	4.47	3.42 (28)	3.74	0.84 (0.47 to 1.50)
Site unknown	22.22 (84)	20.50	17.21 (141)	18.02	0.88 (0.67 to 1.15)
Other cancers	51.59 (195)	47.19	37.96 (311)	39.39	0.83 (0.70 to 1.00)

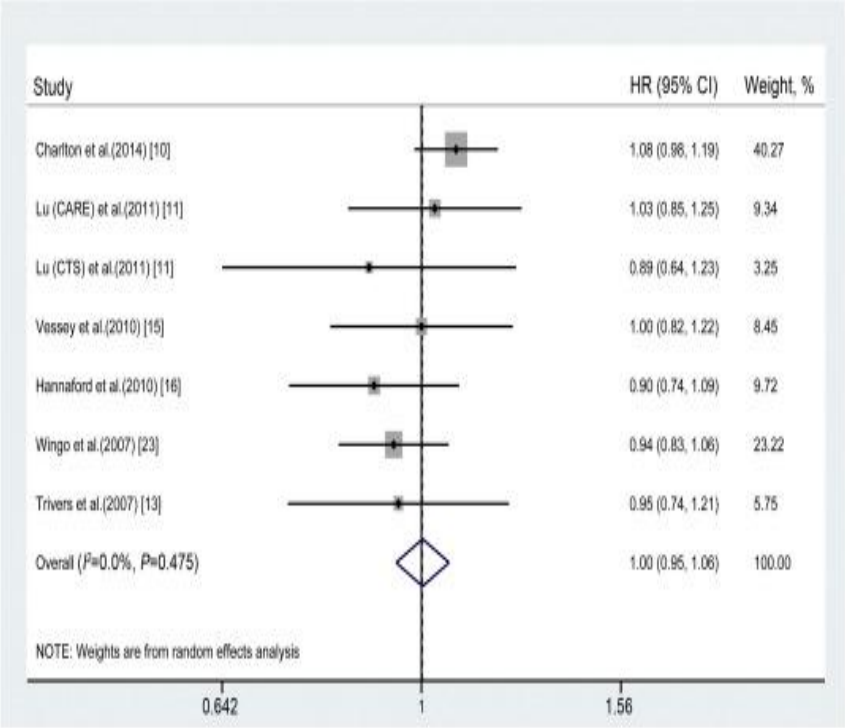
Riduzione significativa di morte per: Ca colon-retto, corpo uterino, ovaio

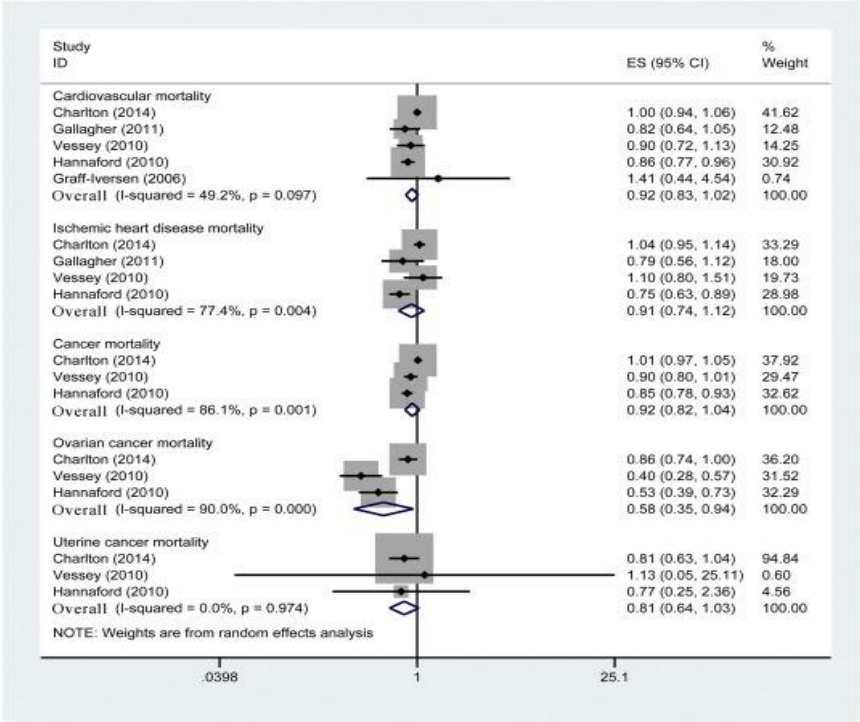
No aumento significativo di morte per altri tumori non ginecologici

Overall K death RR 0.85 (0.78-0.93)

Hannaford et al, 2010 BMJ

Meta-analysis of oral contraceptive use and risks of all-breast cancer (RR1) and cardiovascular death (0.81)



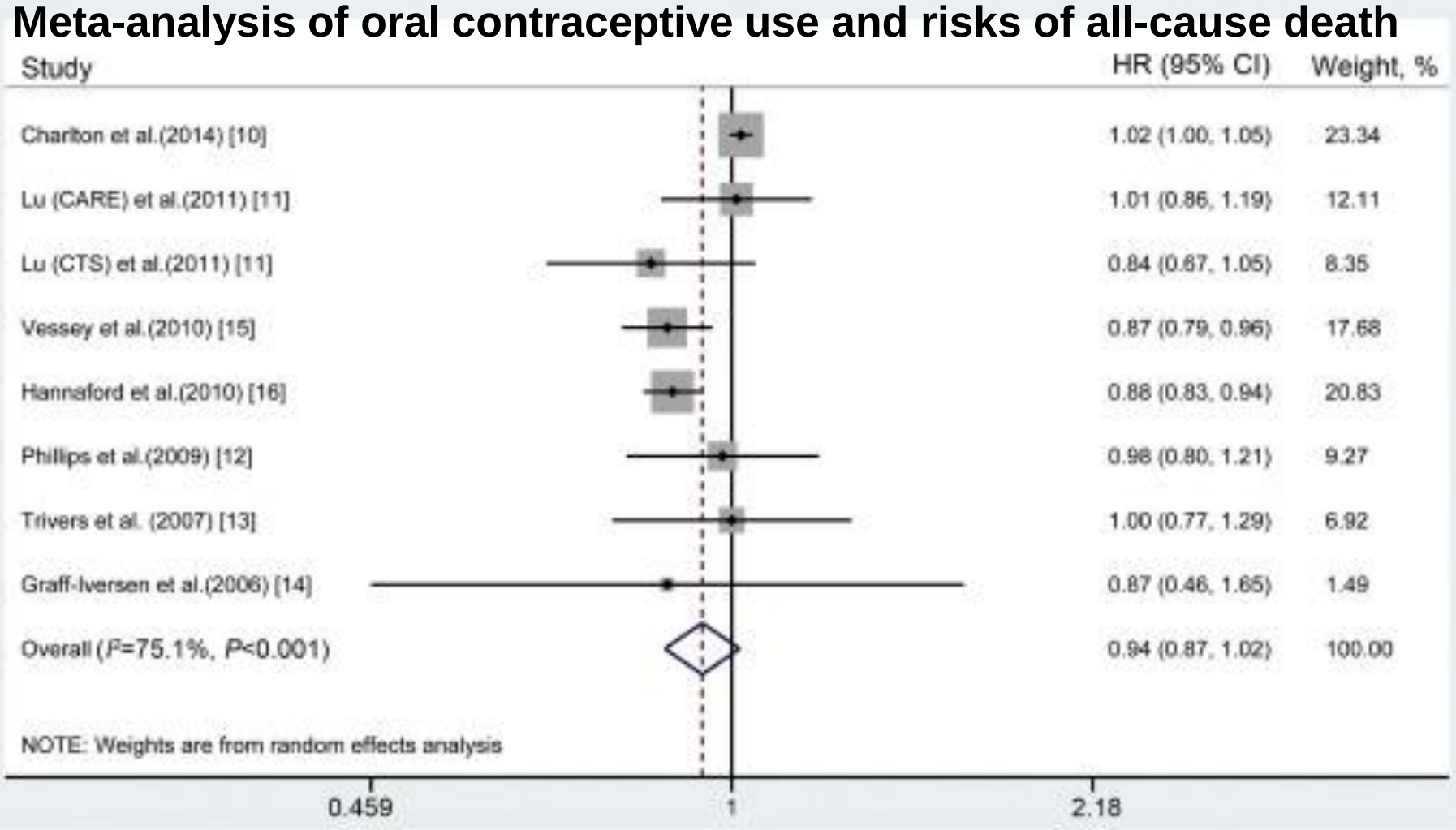


Ever use of OCs was not associated with mortality from all causes (hazard ratio [HR] 0.94; 95% CI 0.87–1.02) or breast cancer (HR 1.00; 95% CI 0.95–1.06). Neither the duration of OC use nor the time since last OC use was associated with all-cause or breast cancer mortality.

In an analysis of a small number of studies, ever users were at **decreased risk of mortality from ovarian cancer (HR 0.58; 95% CI 0.35–0.94).**

Guo-Chao Zhong, Jia-Hao Cheng, Xiang-Long Xu, Kang Wang International Journal of Gynecology & Obstetrics, 2015

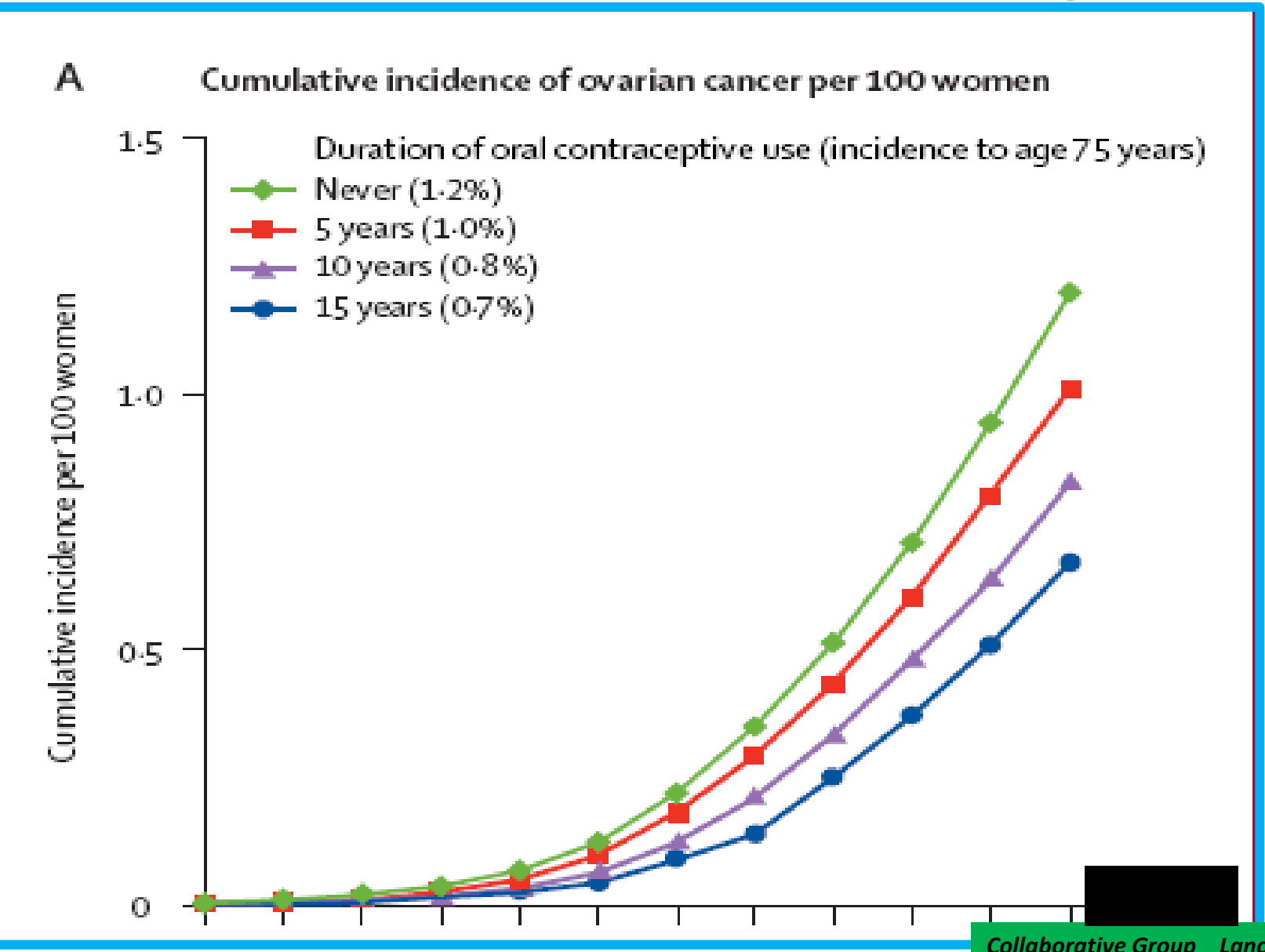
Contraccettivi ormonali: bordeline ridotta mortalità per tutte le cause



Overall all-cause death RR 0.94 (0.87-1.02)

Guo-Chao Zhong, Jia-Hao Cheng, Xiang-Long Xu, Kang Wang International Journal of Gynecology & Obstetrics, 2015

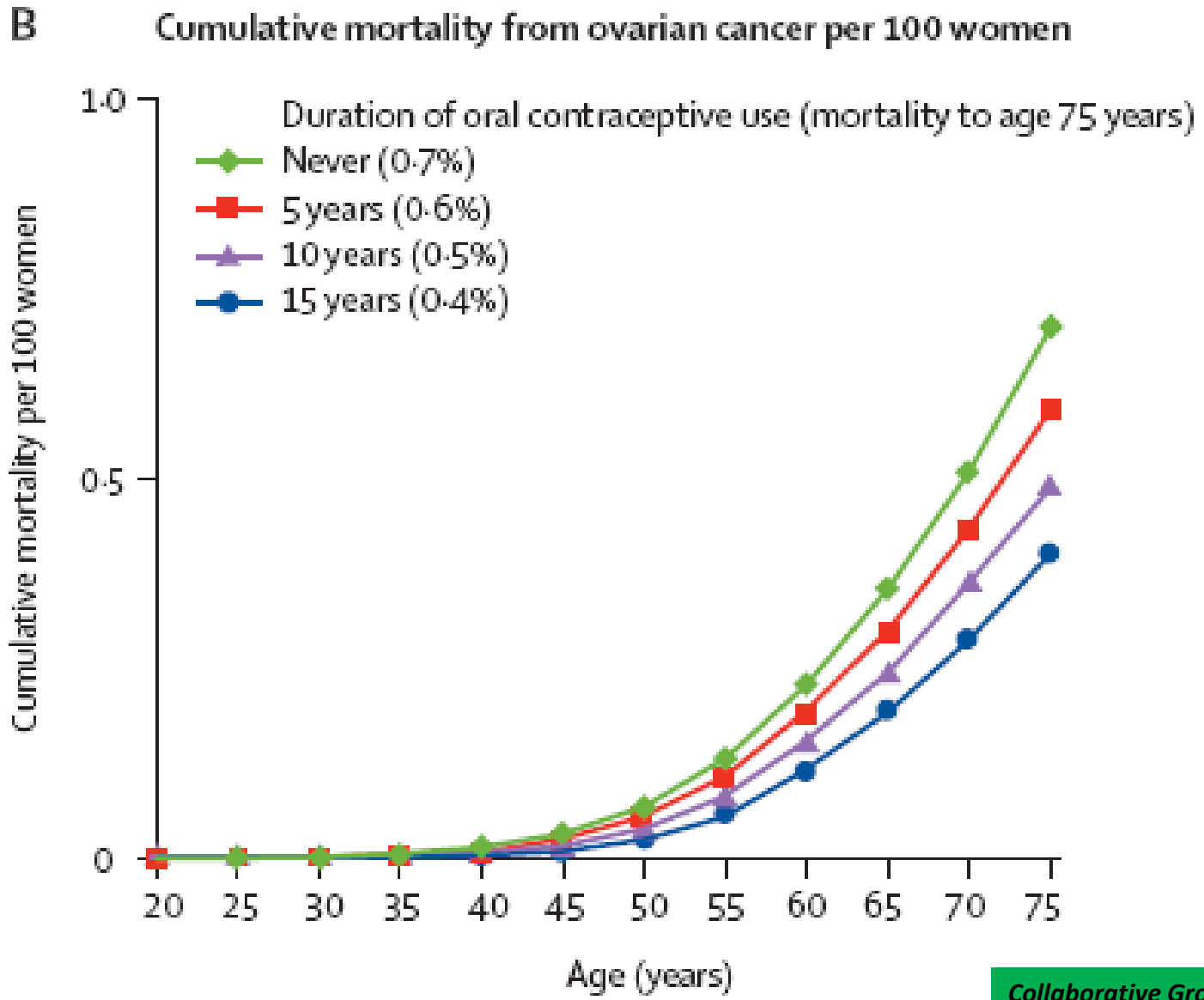
Meno Cancro ovarico: il più importante beneficio dei Contraccettivi Ormonali, durata dipendente



RR-1/5 ogni 5 anni

Collaborative Group Lancet 2008; 371: 303–14

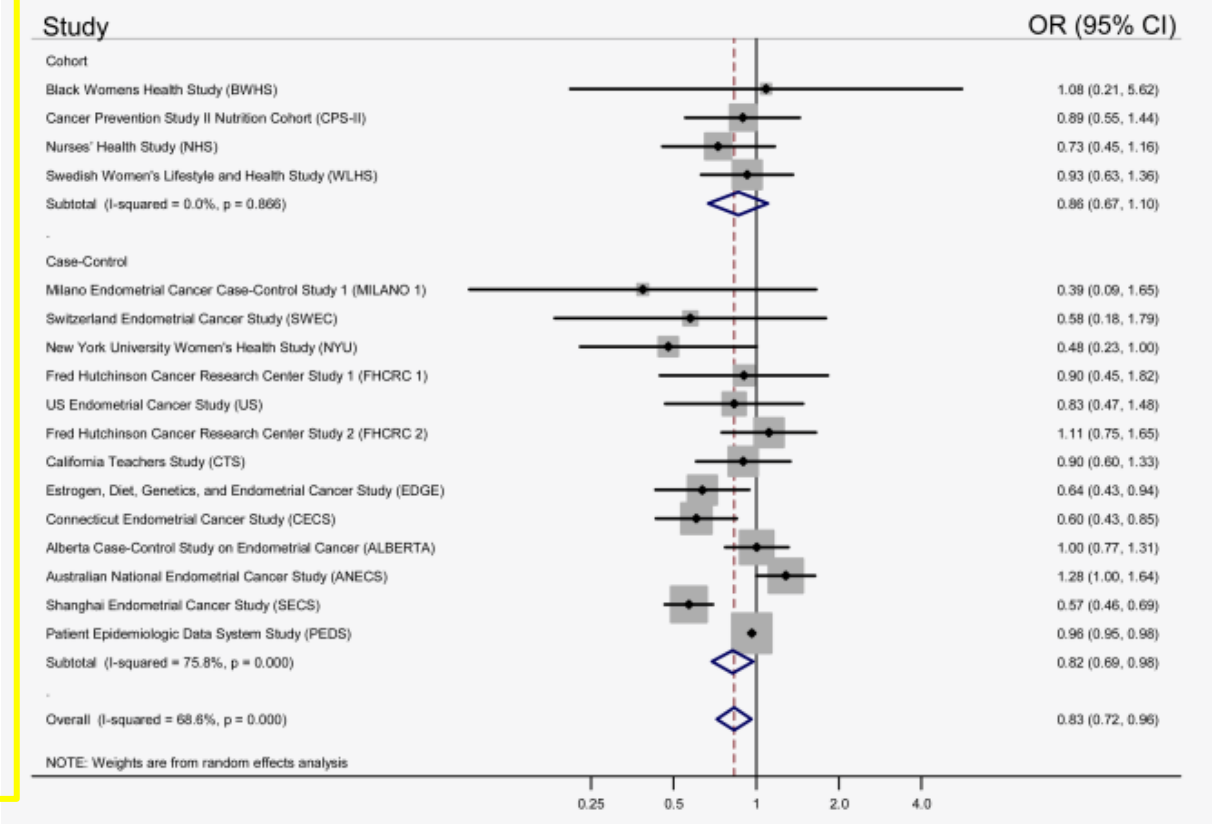
Piu' si usano contraccettivi ormonali meno si muore di cancro ovarico



Collaborative Group Lancet 2008; 371: 303–14

Le spirali, anche inerti, riducono il rischio di cancro endometriale: effetto ormonale, risposta da corpo estraneo, sfaldamento di cellule cancerogene o bias?

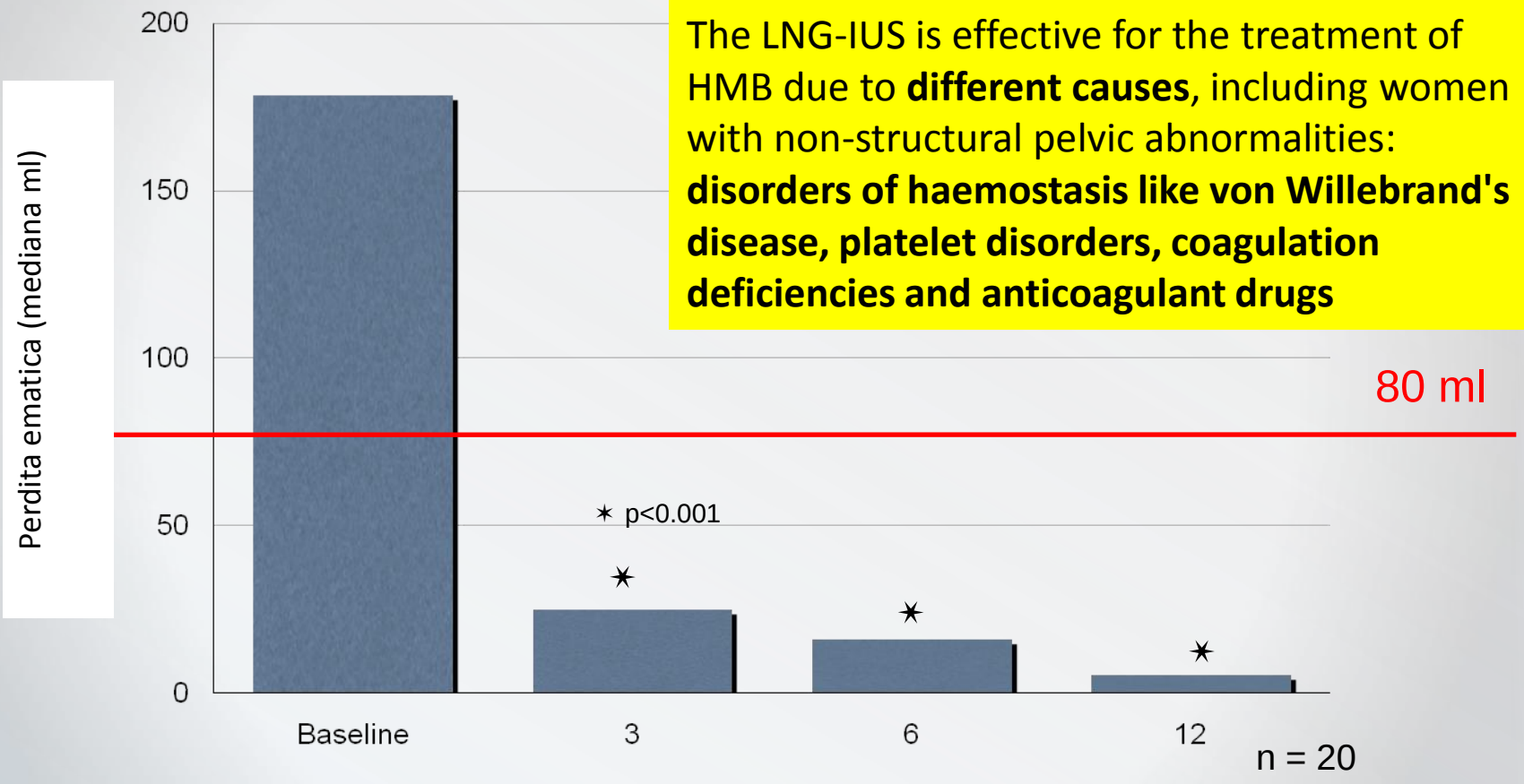
Reduced risk of EC was observed for inert IUDs (pooled-OR = 0.69, 95% CI = 0.58–0.82), older age at first use (≥35 years pooled-OR = 0.53, 95% CI = 0.43–0.67), older age at last use (≥45 years pooled-OR = 0.60, 95% CI = 0.50–0.72), longer duration of use (≥10 years pooled-OR = 0.61, 95% CI = 0.52–0.71) and recent use (within 1 year of study entry pooled-OR = 0.39, 95% CI = 0.30–0.49).



Intrauterine devices and endometrial cancer risk: A pooled analysis of the Epidemiology of Endometrial Cancer Consortium

International Journal of Cancer
Volume 136, Issue 5, 2015

Riduzione con LNG IUS della perdita ematica da quasi ogni causa in donne con menorragia e protezione oncologica: SIR 0.25-0.50 Endom. K 0.60 Ovarian K!!!



The LNG-IUS is effective for the treatment of HMB due to **different causes**, including women with non-structural pelvic abnormalities: **disorders of haemostasis like von Willebrand's disease, platelet disorders, coagulation deficiencies and anticoagulant drugs**

SIR endometrial adenocarcinoma 0.50 (95%.35-0.70 for 1 insertion) and 0.25 (95% CI 0.05-0.73; after two purchases). SIR Ovarian cancer 0.60 (95% CI 0.45-0.76) !!!

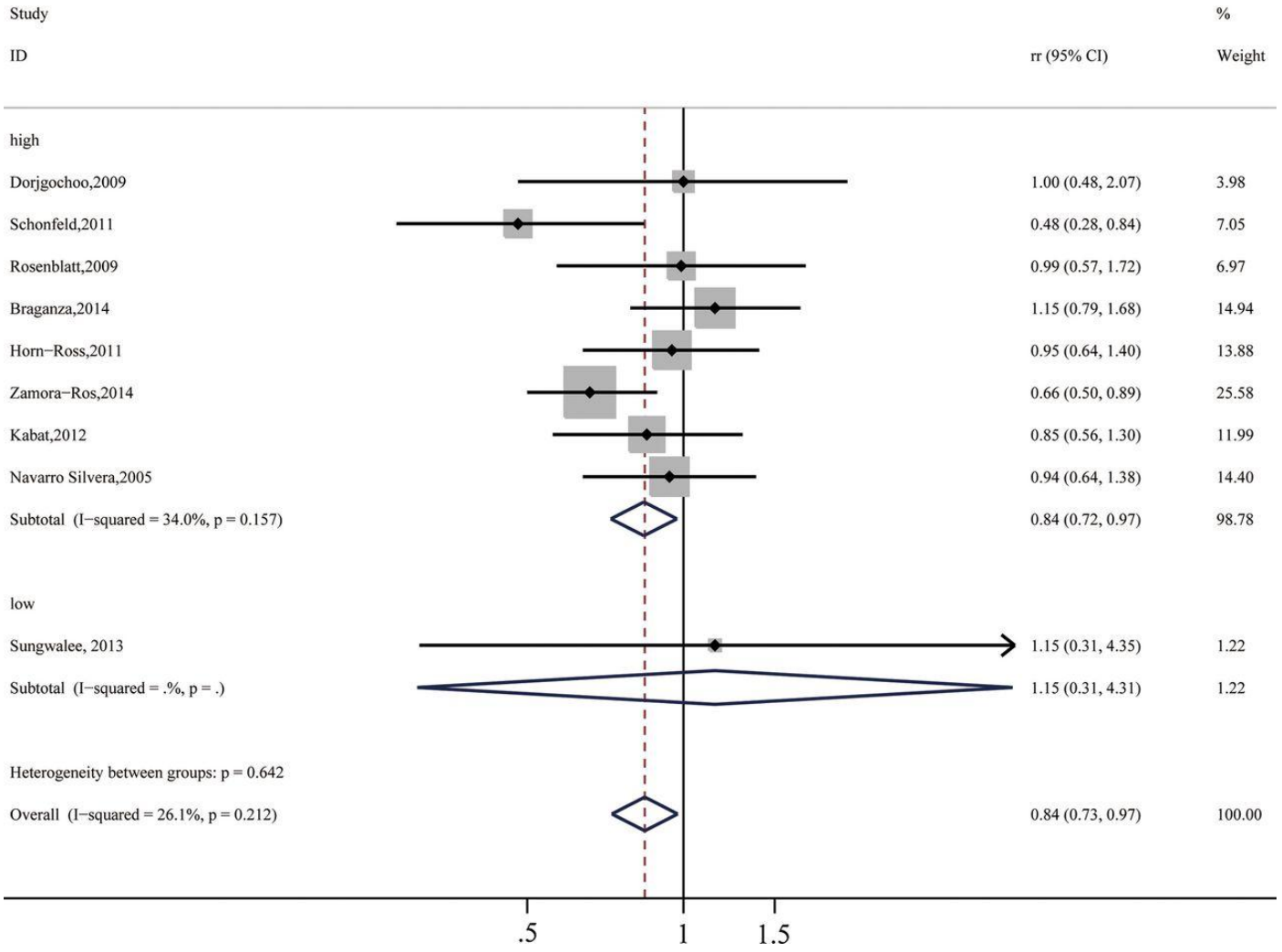
Soini Obstet Gynecol. 2014

	Non users	48 months	49-72 months	73-96 months	>97	All durations
Oesoph & stom	1	0.8	0.8	0.7	0.6	0.7
Rectum& colon	1	1.0	1.1 (0.7-1.6)	0.8	0.8	0.9
Liver&gallbladder	1	1.4 (0.4-4.2)	1.0	1.4 (0.3-5)	0.8	1.1
Pancreas	1	0.9	0.8	0.6	1.2 (0.6-2.3)	1.0
Lung	1	1.1	1.4	1.7 (1-2.8)	1.4 (0.9-2.1)	1.4
Skin melanoma	1	0.6	0.7	1.0	1.0	0.8
Skin other	1	1.4	1.5	1.1	1.0	1.2
Bladder&kidney	1	0.4	1.0	1.1	0.7	0.8
Brain	1	0.8	0.2	0.8	0.8	0.7
Thyroid	1	0.7	1.5	0.4	1.2	1.0
Lynph&haem	1	1.2 (0.8-1.8)	1.2 (0.7-1.9)	1.1	0.9	1.1 (0.8-2.1)

RR cancer in relation to total duration OC use (months)

Vessey M. , Yeates D . 2013

RR for the longest vs shortest duration of OC use with the risk of thyroid cancer was 0.84 (95% CI 0.73–0.97)



Forest plot (fixed-effects model) of OC use (highest versus lowest) and thyroid cancer risk (stratified by high- and low-quality studies).

Lang Wu, and Jingjing Zhu Hum. Reprod. 2015;30:2234-2240

human reproduction

TERAPIE MEDICHE DELLE DISFUNZIONI SESSUALI

Giovedì 18 febbraio 2016 Aviano ore 14.30-19.30

COME PROTEGGERE LA FERTILITÀ

Giovedì 10 marzo 2016 Aviano ore 14.30-19.30

Tel 338 6672444 delpuplino@libero.it