12° Congresso Nazionale AME

Associazione Medici Endocrinologi

6th Joint Meeting with AACE

American Association of Clinical Endocrinologists

Update in Endocrinologia Clinica

7-10 novembre 2013

Bari, Sheraton Nicolaus Hotel & Conference Center

AULA 4

Simposio 16

Terapie endocrino-metaboliche e rischio oncologico

Estroprogestinici

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Cancro della mammella

Bari,
7-10 novembre 2013

Il cancro della mammella è una neoplasia ormono-sensibile

Nel mondo è la seconda causa di morte dopo il tumore del polmone e per le donne rappresenta la principale causa di morte per neoplasia

Fattori di rischio per carcinoma della mammella

Non modificabili

- Età

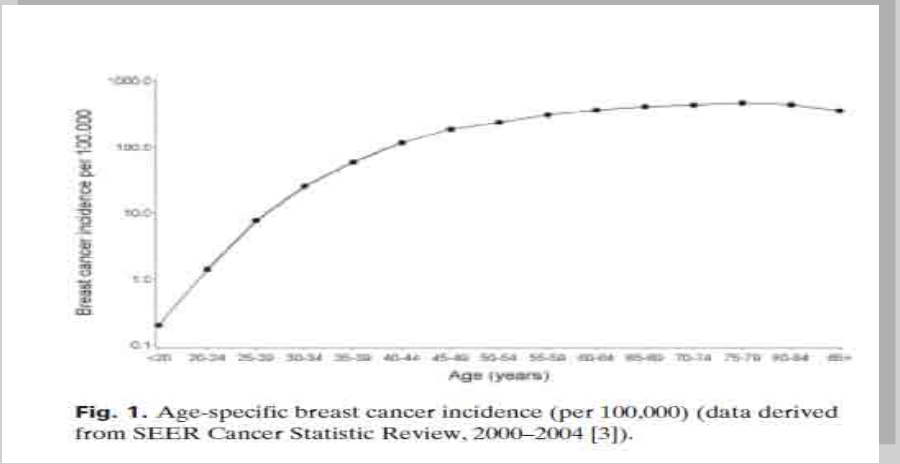

Fig. 1. Age-specific breast cancer incidence (per 100,000) (data derived from SEER Cancer Statistic Review, 2000–2004 [3]).

- Razza, etnia, migrazione
- Fattori genetici/familiarità
- Età del menarca/menopausa
- Densità della mammella
- Ormoni endogeni
- Patologie benigne

Breast Care 2009;4:82–87

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Modificabili

- Dieta/consumo di alcool
- Fumo di sigaretta
- Attività fisica
- Obesità
- Età della prima gravidanza
- Allattamento al seno
- *Terapia ormonale contraccettiva/sostitutiva (?)*

Breast Care 2009;4:82–87

Genetics of Breast and Ovarian Cancer (PDQ®)

Last Modified: 09/04/2013

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7-10 novembre 2013

Other Risk Factors for Breast Cancer

Other risk factors for breast cancer include age, reproductive and menstrual history, hormone therapy, radiation exposure, mammographic breast density, alcohol intake, physical activity, anthropometric variables, and a history of benign breast disease. (Refer to the PDQ summary on Breast Cancer Prevention for more information.) These factors, including their role in the etiology of breast cancer among *BRCA1/BRCA2* mutation carriers, are considered in more detail in other reviews.[13-15] Brief summaries are given below, highlighting, where possible, the effect of these risk factors in women who are genetically susceptible to breast cancer. (Refer to the Clinical management of BRCA mutation carriers section of this summary for more information about their effects in *BRCA1/BRCA2* mutation carriers.)

Oral contraceptives

Oral contraceptives (OCs) may produce a slight increase in breast cancer risk among long-term users, but this appears to be a short-term effect. In a meta-analysis of data from 54 studies, the risk of breast cancer associated with OC use did not vary in relationship to a family history of breast cancer.[21]

OCs are sometimes recommended for ovarian cancer prevention in *BRCA1* and *BRCA2* mutation carriers. Although the data are not entirely consistent, a meta-analysis concluded that there was no significant increased risk of breast cancer with OC use in *BRCA1/BRCA2* mutation carriers.[22] However, use of OCs formulated before 1975 was associated with an increased risk of breast cancer (summary relative risk [SRR], 1.47; 95% CI, 1.06–2.04).[22] (Refer to the Reproductive factors section in the Clinical management of BRCA mutation carriers section of this summary for more information.)

Hormone replacement therapy

Data exist from both observational and randomized clinical trials regarding the association between postmenopausal HRT and breast cancer. A meta-analysis of data from 51 observational studies indicated a RR of breast cancer of 1.35 (95% CI, 1.21–1.49) for women who had used HRT for 5 or more years after menopause.[23] The Women's Health Initiative (WHI), a randomized controlled trial (NCT00000611) of about 160,000 postmenopausal women, investigated the risks and benefits of HRT. The estrogen-plus-progestin arm of the study, in which more than 16,000 women were randomly assigned to receive combined HRT or placebo, was halted early because health risks exceeded benefits.[24,25] Adverse outcomes prompting closure included significant increase in both total (245 vs. 185

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Estroprogestinici e contraccezione

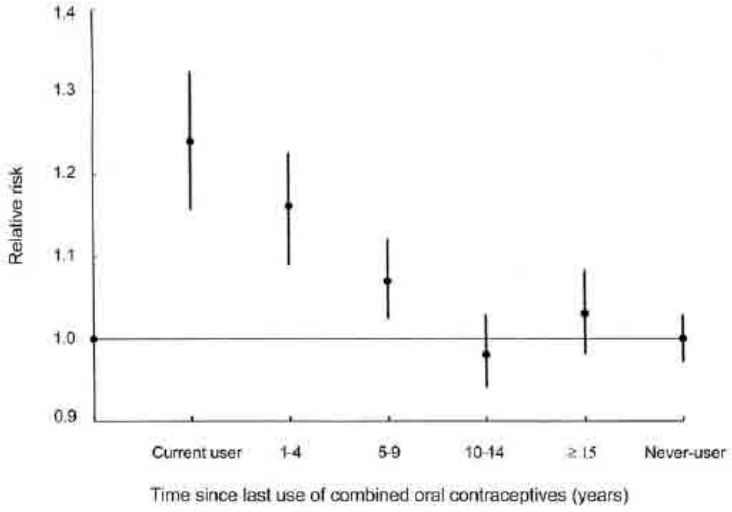
Oxford meta-analysis (CGHFBC, 1996)

Collaborative Group on Hormonal Factors in Breast Cancer

Modesto incremento di rischio di cancro della mammella (RR 1.24) che sembra correlato al precoce inizio della terapia EP (< 20 anni)
Il rischio torna alla norma dopo 10 anni dalla sospensione

Meta-analisi di 54 studi condotti in 25 paesi

Figure 2. Relative risk for breast cancer by time since last use of combined oral contraceptives



From Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)
Relative risk (given with 95% confidence interval [CI]) relative to no use, stratified by study, age at diagnosis, parity, age at first birth and age at which risk for conception ceased.

A prospective study of oral contraceptive use and risk of breast cancer (Nurses' Health Study, United States)

Studio prospettico
condotto dal 1976 al 1992 su 121,700 donne

Rischio di cancro della mammella

Per l' intero gruppo RR 1.07
Per le "past users" RR 1.06
Per le "corrent users" RR 1.53

Women's CARE (Marchbanks et al., 2002)

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Caso-controllo (circa 10000) donne tra i 35 e i 64 annni

TABLE 2. RISK OF BREAST CANCER ACCORDING TO THE USE OF COMBINATION ORAL CONTRACEPTIVES.*

VARIABLE	CASE SUBJECTS (N=4575)	CONTROLS (N=4682)	ODDS RATIO (95% CI)
	number		
No use	1032	980	1.0
Any use	3497	3658	0.9 (0.8–1.0)
Current use†	200	172	1.0 (0.8–1.3)
Former use	3289	3481	0.9 (0.8–1.0)‡
Duration of use			
<1 yr	782	822	0.9 (0.8–1.1)
1 to <5 yr	1200	1280	0.9 (0.8–1.0)
5 to <10 yr	848	882	0.9 (0.8–1.0)
10 to <15 yr	426	466	0.8 (0.7–1.0)‡
≥15 yr	234	202	1.0 (0.8–1.3)
Age at first use			
<15 yr	72	79	0.9 (0.6–1.2)
15 to 19 yr	1239	1272	1.0 (0.8–1.1)
20 to 24 yr	1260	1369	0.9 (0.8–1.0)‡
25 to 29 yr	587	592	0.9 (0.8–1.1)
30 to 34 yr	209	239	0.8 (0.6–1.0)‡
35 to 39 yr	84	67	1.2 (0.8–1.6)
≥40 yr	38	35	1.0 (0.6–1.6)
Time since last use			
Current use	200	172	1.0 (0.8–1.3)
7 mo to <5 yr	165	207	0.7 (0.5–0.9)‡
5 to <10 yr	244	239	0.9 (0.8–1.2)
10 to <15 yr	426	418	0.9 (0.8–1.1)
15 to <20 yr	650	717	0.9 (0.7–1.0)
≥20 yr	1803	1899	0.9 (0.8–1.0)
High estrogen dose§			
Any use	1082	1265	0.8 (0.7–0.9)‡
Current use	7	10	0.7 (0.2–1.8)
Former use	1074	1255	0.8 (0.7–0.9)‡
Low estrogen dose¶			
Any use	1460	1560	0.9 (0.8–1.0)
Current use	183	160	1.0 (0.8–1.3)
Former use	1267	1398	0.9 (0.8–1.0)

TABLE 4. RISK OF BREAST CANCER ACCORDING TO THE TYPE OF PROGESTIN.*

VARIABLE	CASE SUBJECTS (N=4575)	CONTROLS (N=4682)	ODDS RATIO (95% CI)
	number		
No use	1032	980	1.0
Estrane progestins			
Any use	2439	2598	0.9 (0.8–1.0)
Current use†	113	94	1.1 (0.8–1.5)
Ethynodiol diacetate			
Any use	313	315	1.0 (0.8–1.2)
Current use	15	4	3.5 (1.1–10.7)‡
Norethindrone			
Any use	1993	2143	0.9 (0.8–1.0)‡
Current use	59	51	1.0 (0.7–1.6)
Norethindrone acetate			
Any use	241	244	1.0 (0.8–1.2)
Current use	40	39	1.1 (0.7–1.8)
Norethynodrel			
Any use	163	162	0.9 (0.7–1.2)
Current use	0	0	—
Gonane progestins			
Any use	649	678	1.0 (0.8–1.2)
Current use	85	80	1.0 (0.7–1.5)
Desogestrel, norgestimate, or gestodene§			
Any use	91	97	1.0 (0.7–1.3)
Current use	28	27	0.9 (0.5–1.7)
Levonorgestrel			
Any use	121	114	1.1 (0.8–1.5)
Current use	32	33	0.9 (0.5–1.5)
Norgestrel			
Any use	497	513	1.0 (0.9–1.3)
Current use	28	20	1.4 (0.8–2.5)
Other¶			
Any use	57	76	0.7 (0.5–1.1)
Current use	0	0	—

Women's CARE (Marchbanks et al., 2002)

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Caso-controllo (circa 10000) donne tra i 35 e i 64 annni

TABLE 2. RISK OF BREAST CANCER ACCORDING TO THE USE OF COMBINATION ORAL CONTRACEPTIVES.*

VARIABLE	CASE SUBJECTS (N=4575)	CONTROLS (N=4682)	ODDS RATIO (95% CI)
	number		
No use	1032	980	1.0
Any use			
Current u			
Former u			
Duration			
<1 yr			
1 to <			
5 to <			
10 to <			
≥15 yr			
Age at fi			
<15 yr			
15 to			
20 to			
25 to			
30 to			
35 to			
≥40 yr	38	35	1.0 (0.6–1.6)
Time since last use			
Current use	200	172	1.0 (0.8–1.3)
7 mo to <5 yr	165	207	0.7 (0.5–0.9)‡
5 to <10 yr	244	239	0.9 (0.8–1.2)
10 to <15 yr	426	418	0.9 (0.8–1.1)
15 to <20 yr	650	717	0.9 (0.7–1.0)
≥20 yr	1803	1899	0.9 (0.8–1.0)
High estrogen dose§			
Any use	1082	1265	0.8 (0.7–0.9)‡
Current use	7	10	0.7 (0.2–1.8)
Former use	1074	1255	0.8 (0.7–0.9)‡
Low estrogen dose¶			
Any use	1460	1560	0.9 (0.8–1.0)
Current use	183	160	1.0 (0.8–1.3)
Former use	1267	1398	0.9 (0.8–1.0)

TABLE 4. RISK OF BREAST CANCER ACCORDING TO THE TYPE OF PROGESTIN.*

VARIABLE	CASE SUBJECTS (N=4575)	CONTROLS (N=4682)	ODDS RATIO (95% CI)
	number		
Gonane progestins			
Any use	649	678	1.0 (0.8–1.2)
Current use	85	80	1.0 (0.7–1.5)
Desogestrel, norgestimate, or gestodene§			
Any use	91	97	1.0 (0.7–1.3)
Current use	28	27	0.9 (0.5–1.7)
Levonorgestrel			
Any use	121	114	1.1 (0.8–1.5)
Current use	32	33	0.9 (0.5–1.5)
Norgestrel			
Any use	497	513	1.0 (0.9–1.3)
Current use	28	20	1.4 (0.8–2.5)
Other¶			
Any use	57	76	0.7 (0.5–1.1)
Current use	0	0	—

Non vi è aumento di rischio correlabile con l' uso di EP, né con il tempo di terapia o l' età di inizio. Non c' è differenza tra diversi progestinici o dose di estrogeni

Women's Lifestyle and Health study (cohort) (Kumle et al., 2002)

Circa 100.000 donne (34-49 anni) tra Svezia e Norvegia al 1991 al 1999

Table 2 RRs and 95% CIs of developing breast cancer according to use of OCs, The Women's Lifestyle and Health Study

Use of OCs	Study population	Breast cancer cases	RR (95% CI)	
			Age-adjusted	Multivariate[a]
Never-users	28,171	261	1.0 (reference)	1.0 (reference)
Ever-users	74,856	747	1.2 (1.1–1.4)	1.3 (1.1–1.5)
Current/recent users at start of follow-up	9,299	91	1.6 (1.2–2.0)	1.6 (1.2–2.1)
Former users at start of follow-up	65,557	656	1.2 (1.1–1.4)	1.2 (1.1–1.4)
Duration of use (yrs)				
<5	38,742	384	1.2 (1.0–1.4)	1.2 (1.0–1.5)
5–9	18,876	178	1.3 (1.0–1.5)	1.2 (1.0–1.5)
10–14	10,803	113	1.4 (1.1–1.8)	1.4 (1.1–1.8)
15+	5,441	63	1.3 (1.0–1.8)	1.3 (1.0–1.8)
Test for trend			$P = 0.001$	$P = 0.005$

[a] Multivariate analysis, adjusted for: age (continuous variable), parity (0, 1, 2, 3+), age at first birth (−20, 21–24, 25+), age at menarche (continuous variable), use of HRT (ever/never), menopausal status (pre-/postmenopausal), history of breast cancer in first-degree relatives (yes/no), duration of breastfeeding (continuous variable), BMI (continuous variable), region (Sweden and five health regions in Norway), and a term for interaction between BMI and menopausal status.

Women's Lifestyle and Health study (cohort) (Kumle *et al.*, 2002)

Circa 100.000 donne (34-49 anni) tra Svezia e Norvegia al 1991 al 1999

Le donne che utilizzano o hanno utilizzato EP hanno un aumentato rischio di sviluppare il cancro al seno.
Uso prima dei 20 anni e prima della prima gravidanza non sembrano correlati ad incremento del rischio
Il rischio non sembra ridursi con il tempo

Oral Contraceptive Use as a Risk Factor for Premenopausal Breast Cancer: A Meta-analysis

Mayo Clin Proc. 2006;81(10):1290-1302

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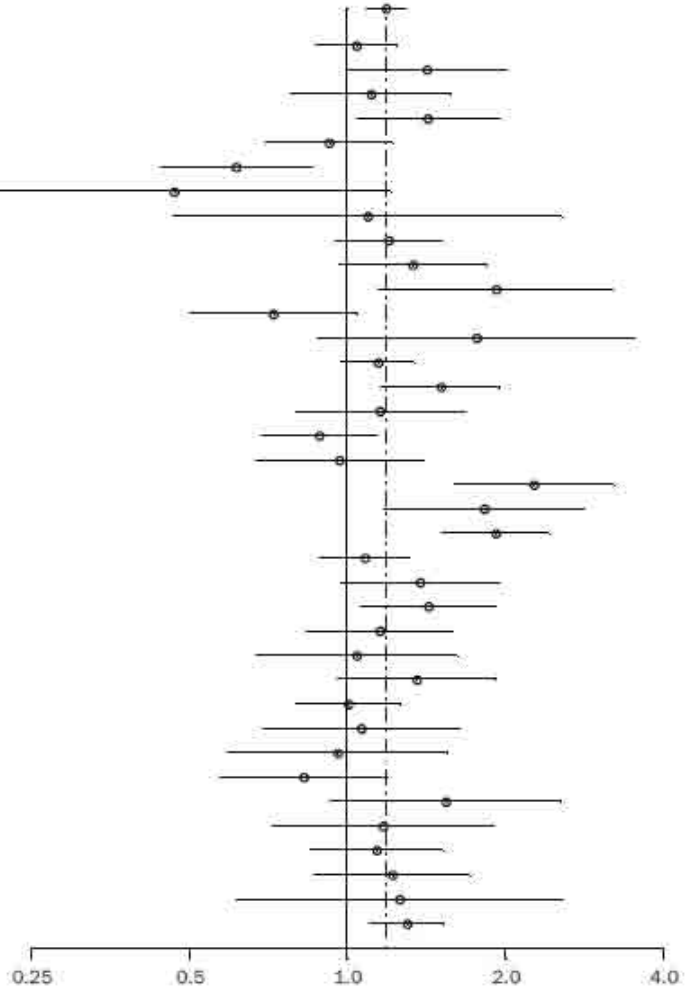
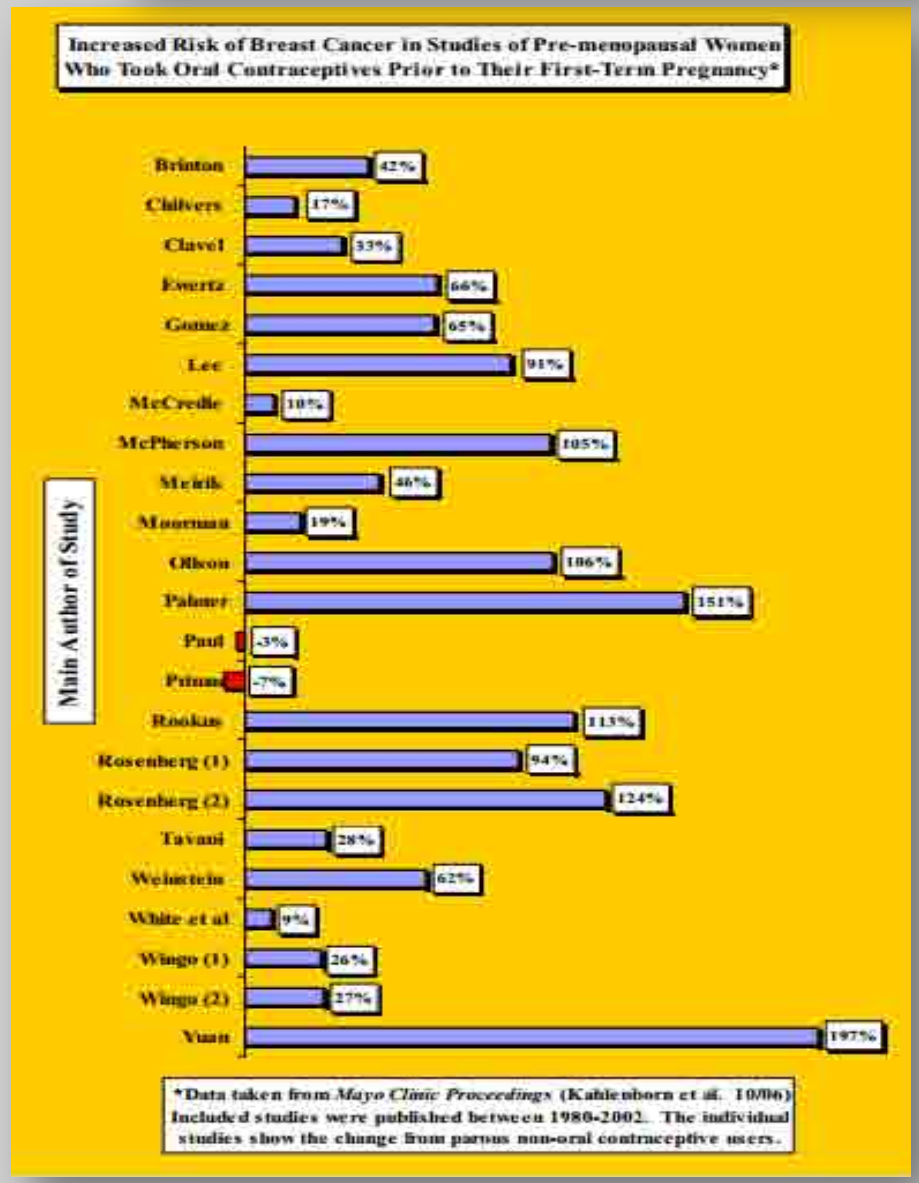
Reference	Cases/controls: OC users	Cases/controls: OC nonusers	OR (95% CI)	*P* value
All			1.19 (1.09-1.29)	9.5×10^{-5}
Wingo,[72] 1993*	117/976	328/298	1.04 (0.87-1.24)	.70
Wingo,[73] 1993†	432/556	57/104	1.42 (1-2)	.058
White,[71] 1994	689/879	58/82	1.11 (0.78-1.57)	.63
Weinstein,[74] 1991	175/145	151/178	1.42 (1.04-1.94)	.031
Ursin,[70] 1999	618/626	124/116	0.92 (0.7-1.22)	.62
Traina,[69] 1996	103/138	197/162	0.61 (0.44-0.85)	.0047
Tessaro,[68] 2001‡	40/139	8/13	0.47 (0.18-1.21)	.19
Tessaro,[68] 2001§	44/146	8/29	1.09 (0.47-2.56)	.99
Tavani,[67] 1999	221/227	358/441	1.2 (0.95-1.51)	.14
Shapiro,[63] 2000*	91/274	98/393	1.33 (0.96-1.84)	.099
Shapiro,[63] 2000†	36/140	34/254	1.92 (1.15-3.21)	.017
Rosenberg,[66] 1992*	98/225	79/131	0.72 (0.5-1.04)	.099
Rosenberg,[66] 1992†	66/118	13/41	1.76 (0.88-3.53)	.15
Rosenberg,[75] 1996*	455/606	617/940	1.14 (0.98-1.34)	.10
Rosenberg,[75] 1996†	184/421	134/462	1.51 (1.16-1.95)	.0023
Rookus,[65] 1994	613/605	58/66	1.15 (0.8-1.67)	.51
Primic-Zakelj,[64] 1995	250/249	251/221	0.88 (0.69-1.14)	.37
Paul,[61] 1990	345/1081	43/130	0.96 (0.67-1.39)	.92
Palmer,[62] 1995	119/222	65/275	2.27 (1.6-3.22)	5.4×10^{-6}
Olsson,[58] 1989	143/329	31/130	1.82 (1.18-2.82)	.0092
WHO study,[60] 1990	160/1613	141/2722	1.91 (1.51-2.42)	5.2×10^{-8}
Newcomb,[59] 1996	862/1555	188/366	1.08 (0.89-1.31)	.47
Moorman,[56] 2001	428/328	75/79	1.37 (0.97-1.94)	.087
Meirik,[57] 1986	326/371	96/156	1.43 (1.06-1.92)	.021
McPherson,[54] 1987	240/229	111/122	1.15 (0.84-1.58)	.42
McCredie,[53] 1998	418/366	46/42	1.04 (0.67-1.62)	.94
Marcus,[55] 1999	428/328	76/79	1.36 (0.96-1.92)	.10
Marchbanks,[52] 2002	1264/1305	165/171	1.0 (0.8-1.26)	.98
Lee,[50] 1987	50/302	47/302	1.06 (0.69-1.63)	.86
Lee,[51] 1992	41/80	68/127	0.96 (0.59-1.54)	.95
Le,[49] 1985	161/217	79/88	0.83 (0.57-1.19)	.35
Gomes,[48] 1995	35/60	64/169	1.54 (0.93-2.56)	.12
Ewertz,[47] 1992	165/167	38/45	1.17 (0.72-1.9)	.61
Clavel,[46] 1991	204/204	154/175	1.14 (0.85-1.52)	.43
UK National,[45] 1989	688/675	67/80	1.22 (0.86-1.71)	.30
Chie,[44] 1998	13/26	84/211	1.26 (0.62-2.56)	.66
Brinton,[43] 1995	1259/1074	389/431	1.3 (1.11-1.52)	.0015



Oral Contraceptive Use as a Risk Factor for Premenopausal Breast Cancer: A Meta-analysis



Incremento del rischio di carcinoma della mammella nelle donne che hanno utilizzato EP prima della prima gravidanza.
L'uso precoce sembra inoltre associato a forme più aggressive di cancro

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

BMJ 2007;335:651

Bari,
7-10 novembre 2013

Recruitment 1968-9 Ever users (n=23 377), never users (n=23 796)

Excluded from analysis (n=1223):
- No general practitioner observation (n=772)
- Previous cancer (n=90)
- Information supplied by doctor related to pregnancy only (n=75)
- Covariate information missing (n=286)

Women not flagged (n=10 900)

	Left age <38		Left age ≥38	
	Ever	Never	Ever	Never
Cancer	6	7	11	14
No cancer	5366	2991	1443	1062
Total woman years	14 447	9086	8851	7011

Women flagged (n=35 050)

	Position in oral contraception study at 1996					
	Under general practitioner observation		Left age <38		Left age ≥38	
	Ever	Never	Ever	Never	Ever	Never
Cancer	728	566	17	8	174	120
No cancer	6614	3957	7654	4072	6749	4391
Total woman years	179 727	121 144	28 428	15 580	99 844	71 548

General practitioner observation dataset

	Used oral contraception	
	Ever	Never
Cancer	936	715
No cancer	27 826	16 473
Total woman years	331 297	224 369

Women flagged (n=35 050)

	Position in oral contraception study at 2004					
	Under general practitioner observation, 1996		Left age <38		Left age ≥38	
	Ever	Never	Ever	Never	Ever	Never
Cancer	1048	786	598	8	822	577
No cancer	6294	3737	7073	4072	6101	3934
Total woman years	231 414	151 835	261 152	15 580	228 853	155 837

Main dataset

	Used oral contraception	
	Ever	Never
Cancer	2 485	1 392
No cancer	26 277	15 796
Total woman years	744 717	539 349

Follow up

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

Bari,
7-10 novembre 2013

Recruitment 1968-9 Ever users (n=23 377), never users (n=23 796)

Table 1 | Characteristics of women who ever or never used oral contraceptives

Characteristics	No (%) of ever users of oral contraceptives	No (%) of never users of oral contraceptives
Age at recruitment (years):		
<30	18 305 (63.6)	8854 (51.5)
30-39	8690 (30.2)	6579 (38.3)
40-49	1744 (6.1)	1724 (10.0)
50-59	23 (0.1)	31 (0.2)
Smoking at recruitment (cigarettes per day):		
0	15 054 (52.3)	10 371 (60.3)
1-14	7986 (27.8)	4164 (24.2)
≥15	5722 (19.9)	2653 (15.4)
Parity at recruitment:		
0	4862 (16.9)	3458 (20.1)
1	6570 (22.8)	4465 (26.0)
2	9179 (31.9)	5472 (31.8)
≥3	8151 (28.3)	3793 (22.1)
Social class at recruitment:		
Non-manual	10 347 (36.0)	6630 (38.6)
Manual	18 415 (64.0)	10 558 (61.4)
Never used hormone replacement therapy	25 056 (87.2)	15 453 (90.0)
Ever used hormone replacement therapy	3695 (12.9)	1716 (10.0)

Values for age, smoking, parity, and social class based on main dataset and for use of hormone replacement therapy on general practitioner observation dataset.

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Table 2 | Risk of cancer among ever and never users of oral contraceptives in main dataset and in general practitioner observation dataset

Malignancies	ICD-8 code	Ever users		Never users		Relative risk† (95% CI)
		Observed rate (No of women)	Standardised rate	Observed rate (No of women)	Standardised rate	
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)
General practitioner observation dataset‡:						
Large bowel or rectum	153 and 154	19.63 (66)	22.07	25.85 (59)	26.11	0.85 (0.59 to 1.20)
Gallbladder or liver	155 and 156	2.08 (7)	3.06	2.63 (6)	2.76	1.11 (0.37 to 3.30)
Lung	162	19.91 (67)	19.47	17.07 (39)	18.87	1.03 (0.70 to 1.53)
Melanoma	172	14.57 (49)	15.26	14.90 (34)	14.81	1.03 (0.66 to 1.60)
Breast	174	100.68 (337)	108.12	111.46 (253)	105.96	1.02 (0.87 to 1.20)
Invasive cervix	180	21.44 (72)	20.78	13.15 (30)	13.94	1.49 (0.97 to 2.28)
Uterine body	182	6.24 (21)	6.24	15.33 (35)	13.27	0.47 (0.27 to 0.81)
Ovary	183	9.81 (33)	10.25	21.90 (50)	20.28	0.51 (0.33 to 0.78)
Central nervous system or pituitary	191,1943	4.16 (14)	4.10	1.31 (3)	1.27	3.23 (0.93 to 11.24)
Site unknown	199	6.54 (22)	7.01	10.50 (24)	8.97	0.78 (0.44 to 1.39)
Other cancers		91.13 (305)	94.60	103.90 (236)	98.58	0.96 (0.81 to 1.14)
Main gynaecological	180,182,183	37.53 (126)	37.36	50.46 (115)	47.56	0.79 (0.61 to 1.01)
Any cancer	140-209	282.53 (936)	295.96	318.67 (715)	306.59	0.97 (0.88 to 1.06)

Table 2 | Risk of cancer among ever and never users of oral contraceptives in main dataset and in general practitioner observation dataset

		Ever users		Never users		
Malignancies	ICD-8 code	Observed rate (No of women)	Standardised rate	Observed rate (No of women)	Standardised rate	Relative risk† (95% CI)
Main dataset*:						
Invasive cervix	180	21.44 (72)	20.78	13.15 (30)	13.94	1.49 (0.97 to 2.28)
Uterine body	182	6.24 (21)	6.24	15.33 (35)	13.27	0.47 (0.27 to 0.81)
Ovary	183	9.81 (33)	10.25	21.90 (50)	20.28	0.51 (0.33 to 0.78)
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Any cancer	140-209	282.53 (936)	295.96	318.67 (715)	306.59	0.97 (0.88 to 1.06)

Le donne che hanno utilizzato OC mostrano:

- significativa riduzione del rischio (12%) di sviluppare cancro del colon, retto e ovaio.
- nessuna modificazione di rischio del cancro al seno
- incremento non significatico del rischio di cancro del polmone, cervice uterina, ipofisi, SNC per l' uso > 8 anni

Oral contraceptive use and cancer. Findings in a large cohort study, 1968–2004

British Journal of Cancer (2006) 95, 385 – 389

Bari,
7-10 novembre 2013

Circa 17000 donne tra i 25 e i 39 anni reclutate in Inghilterra e Scozia tra il 1968 e il 1974

Table I Cancer (ICD order) in relation to total duration of OC use

	Total duration of oral contraceptive use (months)									
	Nonuser		Up to 48		49 to 96		97 or more		All durations	
Cancer site	No	RR	No	RR	No	RR	No	RR	No	RR
Oesophagus and stomach (1,2,3)	19	1.0	7	0.8 (0.3–1.9)	9	0.7 (0.3–1.7)	7	0.5 (0.2–1.2)	23	0.6 (0.3–1.3)
Rectum and colon (1,4)	56	1.0	26	1.1 (0.6–1.7)	23	0.8 (0.4–1.2)	26	0.8 (0.5–1.2)	75	0.8 (0.6–1.2)
Lung (1,2,3,5)	30	1.0	17	1.2 (0.6–2.3)	30	1.5 (0.8–2.5)	38	1.4 (0.8–2.3)	85	1.4 (0.9–2.1)
Malignant melanoma (1,2,3,6)	40	1.0	9	0.4 (0.2–0.9)	21	0.9 (0.5–1.5)	24	1.0 (0.6–1.7)	54	0.8 (0.5–1.2)
Other skin (1,2,3)	128	1.0	61	1.1 (0.8–1.5)	86	1.2 (0.9–1.6)	77	1.0 (0.7–1.3)	224	1.1 (0.9–1.4)
Breast (1,3,7)	314	1.0	141	0.9 (0.8–1.1)	182	0.9 (0.8–1.1)	207	1.0 (0.8–1.2)	530	1.0 (0.8–1.1)
Uterine cervix (1,2,3,5,8)	6	1.0	9	2.9 (0.9–9.9)	16	3.3 (1.2–10.4)	28	6.1 (2.5–17.9)	53	4.2 (1.8–12.0)
Uterine body (1,4)	50	1.0	12	0.6 (0.3–1.1)	11	0.4 (0.2–0.8)	4	0.1 (0.0–0.4)	27	0.3 (0.2–0.6)
Ovary (1)	58	1.0	28	1.0 (0.6–1.7)	10	0.3 (0.1–0.6)	10	0.3 (0.1–0.5)	48	0.5 (0.3–0.7)
Kidney and bladder (1,4)	24	1.0	6	0.6 (0.2–1.5)	15	1.1 (0.6–2.2)	11	0.7 (0.3–1.5)	32	0.8 (0.5–1.5)
Lymphomas and leukaemias (1)	47	1.0	23	1.1 (0.6–1.8)	28	1.0 (0.6–1.7)	32	1.1 (0.7–1.7)	83	1.1 (0.7–1.6)
Other known (1)	54	1.0	34	1.2 (0.8–1.9)	26	0.8 (0.5–1.3)	36	1.1 (0.7–1.7)	96	1.0 (0.7–1.5)
Uncertain (1,3)	14	1.0	6	1.0 (0.3–2.7)	9	1.1 (0.4–2.6)	19	1.8 (0.9–3.9)	34	1.4 (0.7–2.7)

Bari,
7-10 novembre 2013

Oral contraceptive use and cancer. Findings in a large cohort study, 1968–2004

British Journal of Cancer (2006) 95, 385 – 389

Circa 17000 donne tra i 25 e i 39 anni reclutate in Inghilterra e Scozia tra il 1968 e il 1974

Non si dimostra un incremento del rischio di cancro alla mammella

Cancro dell' utero e cancro dell' ovaio sono negativamente correlati con l' uso di EP

Il cancro della cervice mostra una forte e positiva associazione con la durata della terapia

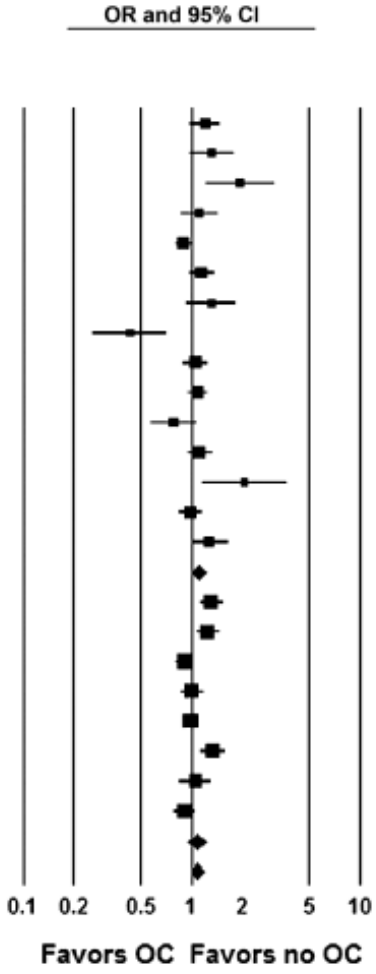
Oral Contraceptive Use and Risk of Breast, Cervical, Colorectal, and Endometrial Cancers: A Systematic Review

Bari,
7-10 novembre 2013

Cancer Epidemiol Biomarkers Prev; 1–13. ©2013 AACR.

In collaboration with an experienced librarian, we conducted searches of PubMed, Embase, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov to identify relevant published literature. Our searches were date-limited to articles published from January 1, 1990 to June 29, 2012. For the outcomes presented in this article,

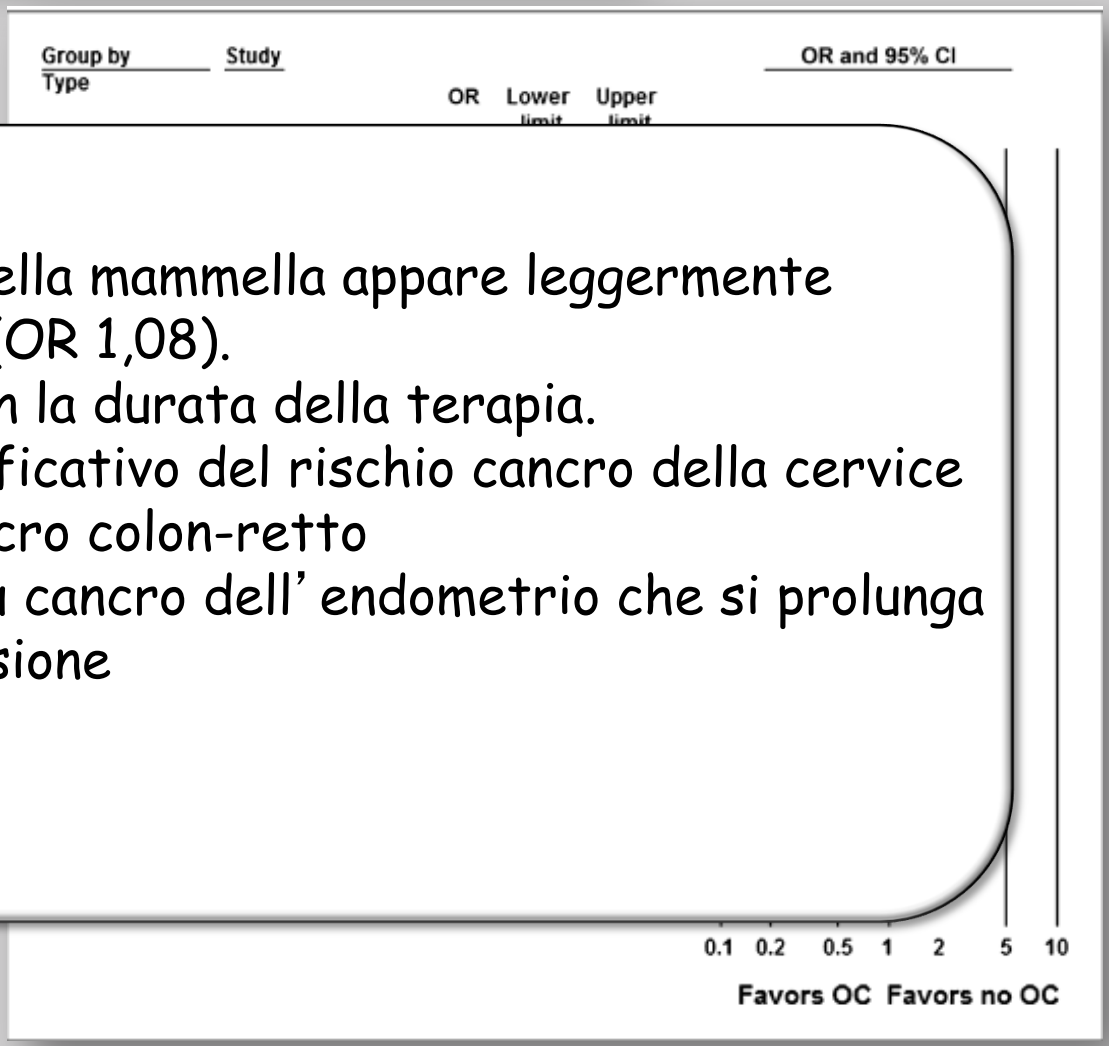
Group by Type	Study	OR	Lower limit	Upper limit
Case–control	Shapiro, 2000	1.200	0.980	1.470
Case–control	Van Hoffin, 2000	1.310	0.959	1.789
Case–control	Gomes, 2001	1.930	1.194	3.120
Case–control	Moorman, 2001	1.110	0.858	1.436
Case–control	Marchbanks, 2002	0.900	0.801	1.011
Case–control	Althuis, 2003	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



Bari,
7-10 novembre 2013

Oral Contraceptive Use and Risk of Breast, Cervical, Colorectal, and Endometrial Cancers: A Systematic Review

Cancer Epidemiol Biomarkers Prev; 1–13. ©2013 AACR.



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June 29, 201

Il rischio di cancro della mammella appare leggermente (slightly) aumentato (OR 1,08).
Nessuna relazione con la durata della terapia.
Incremento non significativo del rischio cancro della cervice
Riduzione rischio cancro colon-retto
Effetto protettivo su cancro dell' endometrio che si prolunga anche dopo la sospensione

Possibili bias

Bari,
7-10 novembre 2013

- ✓ Dosaggi e formulazioni degli EP
- ✓ Età delle donne incluse
- ✓ Disegno e tempo di osservazione degli studi
- ✓ Diversi paesi

Possibili bias

Bari,
7-10 novembre 2013

- ✓ Se l' uso di EP prima della prima gravidanza è associato a forme più aggressive di cancro, le donne affette potrebbero non essere incluse perché già decedute o a causa del disegno dello studio

- ✓ Diverse possibilità di accedere ad esami radiologici

Bari,
7-10 novembre 2013

Fattori di rischio per cancro della mammella ed EP

Review article

Contraception 80 (2009) 372–380

Oral contraceptives and family history of breast cancer☆,☆☆

Bari,
7-10 novembre 2013

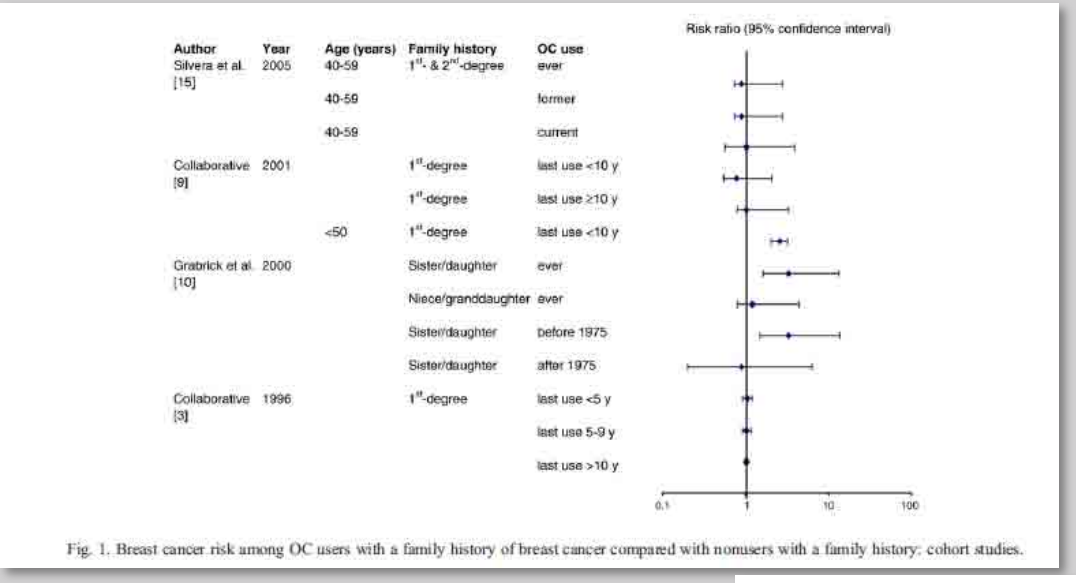


Fig. 1. Breast cancer risk among OC users with a family history of breast cancer compared with nonusers with a family history: cohort studies.

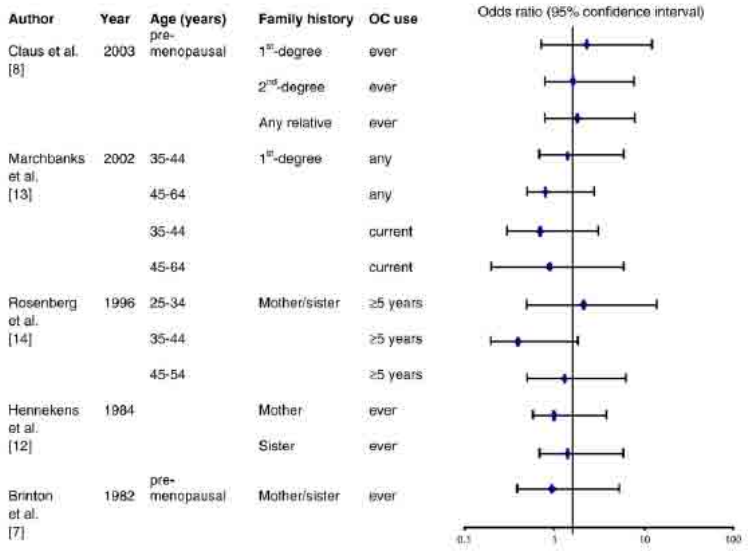


Fig. 2. Breast cancer risk among OC users with a family history of breast cancer compared with nonusers with no family history: case-control studies.

Review article
Contraception 80 (2009) 372–380

Oral contraceptives and family history of breast cancer☆,☆☆

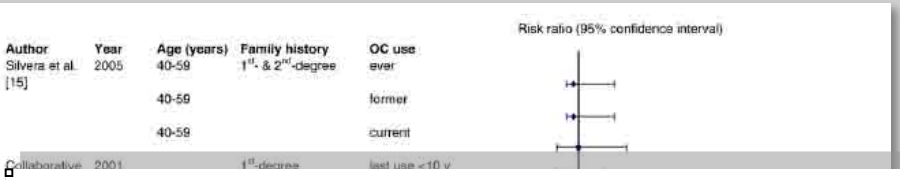


Fig. 1. Breast ca

Dati controversi:

- ✓aumento del rischio in donne che hanno fatto uso di EP prima del 1975
- ✓mancanza dati su tipo EP
- ✓differente definizione di "storia familiare"

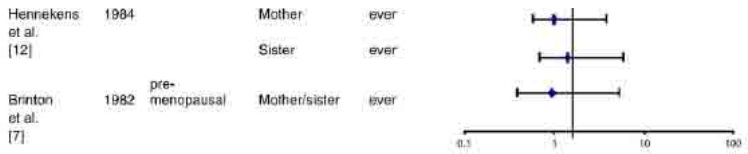


Fig. 2. Breast cancer risk among OC users with a family history of breast cancer compared with nonusers with no family history: case-control studies.

Bari,
7-10 novembre 2013

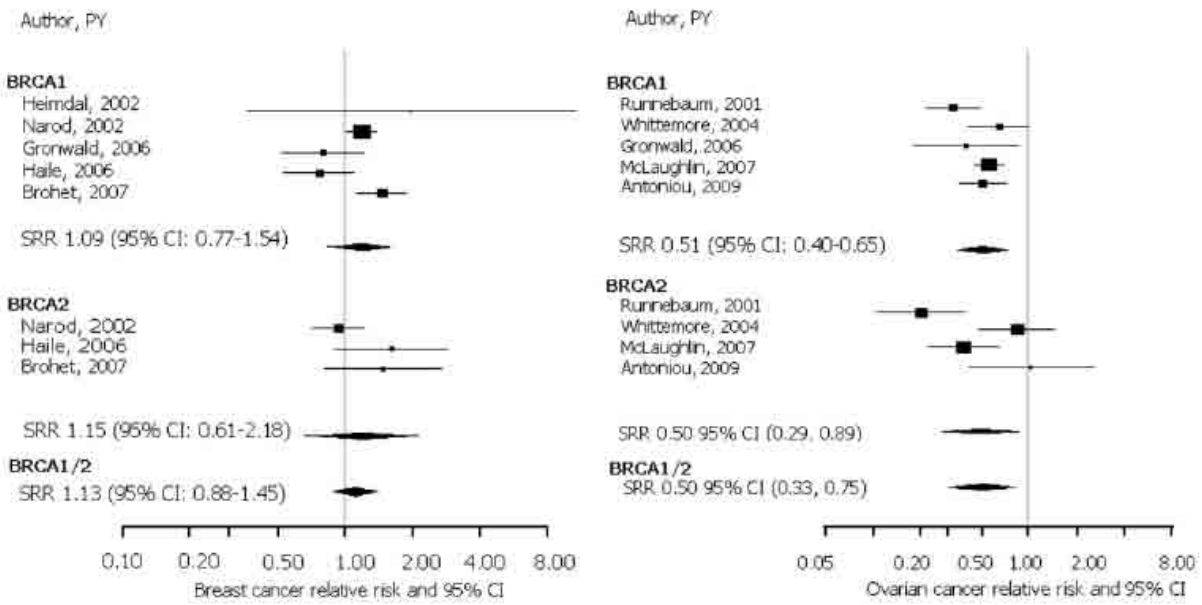
Table II Effect of OC use on breast cancer risk in BRCA mutation carriers.

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 (Heimdal *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

Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: A meta-analysis

EUROPEAN JOURNAL OF CANCER 46 (2010) 2275–2284

S. Iodice [a,*], M. Barile [b], N. Rotmensz [a], I. Feroce [b], B. Bonanni [b], P. Radice [c], L. Bernard [d], P. Maisonneuve [a], S. Gandini [a]



Forest plot and summary relative risk on the association between OC use and breast cancer (left) and ovarian cancer (right) in carriers.

PY: publication year; SRR: Summary Relative Risk; CI confidence intervals

Fig. 2 – Association between oral contraceptives (OC) use and breast or ovarian cancer in BRCA1/2 carriers.

Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: A meta-analysis

EUROPEAN JOURNAL OF CANCER 46 (2010) 2275–2284

S. Iodice [a,*], M. Barile [b], N. Rotmensz [a], L. Feroce [b], B. Bonanni [b], P. Radice [c], L. Bernard [d]

Nessuna evidenza di un significativo incremento del rischio di cancro della mammella nelle donne che usano EP, per l'uso degli EP più recenti e nei primi dieci anni dalla sospensione

Il rischio di cancro dell'ovaio decresce parallelamente al prolungarsi dell'uso di EP

Forest plot and summary relative risk on the association between OC use and breast cancer (left) and ovarian cancer (right) in carriers.
PY: publication year; SRR: Summary Relative Risk; CI confidence intervals

Fig. 2 – Association between oral contraceptives (OC) use and breast or ovarian cancer in BRCA1/2 carriers.

Patologia mammaria benigna

Con il termine di patologia mammaria benigna si intendono una serie eterogenea di lesioni diverse per istologia e storia naturale.

Nelle donne sottoposte a biopsia per patologia benigna:
- ✓ 70% lesioni non proliferative
- ✓ 26% iperplasia tipica con aumento rischio 2 volte
- ✓ 4% iperplasia atipica aumento rischio 5 volte

Dati controversi
- ✓ effetto protettivo su iperplasia tipica
- ✓ nessun effetto su iperplasia atipica
- ✓ possibile incremento di iperplasia atipica

Composizione EP

Bari,
7-10 novembre 2013

Table 5 RRs and 95% CIs of developing breast cancer according to exclusive use of progestin-only oral pills (POPs) or combined OCs (COCs), The Women's Lifestyle and Health Study

Use of OCs	Study population	Breast cancer cases	RR (95% CI)	
			Age-adjusted	Multivariate[a]
Never-users	28,171	261	1.0 (reference)	1.00 (reference)
Ever-users of				
POPs	3,435	29	1.1 (0.8–1.6)	1.1 (0.8–1.7)
COCs	42,811	444	1.3 (1.1–1.5)	1.3 (1.1–1.6)
Both POPs and COCs or missing values on brand	28,610	274	1.2 (1.0–1.4)	1.2 (1.0–1.4)
Current/recent users at start of follow-up				
POPs	2,189	25	1.6 (1.1–2.5)	1.6 (1.0–2.4)
COCs	6,691	60	1.6 (1.2–2.2)	1.5 (1.0–2.0)
Age-stratified analysis				
Current/recent users at start of follow-up				
Age at start of follow-up 30–39 yrs[b]				
Never-users	8,829	41	1.0 (reference)	1.0 (reference)
POPs	1,251	8	1.6 (0.8–3.4)	1.7 (0.8–3.7)
COCs	5,130	36	1.9 (1.2–3.1)	2.0 (1.2–3.2)
Age at start of follow-up 40–49 yrs				
Never-users	19,342	220	1.0 (reference)	1.0 (reference)
POPs	938	17	1.7 (1.0–2.8)	1.6 (0.9–2.6)
COCs	1,561	24	1.5 (1.0–2.3)	1.2 (0.7–1.9)

Contraception 85 (2012) 342–350 Original research article

Oral contraceptive formulation and risk of breast cancer☆,☆☆

Bari,
7-10 novembre 2013

Table 2
Risk of breast cancer according to OC formulation in the Women's CARE Study among women who reported exclusive use of a combination OC formulation that was used by at least 50 women[a]

Variable	100 mcg mestranol/1.0 mg ethynodiol diacetate			35 mcg ethinyl estradiol/0.5 mg norethindrone			35 mcg ethinyl estradiol/1.0 mg norethindrone			50 mcg mestranol/1.0 mg norethindrone		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total no. of subjects	1124	1085		1089	1034		1234	1172		1221	1206	
General use												
No use[b]	1032	980	1.0	1032	980	1.0	1032	980	1.0	1032	980	1.0
Ever use	81	95	0.8 (0.6–1.1)	47	44	1.2 (0.7–1.8)	192	179	1.0 (0.8–1.3)	179	213	0.8 (0.7–1.1)
Current use[c]							7	6	1.0 (0.3–3.0)			
Former use	81	95	0.8 (0.6–1.1)	46	43	1.2 (0.7–1.8)	185	173	1.0 (0.8–1.3)	177	213	0.8 (0.6–1.1)
Duration of use												
<2 years	19	23	0.8 (0.4–1.5)	28	26	1.2 (0.7–2.0)	70	68	0.9 (0.6–1.4)	50	65	0.8 (0.5–1.2)
2+ years	62	72	0.8 (0.5–1.1)	19	18	1.2 (0.6–2.3)	122	111	1.0 (0.8–1.4)	129	148	0.8 (0.6–1.1)
Time since last use												
Current use							7	6	1.0 (0.3–3.0)			
7 months–<5 years							13	11	1.1 (0.5–2.5)	8	7	1.2 (0.4–3.4)
5+ years	81	95	0.8 (0.6–1.1)	46	43	1.2 (0.7–1.8)	172	162	1.0 (0.8–1.3)	169	206	0.8 (0.6–1.0)

Variable	80 mcg mestranol/1.0 mg norethindrone			100 mcg mestranol/2.0 mg norethindrone			100 mcg mestranol/2.5 mg norethynodrel			30 mcg ethinyl estradiol/0.3 mg norgestrel		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total no. of subjects	1177	1168		1171	1137		1097	1047		1138	1081	
General use												
No use[b]	1032	980	1.0	1032	980	1.0	1032	980	1.0	1032	980	1.0
Ever use	132	178	0.7 (0.6–0.9)*	129	146	0.8 (0.6–1.1)	55	57	0.9 (0.6–1.3)	95	90	1.0 (0.7–1.4)
Current use[c]												
Former use	131	178	0.7 (0.6–0.9)*	129	146	0.8 (0.6–1.1)	55	57	0.9 (0.6–1.3)	85	86	1.0 (0.7–1.3)
Duration of use												
<2 years	40	60	0.6 (0.4–0.99)*	55	52	1.1 (0.7–1.6)	21	27	0.8 (0.4–1.4)	41	28	1.5 (0.9–2.6)
2+ years	92	118	0.8 (0.6–1.0)	74	94	0.7 (0.5–0.9)*	34	30	1.0 (0.6–1.7)	53	62	0.8 (0.5–1.1)
Time since last use												
Current use												
7 months–<5 years												
5+ years	131	175	0.7 (0.6–0.96)*	129	145	0.8 (0.6–1.1)	55	57	0.9 (0.6–1.3)	83	82	1.0 (0.7–1.4)

Variable	50 mcg ethinyl estradiol/0.5 mg norgestrel			35 mcg ethinyl estradiol/0.5 mg (7 days), 0.75 mg (7 days), 1.0 mg (7 days) norethindrone		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total no. of subjects	1112	1085		1062	1038	
General use						
No use[b]	1032	980	1.0	1032	980	1.0
Ever use	68	94	0.8 (0.5–1.1)	20	48	0.5 (0.3–0.8)*
Current use[c]						
Former use	68	92	0.8 (0.5–1.1)	18	44	0.5 (0.3–0.8)*
Duration of use						
<2 years	24	25	1.1 (0.6–2.0)	7	17	0.5 (0.2–1.4)
2+ years	44	69	0.6 (0.4–0.98)*	13	31	0.4 (0.2–0.8)*
Time since last use						
Current use						
7 months–<5 years						
5+ years	67	91	0.8 (0.5–1.1)	18	38	0.5 (0.3–0.97)*

Contraception 85 (2012) 342–350 Original research article

Oral contraceptive formulation and risk of breast cancer☆,☆☆

Table 2
Risk of breast cancer according to OC formulation in the Women's CARE Study among women who reported exclusive use of a combination OC formulation that was used by at least 50 women[a]

Variable	100 mcg mestranol/1.0 mg ethynodiol diacetate			35 mcg ethinyl estradiol/0.5 mg norethindrone			35 mcg ethinyl estradiol/1.0 mg norethindrone			50 mcg mestranol/1.0 mg norethindrone		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total no. of subjects	1124	1085		1089	1034		1234	1172		1221	1206	
General use												
No use[b]	1032	980	1.0	1032	980	1.0	1032	980	1.0	1032	980	1.0
Ever use	81	95	0.8 (0.6–1.1)	47	44	1.2 (0.7–1.8)	192	179	1.0 (0.8–1.3)	179	213	0.8 (0.7–1.1)
Current use[c]							7	6	1.0 (0.3–3.0)			
Former use	81	95	0.8 (0.6–1.1)	46	43	1.2 (0.7–1.8)	185	173	1.0 (0.8–1.3)	177	213	0.8 (0.6–1.1)
Duration of use												
<2 years	19	23	0.8 (0.4–1.5)	28	26	1.2 (0.7–2.0)	70	68	0.9 (0.6–1.4)	50	65	0.8 (0.5–1.2)
2+ years	62	72	0.8 (0.5–1.1)	19	18	1.2 (0.6–2.3)	122	111	1.0 (0.8–1.4)	129	148	0.8 (0.6–1.1)
Time since last use												
Current use							7	6	1.0 (0.3–3.0)			
7 months–<5 years							13	11	1.1 (0.5–2.5)	8	7	1.2 (0.4–3.4)
5+ years	81	95	0.8 (0.6–1.1)	46	43	1.2 (0.7–1.8)	172	162	1.0 (0.8–1.3)	169	206	0.8 (0.6–1.0)

Nessuna formulazione è associata ad un aumento significativo del rischio di cancro della mammella

7 months–<5 years												
5+ years	131	175	0.7 (0.6–0.96)*	129	145	0.8 (0.6–1.1)	55	57	0.9 (0.6–1.3)	83	82	1.0 (0.7–1.4)

Variable	50 mcg ethinyl estradiol/0.5 mg norgestrel			35 mcg ethinyl estradiol/0.5 mg (7 days), 0.75 mg (7 days), 1.0 mg (7 days) norethindrone		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total no. of subjects	1112	1085		1062	1038	
General use						
No use[b]	1032	980	1.0	1032	980	1.0
Ever use	68	94	0.8 (0.5–1.1)	20	48	0.5 (0.3–0.8)*
Current use[c]						
Former use	68	92	0.8 (0.5–1.1)	18	44	0.5 (0.3–0.8)*
Duration of use						
<2 years	24	25	1.1 (0.6–2.0)	7	17	0.5 (0.2–1.4)
2+ years	44	69	0.6 (0.4–0.98)*	13	31	0.4 (0.2–0.8)*
Time since last use						
Current use						
7 months–<5 years						
5+ years	67	91	0.8 (0.5–1.1)	18	38	0.5 (0.3–0.97)*

Research article

Comparative actions of progesterone, medroxyprogesterone acetate, drospirenone and nestorone on breast cancer cell migration and invasion

BMC Cancer 2008, 8:166

Taken together, our findings show that P, MPA, DRSP and NES alone or in combination with E2 increase breast cancer cell migration and invasion through the functional modulation of the actin-binding protein moesin and the induction of dynamic rearrangements of the actin cytoskeleton. This suggests that progestins may have an impact on the progression of PR+ breast cancer by altering the ability of cancer cells to interact with the extracellular environment and to eventually move or invade the surrounding environment. The potency of the progestins on these targets is however different, with maximal effects induced by MPA, followed by P, NES and DRSP. These differences in biological efficacy are possibly related to partially discrepant recruitment of extra-nuclear signaling pathways by PR in the presence of each progestin. All together, these findings provide evidence that PR activation might play a role in the progression of ER+/PR+ breast cancers.

Conclusioni

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Non possiamo affermare che l'uso di contraccettivi sia associato ad un incremento del rischio di cancro della mammella

Tuttavia

- ✓ Alcuni studi suggeriscono che il loro uso incrementi leggermente tale rischio specialmente tra le donne più giovani e che iniziano più precocemente
- ✓ Il rischio torna alla norma 10 anni dopo la sospensione della terapia

- ✓ Le donne che usano contraccettivi hanno un aumentato rischio di cancro della cervice, rischio che potrebbe tuttavia essere determinato e/o amplificato da HPV

- ✓ L' uso di contraccettivi riduce il rischio di cancro endometriale, dell' ovaio e del colon retto. Questo effetto protettivo si prolunga nel tempo, anche dopo la sospensione

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Estroprogestinici e terapia sostitutiva

Year	First author (reference)	Study design	Finding
1896	Beatson (1)	Case report	Oophorectomy associated with breast cancer regressions
1968	Feinleib (2)	Cohort analysis	Oophorectomy associated with lower breast cancer risk
1970	MacMahon (3)	International collaborative study	Age at first birth related to breast cancer risk
1973	McGuire (4)	Summary, findings from clinical correlative studies	Estrogen receptor quantitative status correlated with clinical breast cancer response to hormone-directed therapy
1976	Hoover (5)	Incidence rate in cohort vs rate in general population	Exogenous estrogen alone associated with higher breast cancer risk
1980	Ross (6)	Case–control analysis	Exogenous estrogen associated with higher breast cancer risk
1983	Pike (7)	Analysis	Model of endogenous hormonal risk factors with breast cancer
1989	Bergkvist (8)	Cohort analysis	Exogenous estrogen alone and exogenous estrogen plus progestin both associated with higher breast cancer risk
1995	Colditz (9)	Cohort analysis	Exogenous estrogen alone and exogenous estrogen plus progestin both associated with higher breast cancer risk
1997	Collaborative Group on Hormonal Factors in Breast Cancer (10)	Collaborative reanalysis of 51 case–control studies	Hormone therapy (80% exogenous estrogen alone) associated with higher breast cancer risk

1991 Women's Health Initiative
Set di trial clinici più studio osservazionale che hanno coinvolto 161.808 donne sane in menopausa
Trials: valutare effetti di HRT, dieta, calcio e Vit D su cardiopatia, fratture, cancro della mammella e colon-retto

Trial E+P: interrotto dopo circa 5 anni per evidenza di incremento del rischio di cancro

Trial E: interrotto dopo circa 7 anni per evidenza di aumento del rischio di stroke.
Minore incidenza di cancro della mammella, non confermata dallo studio osservazionale.

Conjugated Equine Estrogens and Breast Cancer Risk in the Women's Health Initiative Clinical Trial and Observational Study

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Am J Epidemiol. 2008 June 15; 167(12): 1407–1415.

Fattori confondenti: età delle pazienti, tempo trascorso dalla menopausa, pregressa HRT.

Conjugated Equine Estrogens and Breast Cancer Risk in the Women's Health Initiative Clinical Trial and Observational Study

Bari,
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Am J Epidemiol. 2008 June 15; 167(12): 1407–1415.

Fattori confondenti: età delle pazienti, tempo trascorso dalla menopausa, pregressa HRT.

TABLE 4

Invasive breast cancer hazard ratios for CEE* by years from menopause to first hormone therapy use in the Women's Health Initiative clinical trial, United States, 1993–2004

	No. of years from menopause to first HT* use			
	<5		≥5	
	HR*,†	95% CI*	HR†	95% CI
No prior HT‡	1.12	0.39, 3.21	0.58	0.36, 0.93
Prior HT‡	1.00	0.66, 1.51	0.77	0.33, 1.80

*CEE, 0.625 mg/day of conjugated equine estrogens; HT, postmenopausal hormone therapy; HR, hazard ratio; CI, confidence interval.

†Hazard ratios (and 95% confidence intervals) from Cox model analyses that stratified on baseline age (5-year categories). Numbers of women and breast cancer cases contributing to each hazard ratio estimate are given in table 1.

‡Prior HT was defined relative to enrollment in the clinical trial.

Estrogen Plus Progestin Therapy and Breast Cancer in Recently Postmenopausal Women

Am J Epidemiol 2008;167:1207–1216

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TABLE 3. Hazard ratios for invasive breast cancer for E+P* use by years from menopause to first use of postmenopausal hormones (gap time) and prior hormone therapy use in the US Women's Health Initiative clinical trial (enrollment, 1993–1998)

	Gap time (years)†				HR* for interaction with gap time (<5 vs. ≥5 years) (*p* value)‡
	<5		≥5		
	HR	95% CI*	HR	95% CI	
No prior hormone therapy§	1.77	1.07, 2.93	0.99	0.74, 1.31	0.02
Prior hormone therapy§	2.06	1.30, 3.27	1.30	0.57, 2.99	
HR for interaction with prior hormone therapy (no vs. yes) (*p* value)¶		0.53			

Breast cancer and hormone-replacement therapy in the Million Women Study

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Total duration of use of HRT by type of HRT used at baseline	Cases/population	Relative risk (95% FCI)*
Never users of HRT	2894/392 757	1·00 (0·96–1·04)
Past users of HRT		
<1 year	311/47 606	0·94 (0·84–1·05)
1–4 years	384/55 823	1·01 (0·92–1·12)
5–9 years	230/29 614	1·14 (1·00–1·30)
≥10 years	80/11 654	1·05 (0·84–1·30)
Current users of oestrogen-only HRT		
<1 year	25/4452	0·81 (0·55–1·20)
1–4 years	251/29 582	1·25 (1·10–1·41)
5–9 years	416/47 310	1·32 (1·20–1·46)
≥10 years	277/31 862	1·37 (1·22–1·54)
Current users of oestrogen-progestogen combinations		
<1 year	97/9771	1·45 (1·19–1·78)
1–4 years	582/49 240	1·74 (1·60–1·89)
5–9 years	850/56 912	2·17 (2·03–2·33)
≥10 years	362/23 673	2·31 (2·08–2·56)
Current users of other/unknown HRT types		
<1 year	19/1728	1·63 (1·04–2·56)
1–4 years	83/8794	1·34 (1·08–1·66)
5–9 years	102/10 342	1·42 (1·17–1·72)
≥10 years	59/4739	1·93 (1·50–2·50)

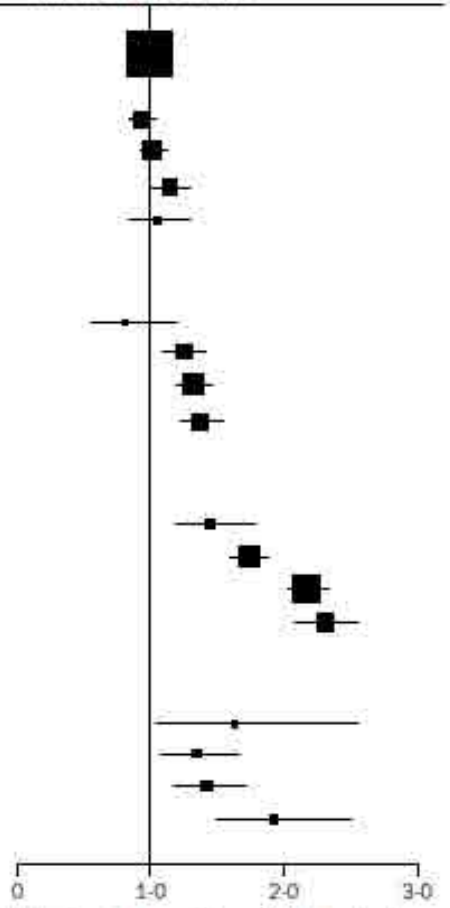

Figure 3: **Relative risk of incident invasive breast cancer in relation to recency, total duration of use, and type of HRT used at baseline**

FCI=floated CI*Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.

Breast cancer and hormone-replacement therapy in the Million Women Study

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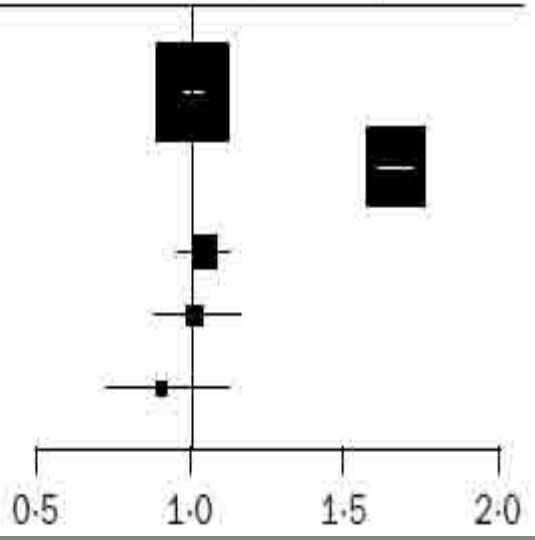
HRT use at baseline	Cases/population	Relative risk (95% FCI)*
Never users	2894/392 757	1·00 (0·97–1·04)
Current users	3202/285 987	1·66 (1·60–1·72)
Last use <5 years previously	579/81 875	1·04 (0·95–1·12)
Last use 5–9 years previously	207/29 395	1·01 (0·88–1·16)
Last use ≥10 years previously	79/12 568	0·90 (0·72–1·12)



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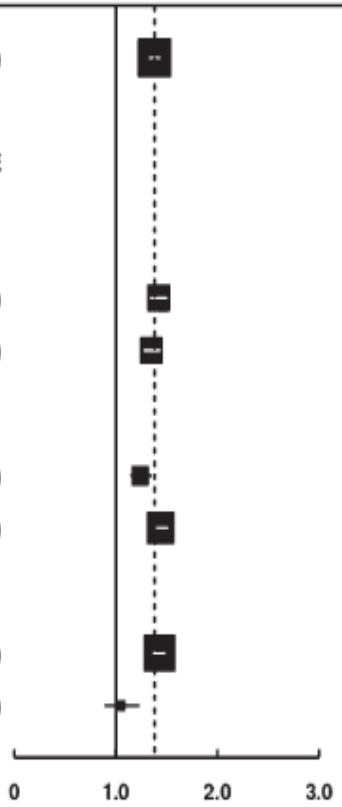
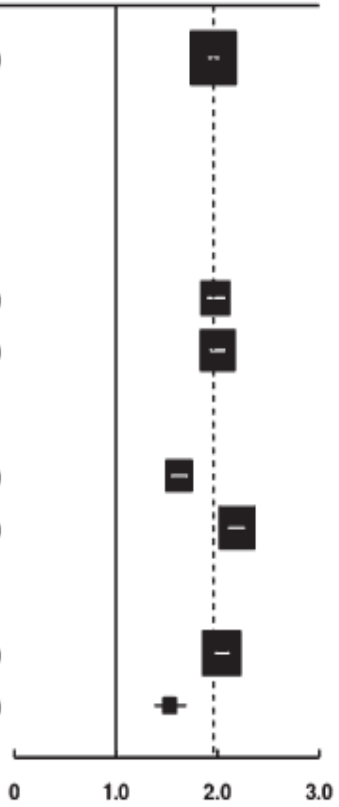
Breast Cancer Risk in Relation to the Interval Between Menopause and Starting Hormone Therapy

J Natl Cancer Inst 2011;103:1–10

	ESTROGEN-ONLY				ESTROGEN-PROGESTIN			
	Years of hormone therapy use*	No. Cases†	RR (95% fCI)	RR (95% fCI)	Years of hormone therapy use*	No. Cases†	RR (95% fCI)	RR (95% fCI)
ALL CURRENT USERS OF HORMONE THERAPY	8.0	2131	1.38 (1.32 to 1.44)		6.8	4292	1.96 (1.90 to 2.02)	
BY AGE AT FIRST USE, DURATION OF USE AND TIME BETWEEN MENOPAUSE AND FIRST USE								
Age at first use of hormone therapy								
Before age 50	9.6	1080	1.42 (1.33 to 1.51)		8.3	1665	1.98 (1.89 to 2.08)	
At age 50 or older	6.5	1000	1.35 (1.27 to 1.44)		5.9	2525	2.00 (1.92 to 2.08)	
Total duration of hormone therapy use								
Less than 5 years	3.4	543	1.24 (1.14 to 1.35)		3.3	1398	1.62 (1.54 to 1.71)	
5 years or longer	9.9	1522	1.44 (1.37 to 1.52)		8.8	2775	2.19 (2.10 to 2.27)	
Time between menopause and first hormone therapy use								
Less than 5 years	8.3	1924	1.43 (1.36 to 1.49)		7.0	3828	2.04 (1.97 to 2.12)	
5 years or longer	5.7	151	1.05 (0.89 to 1.23)		5.4	364	1.53 (1.38 to 1.69)	





Breast cancer and hormone-replacement therapy in the Million Women Study

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Oestrogen-progestagen HRT by: constituents and regimen	Duration of use <5 years: Cases/population	Duration of use <5 years: Relative risk (95% CI)*	Duration of use ⩾5 years: Cases/population	Duration of use ⩾5 years: Relative risk (95% CI)†
All oestrogen-progestagen combinations	679/59 011	1·70 (1·56–1·86)	1212/80 585	2·21 (2·06–2·36)
By progestagen constituent				
Medroxyprogesterone acetate	117/11 280	1·60 (1·33–1·93)	196/12 628	2·42 (2·10–2·80)
Norethisterone	253/24 667	1·53 (1·35–1·75)	390/27 841	2·10 (1·89–2·34)
Norgestrel/levonorgestrel	290/20 952	1·97 (1·74–2·33)	608/38 494	2·23 (2·04–2·44)
By type of regimen				
Sequential	403/33 124	1·77 (1·59–1·97)	778/52 518	2·12 (1·95–2·30)
Continuous	243/23 708	1·57 (1·37–1·79)	388/25 286	2·40 (2·15–2·67)

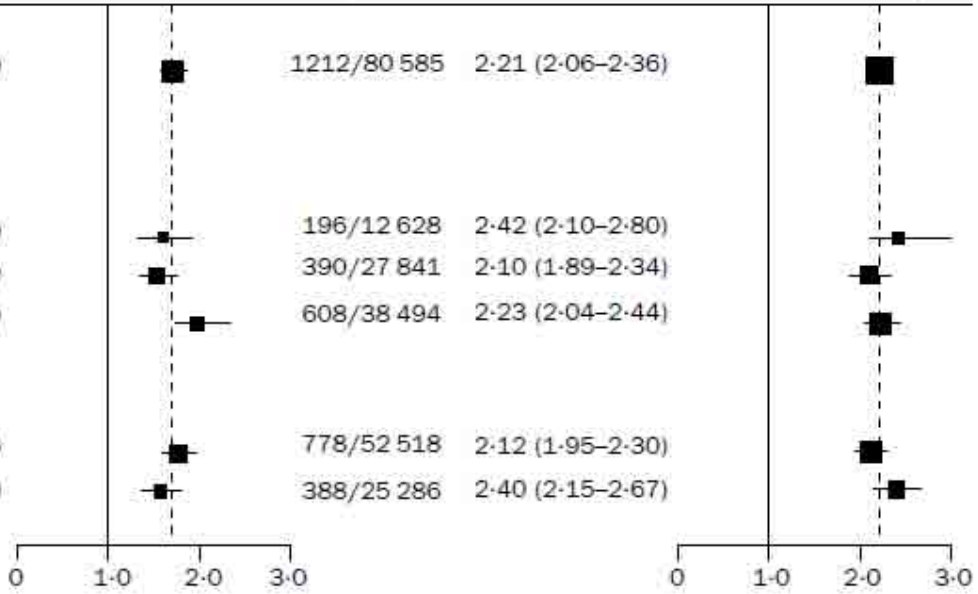

Figure 5: **Relative risk of incident invasive breast cancer by constituent and regimen of oestrogen-progestagen combination HRT used at baseline***

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

Breast Cancer Res Treat (2008) 107:103–111

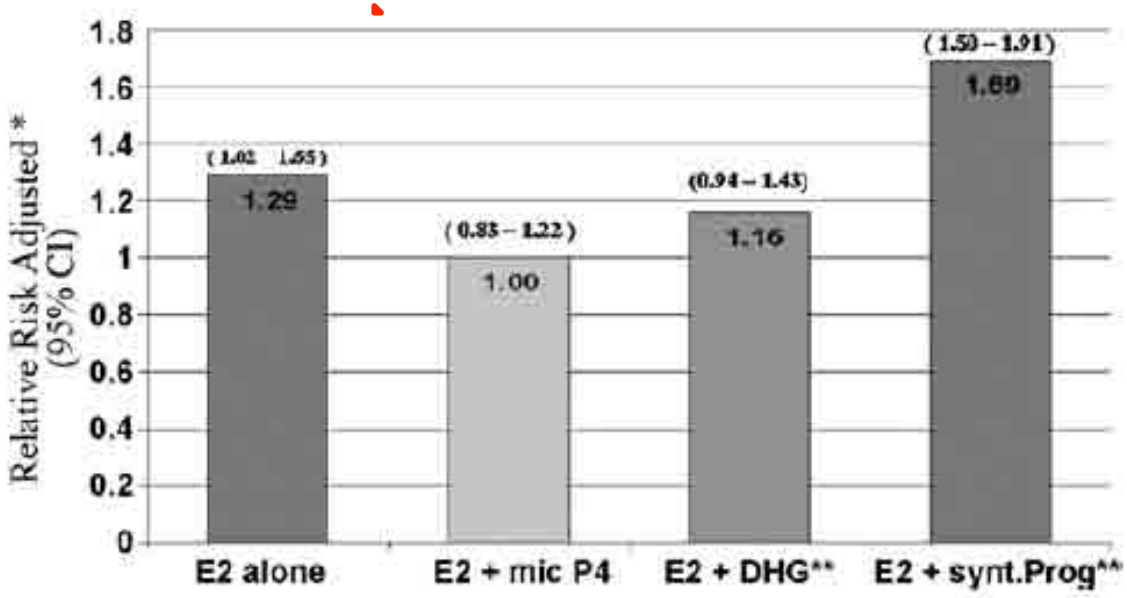

Fig. 2. Relative risks (95% confidence intervals) for invasive breast cancer by type of HRT and type of progestagen, compared with HRT never-use (E3N cohort study) Adapted from Fournier et al. (198) E2: estradiol; mic P4: micronized progesterone; DHG: dydrogesterone; synt. Prog.: synthetic progestins (mainly nomegestrol acetate, promegestone, chlormadinone acetate, cyproterone acetate, medrogestone).

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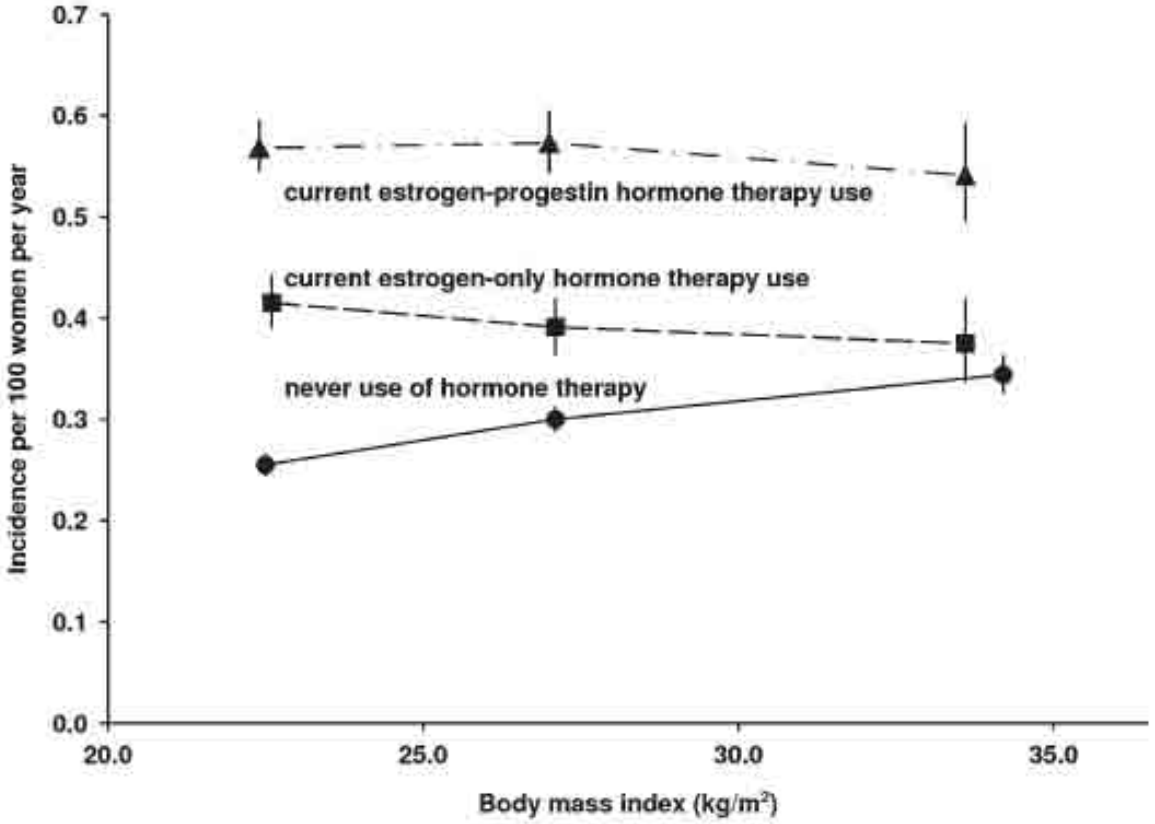
Figure 5. Standardized incidence rates for breast cancer in current users of hormone therapy by the type of hormone therapy used and women's body mass index. Standardized incidence rates per 100 women aged 50–59 years per year were calculated by taking never users of hormone therapy as the standard and standardizing by age, region of residence, socioeconomic status, age at menopause, age at birth of first child, parity, and alcohol consumption. It should be noted that incidence rates are plotted against the mean body mass index within each subgroup. 95% confidence intervals are shown (error bars).



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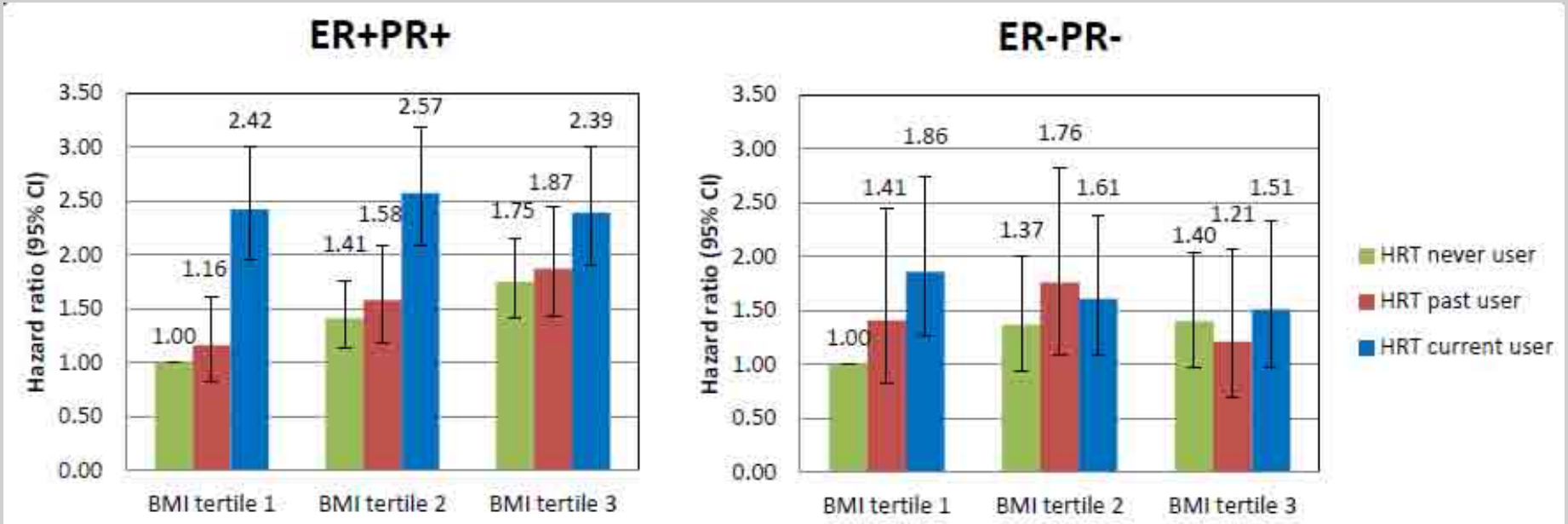

Figure 2 Hazard ratios of ER+PR+ and ER-PR- tumors for increases in BMI across HRT user categories. All models were restricted to postmenopausal women with information on baseline HRT use and stratified by age at recruitment and study center. HRT never users within BMI tertile1 were used as the reference category. BMI tertile 1: ≤22.5 kg/m^2; BMI tertile 2: 22.6 to 25.8 kg/m^2; BMI tertile 3: ≥25.9 kg/m^2. BMI, body mass index; ER, estrogen receptor; HRT, hormone replacement therapy; PR, progesterone receptor.

Ritte *et al. Breast Cancer Research* 2012, **14**:R76

Conclusioni

Bari,
7-10 novembre 2013

Terapia sostitutiva con soli Estrogeni

- ✓ L'uso di soli estrogeni per meno di 5 anni riduce il rischio di cancro della mammella in donne che iniziano la terapia dopo diversi anni dalla menopausa (livello evidenza B)
- ✓ L'uso per un periodo > 5 anni aumenta il rischio di cancro, soprattutto nelle donne che hanno iniziato la terapia subito dopo a menopausa (livello evidenza B)
- ✓ Il rischio si annulla dopo 5 anni dalla sospensione della terapia (livello evidenza B)

Executive Summary: Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement

Terapia sostitutiva combinata E+P

- ✓ Il rischio di cancro della mammella, soprattutto con progesterone sintetico, aumenta progressivamente dopo 5 anni dall' inizio della tp (livello evidenza B)
- ✓ Il rischio si annulla circa 3 anni dopo la sospensione (livello evidenza B)
- ✓ Le donne che iniziano subito dopo la menopausa sono più a rischio (livello evidenza C)

Per ogni donna il rischio assoluto di cancro al seno in corso di terapia con EP varia in funzione del momento di inizio della terapia, della durata della stessa, probabilmente in funzione del tipo di progestinico e del BMI

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