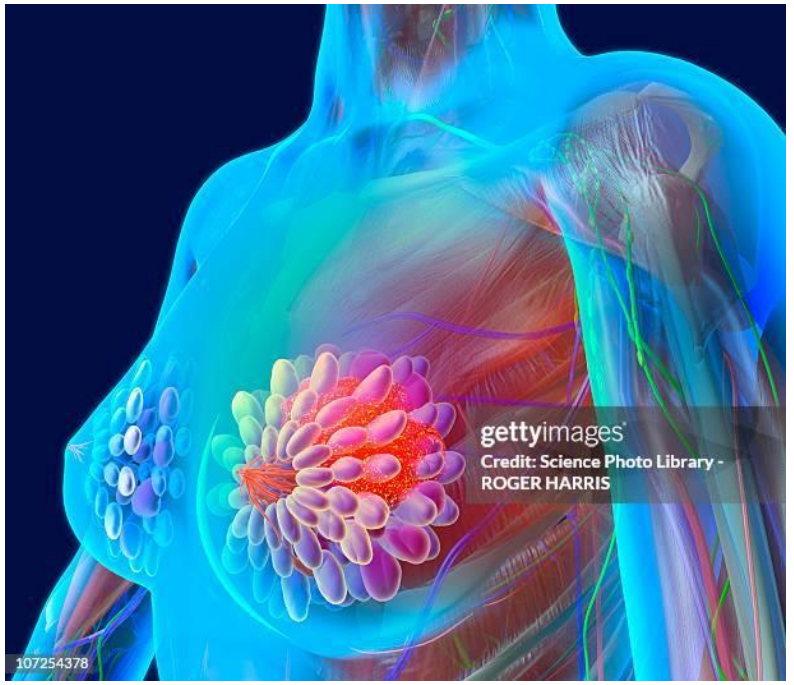
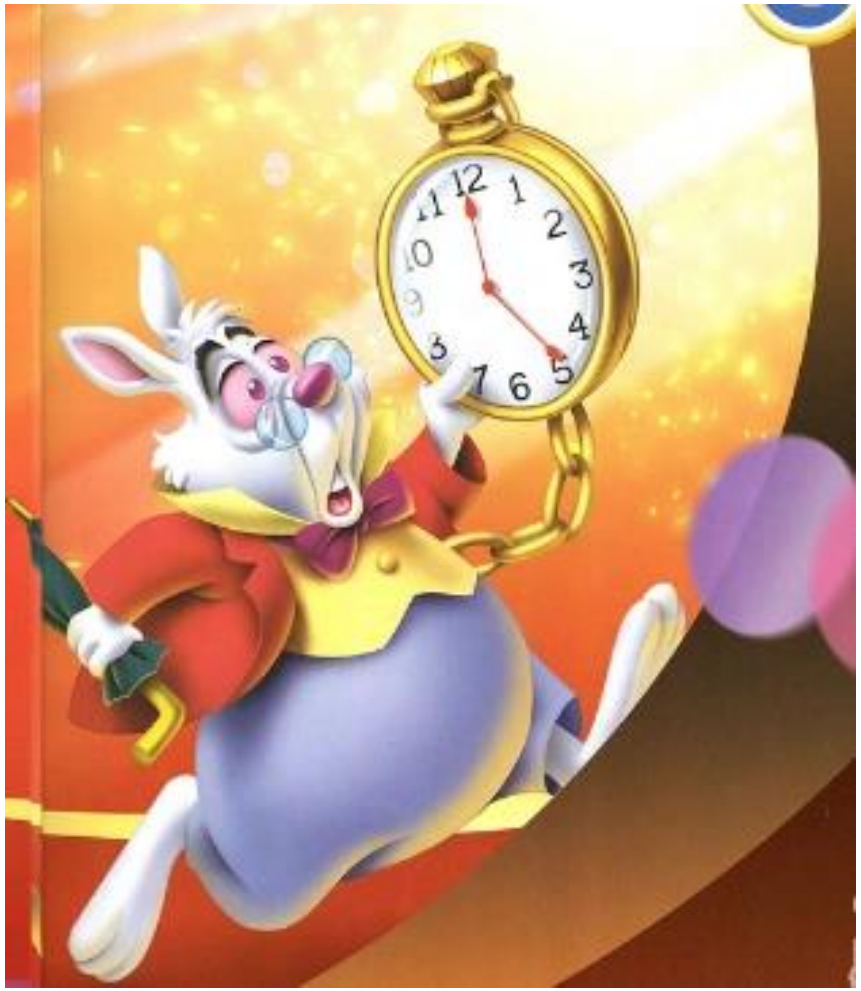
Contraccezione ormonale e rischio di carcinoma mammario nelle donne sane con gBRCA1-2 VP

Dott.ssa Eleonora P.Preti

Dott.ssa Silvia Martella



Concerns .....



- ✓ Ormoni e rischio cancro
- ✓ BRCA e rischio cancro
- ✓ Ormoni e BRCA = cancro ?

Rischio reale o Mistificazione ?

- Dati scientifici di prevenzione su alcuni tipi di cancro (ovaio – endometrio – colon retto)

- Dati scientifici su rischio di tumore alla mammella

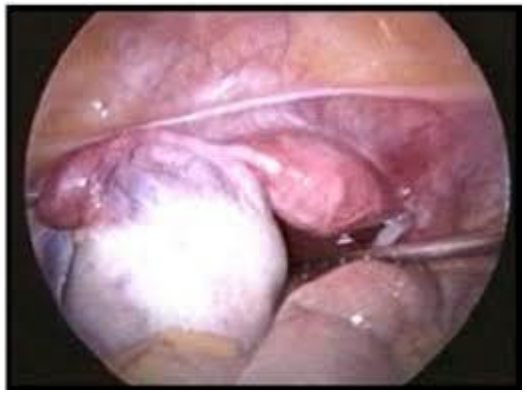
ecancermedicalscience

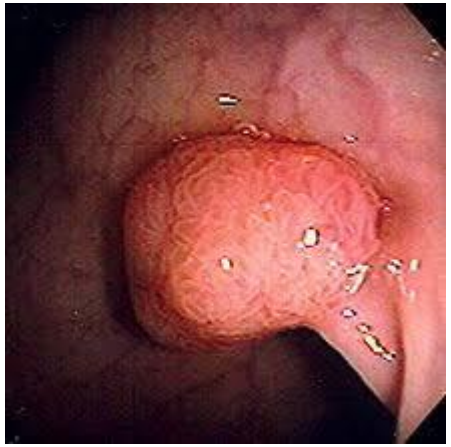
Last 20 years
2435 papers

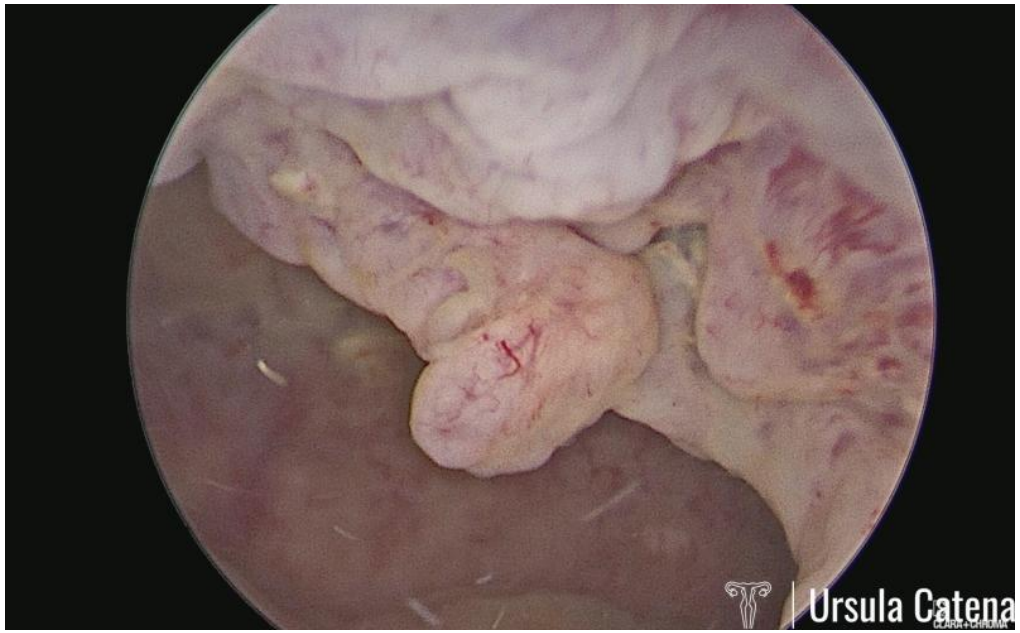
Review of the literature on combined oral contraceptives and cancer

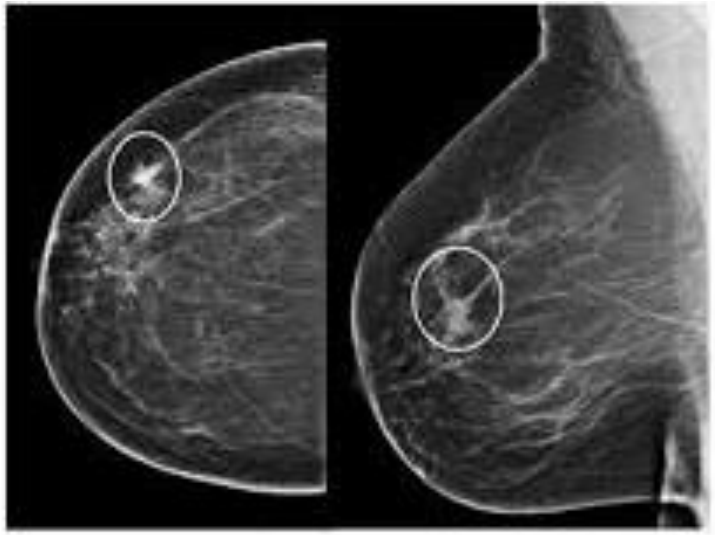
Mustafa Kamani, Utku Akgor and Murat Gültekin

Department of Obstetrics and Gynaecology, Hacettepe University Faculty of Medicine, Ankara 06230, Turkey

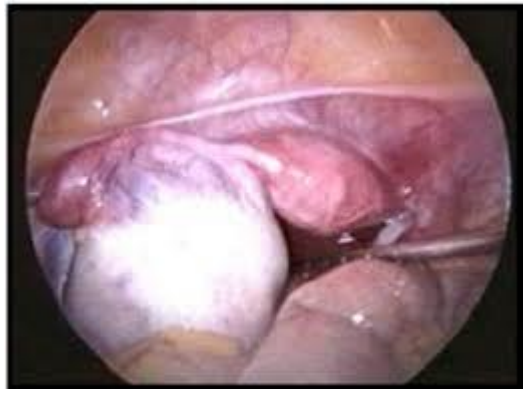






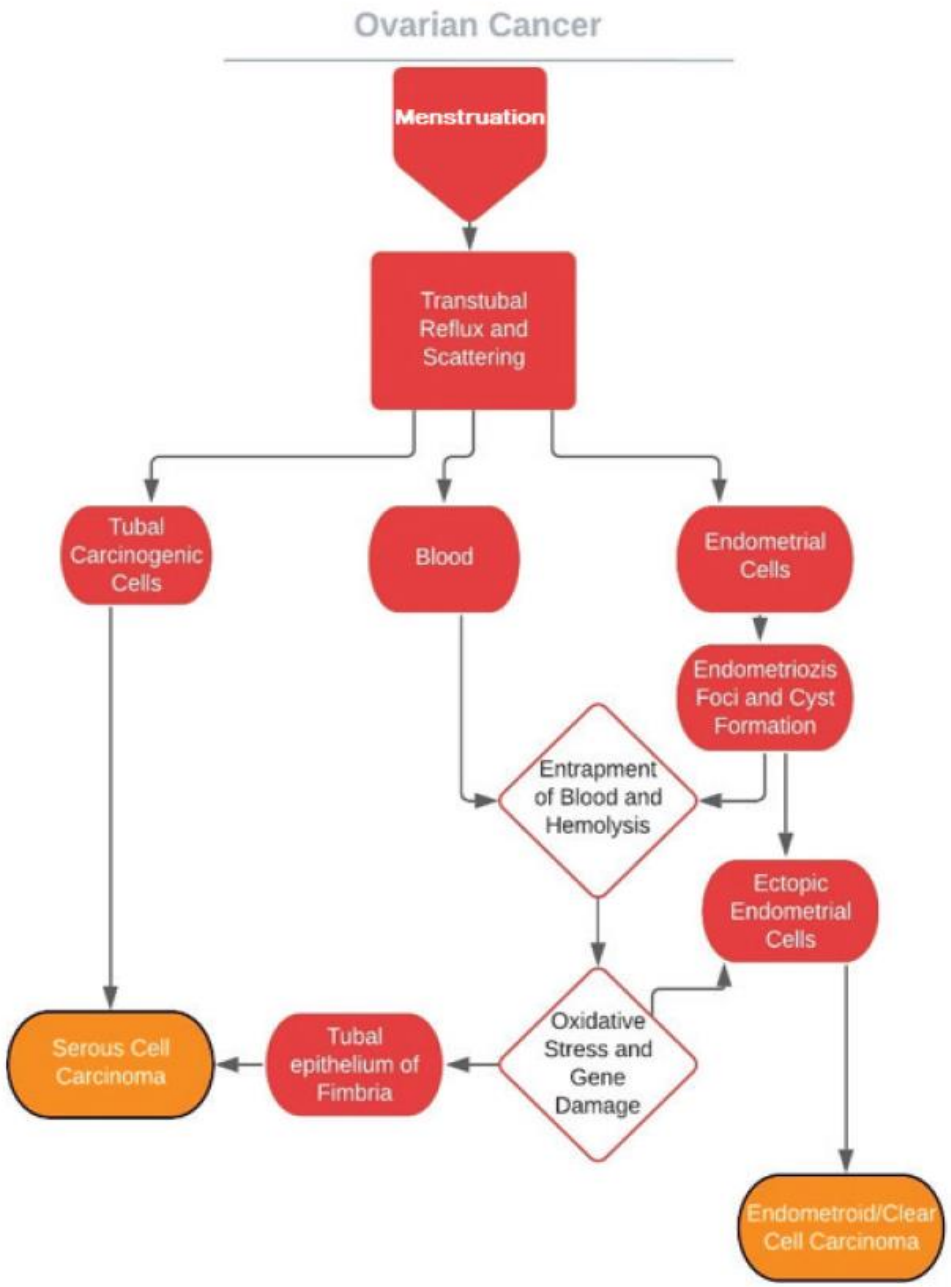


*e*cancer 2022, 16:1416; www.ecancer.org; DOI: https://doi.org/10.3332/ecancer.2022.1416



Last 20 years
2435 papers

- ✓ **Uso continuativo COCs abbassa il rischio di OC**
- ✓ Effetto protettivo con riduzione fino a 50% nell'uso prolungato
  (*Beral V, Bull D, and Green J, et al (2007) - Bosetti C, Negri E, and Trichopoulos D, et al (2002)*
- ✓ Metanalisi , 24 studi, le utilizzatrici hanno una riduzione di OC rispetto alle non utilizzatrici (OR = 0,75 vs 0,66) con una riduzione > 50% nelle utilizzatrici > 10 anni
- ✓ **Riduzione del rischio correlata a tempo di utilizzo**
- ✓ Metanalisi separate hanno trovato vantaggi comparabili nelle donne BRCA



*e*cancer 2022, 16:1416; www.ecancer.org; DOI: https://doi.org/10.3332/ecancer.2022.1416

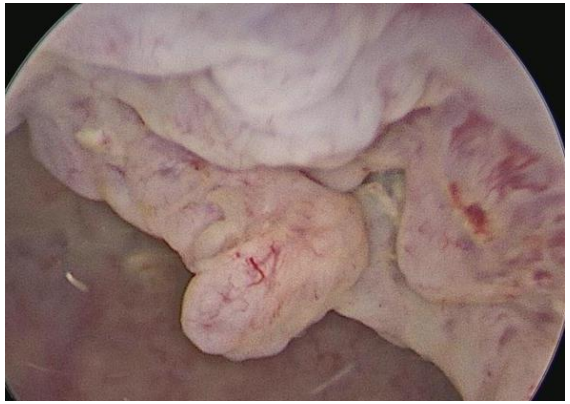
Meta-Analysis > Bull Cancer. 2024 Oct;111(10):918-929. doi: 10.1016/j.bulcan.2024.05.010.
Epub 2024 Sep 10.

The association between oral contraceptive pills and ovarian cancer risk: A systematic review and meta-analysis

Maedeh Arshadi [1], Elahe Hesari [2], Mozhgan Ahmadinezhad [2], Elahe Mansouri Yekta [2], Fateme Ebrahimi [3], Hosein Azizi [4], Shahla Vaziri Esfarjani [5], Maryam Rostami [5], Farzad Khodamoradi [6]

2000 -2023
67 studi

- Ever user vs never user pooled RR 0,69%
- Riduzione rischio statisticamente significativa nell'utilizzo prolungato (> 60 -120 mesi)

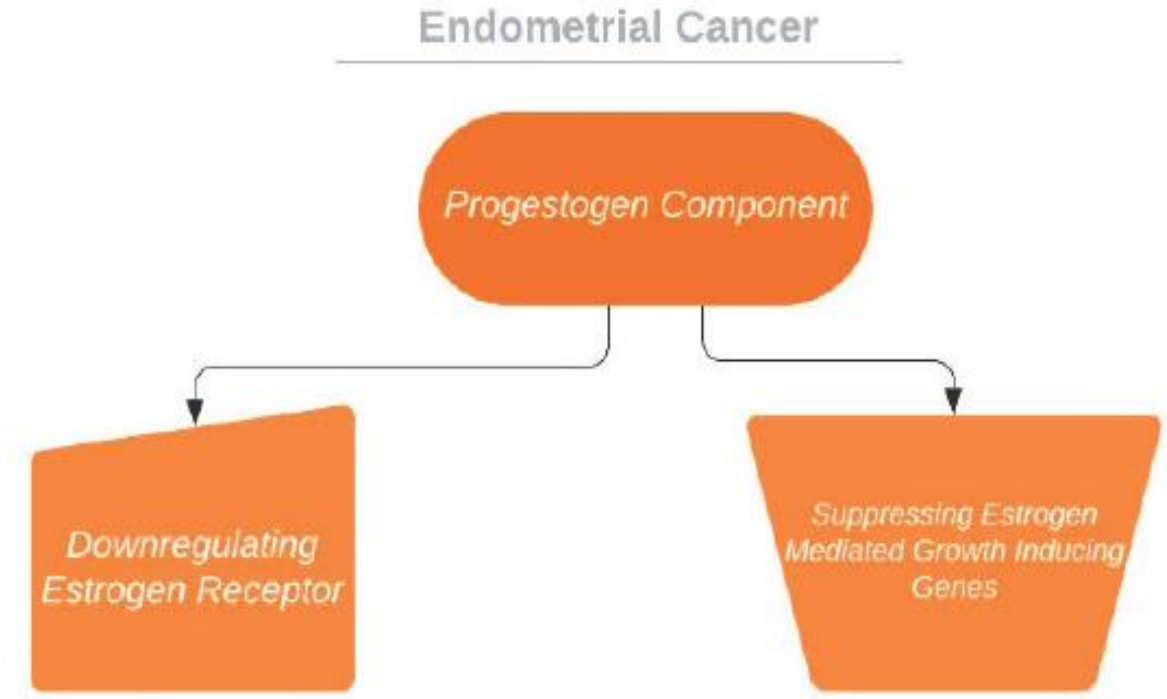


Last 20 years
2435 papers

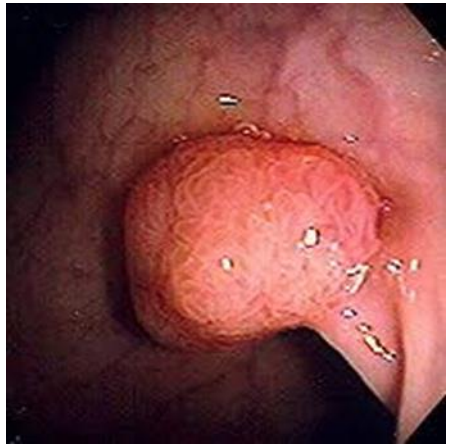
- ✓ **Uso prolungato COCs abbassa il rischio di EC**
  (dopo 10 -15 anni il rischio più basso del 50%)

- ✓ Nurse's Health Cohort Study II (107,069 donne) mostra un più basso rischio di EC nelle utilizzatrici > 10 aa (HR 0,77) vs non users (HR = 0,43)
  Burchardt NA, Shafrir AL, and Kaaks R, *et al* (2021)

- ✓ **Conferma delle metanalisi precedenti**
  Collaborative Group on Epidemiological Studies on Endometrial Cancer (2015)



*e*cancer 2022, 16:1416; www.ecancer.org; DOI: https://doi.org/10.3332/ecancer.2022.1416



- ✓ IARC ha notato una riduzione del rischio di CRC nelle utilizzatrici
- ✓ In due metanalisi (29 e 23 studi) il rischio CRC era del 0,8% nelle ever user vs never user. Correlazione inversa per durata contraccezione Bosetti C, Bravi F, and Negri E, *et al* (2009 Luan NN, Wu L, and Gong TT, *et al* (2015)
- ✓ LA protezione sembra durare più di 35 anni Iversen L, Sivasubramaniam S, and Lee AJ, *et al (2017)*

	Ever versus Never RR
Rennert *et al* [128]	Jews:0.49 (95% CI: 0.39–0.62) Arabs:0.14 (95% CI: 0.04–0.47)
Tsilidis *et al* [133]	0.92 (95% CI: 0.83–1.02)
Lin *et al* [132]	0.67 (95% CI: 0.50–0.89)
Charlton *et al* [130]	1.01 (95% CI: 0.91–1.12)
Iversen *et al* [6]	0.81 (95% CI: 0.66–0.99)
Kabat *et al* [131]	0.83 (95% CI : 0.73–0.94)
Gierisch *et al* [104]	0.86 (95% CI: 1.00–1.17)
Zervoudakis *et al* [134]	1.04 (95% CI: 0.93–1.16)
Brändstedt *et al* [129]	1.05 (95% CI : 0.80–1.37)

GYNECOLOGY

Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study

Lisa Iversen, PhD; Selvaraj Sivasubramaniam, MSc; Amanda J. Lee, PhD; Shona Fielding, PhD; Philip C. Hannaford, MD

46,022 donne
1968-1969
44 aa di FU

- ✓ Riduzione non statisticamente significativa di qualsiasi tumore del 4% (ever vs never users)

TABLE 2
Risk of cancer among "ever" and "never" users of oral contraceptives in the Royal College of General Practitioners' Oral Contraception Study

Malignancies	International Classification of Diseases, version 8	Standardized rate, n[a]		Incidence rate ratio[b] (99% confidence interval)	Attributable risk[c]	Attributable risk, %	Preventive fraction, %
		Ever users	Never users				
Esophagus & stomach	150–151	14.51 (129)	16.59 (73)	0.87 (0.59–1.27)	−2.08		12.5
Colon & rectum	153–154	47.85 (418)	59.16 (270)	0.81 (0.66–0.99)	−11.31		19.1
Liver & gallbladder	155–156	4.65 (41)	5.72 (25)	0.87 (0.45–1.69)	−1.07		18.7
Pancreas	157	13.33 (114)	13.47 (61)	1.00 (0.66–1.52)	−0.14		1.0
Lung	162	59.16 (553)	49.19 (205)	1.17 (0.95–1.45)	9.97	16.8	
Skin							
Melanoma	172	19.76 (173)	18.34 (78)	1.12 (0.78–1.60)	1.42	7.2	
Other	173	103.04 (882)	93.73 (423)	1.11 (0.95–1.29)	9.31	9.0	
Breast	174	159.94 (1422)	155.16 (649)	1.04 (0.91–1.17)	4.78	3.0	
Invasive cervix	180	15.45 (147)	11.56 (45)	1.31 (0.84–2.04)	3.89	25.2	
Endometrium	182	19.42 (168)	29.56 (127)	0.66 (0.48–0.89)	−10.14		34.3
Ovary	183	22.10 (194)	33.27 (142)	0.67 (0.50–0.89)	−11.17		33.6

American Journal of Obstetrics & Gynecology JUNE 2017

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Researches of BC risk among women who use COCs show conflicting results: from no increase in risk to a 20%–30% elevation in risk

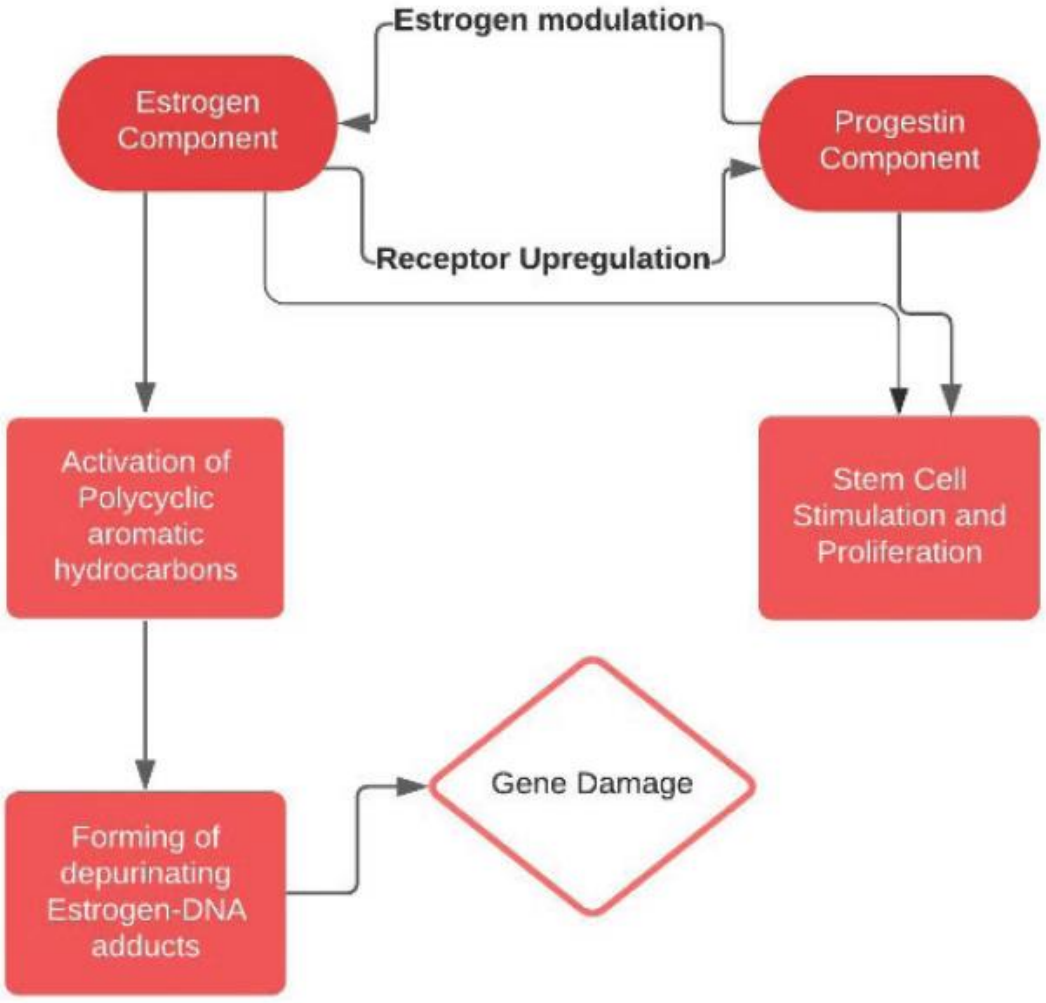

Table 1. Studies reporting no increase in the risk of breast cancer associated with COC use.

	Study design	Risk analysis results
Jordan *et al* [12]	Case–Control Study	0.7% of all cases is attributable to COC use
CDC [13]	Case–Control Study	RR: 0.6–1.6 (not significant)
Nurses' Health Study [14]	Prospective Cohort Study	>10 year COC use RR: 1.11 (95% CI: 0.94–
Marchbanks *et al* [15]	Case–Control Study	Current use; RR: 1.0 (95% CI: 0.8–1.3) Past use; RR: 0.9 (95% CI: 0.8–1.0)
Michels *et al* [16]	Prospective Cohort Study	>10 year COC use RR:1.04 (0.97, 1.11)
Oxford-FPA [5]	Prospective Cohort Study	Ever versus Never RR: 1.0 (95% CI: 0.9–1.1)
RCGP [17]	Prospective Cohort study	Ever versus Never RR: 0.98 (95% CI: 0.87–1.1)

Table 2. Studies reporting an increase in the risk of breast cancer associated with COC use.

	Study design	Never vs Ever RR	Current and recent RR	Past RR (≥5 year)
RCGP [6]	Prospective Cohort Study	1.04 (99% CI: 0.91–1.17)	1.48 (99% CI: 1.10–1.97)	0.75–1.12 (No increased risk)
Mørch *et al* [21]	Prospective Cohort Study	N/A	1.19 (95% CI: 1.13–1.26)	1.05 (95% CI: 0.98–1.13)
Collaborative Group [19]	Meta-Analysis	-Prospective studies (RR ±SD : 1.07 ±0.035) -Case-control studies with population controls (RR ±SD : 1.10 ±0.081) -Case-control studies with hospital controls (RR ±SD : 1.17 ±0.035) -All studies combined (RR ±SD : 1.07 ±0.017)	-Prospective studies (RR ±SD : 1.14 ±0.091) -Case-control studies with population controls (RR ±SD : 1.16 ±0.048) -Case-control studies with hospital controls (RR ±SD : 1.18 ±0.057) -All studies combined (RR ±SD : 1.16 ±0.034)	-Prospective studies (RR ±S 1.14 ±0.091), -Case-control studies with population controls (RR ± 1.16 ±0.048), -Case-control studies with controls (RR ±SD : 1.18 ± -All studies combined (RR : 1.16 ±0.034)
Hunter *et al* [20]	Prospective Cohort Study	N/A	1.33 (95% CI: 1.03–1.73)	1.12 (95% CI: 0.95–1.33)

Re-Evaluating the Association Between Hormonal Contraception and Breast Cancer Risk

Table 1 Comparison of Large (n >1000) Studies Assessing Association Between Breast Cancer and OCPs

Study	n=	Risk/Odds Ratio	Statistically Significant?	RR Compared to the RR of Recent Delivery[7]
CGHFBC (1997)[15]	153,536	RR_{recent}: 1.16 95% CI: 1.08–1.23 $RR_{current}$ 1.24 95% CI: 1.15–1.33	Yes Yes	Lower Lower
CARE (Marchbanks et al 2002)[19]	9257	$OR_{previous}$: 0.9 95% CI: 0.8–1.0 $OR_{current}$: 1.0 95% CI: 0.8–1.3	No No	Lower Lower
Nurses Health Study II (Hunter et al 2010)[21]	116,608	$RR_{current}$: 1.33 95% CI: 1.03–1.73 $RR_{previous}$: 1.12 95% CI: 0.95–1.33	Yes Yes	Lower Lower
Beaber et al (2014)[22]	1867	Ever users* OR: 1.0 95% CI: 0.8–1.3 15 years of use OR: 1.5 95% CI: 1.1–2.2 Users of 20 mcg EE2: OR 1.0 95% CI 0.7–1.8	No Yes No	Lower Lower Lower
Merch et al (2018)[9]	1,800,000	RR (current+recent HC): 1.20 95% CI: 1.14–1.26 Combined OC RR: 1.19 95% CI: 1.13–1.26 LNG-IUD* RR: 1.21 95% CI: 1.11–1.33	Yes Yes Yes	Lower Lower Lower
Hannaford et al (2007)[10]	1,083,000	RR ever users: 0.98 95% CI: 0.87–1.10	No	Lower
Niemeyer Hultstrand et al (2022)[32]	1,652,364	$RR_{current}$ combined OCP: 1.03 95% CI: 0.91–1.16 $RR_{current}$ progestin-only: 1.32 (1.20–1.45)	No Yes	Lower Lower

Note: *Reference is never users.

In all studies the RR compared to RR of recent delivery is LOWER

Breast Cancer: Targets and Therapy, Satish et al, 2023

GYNECOLOGY

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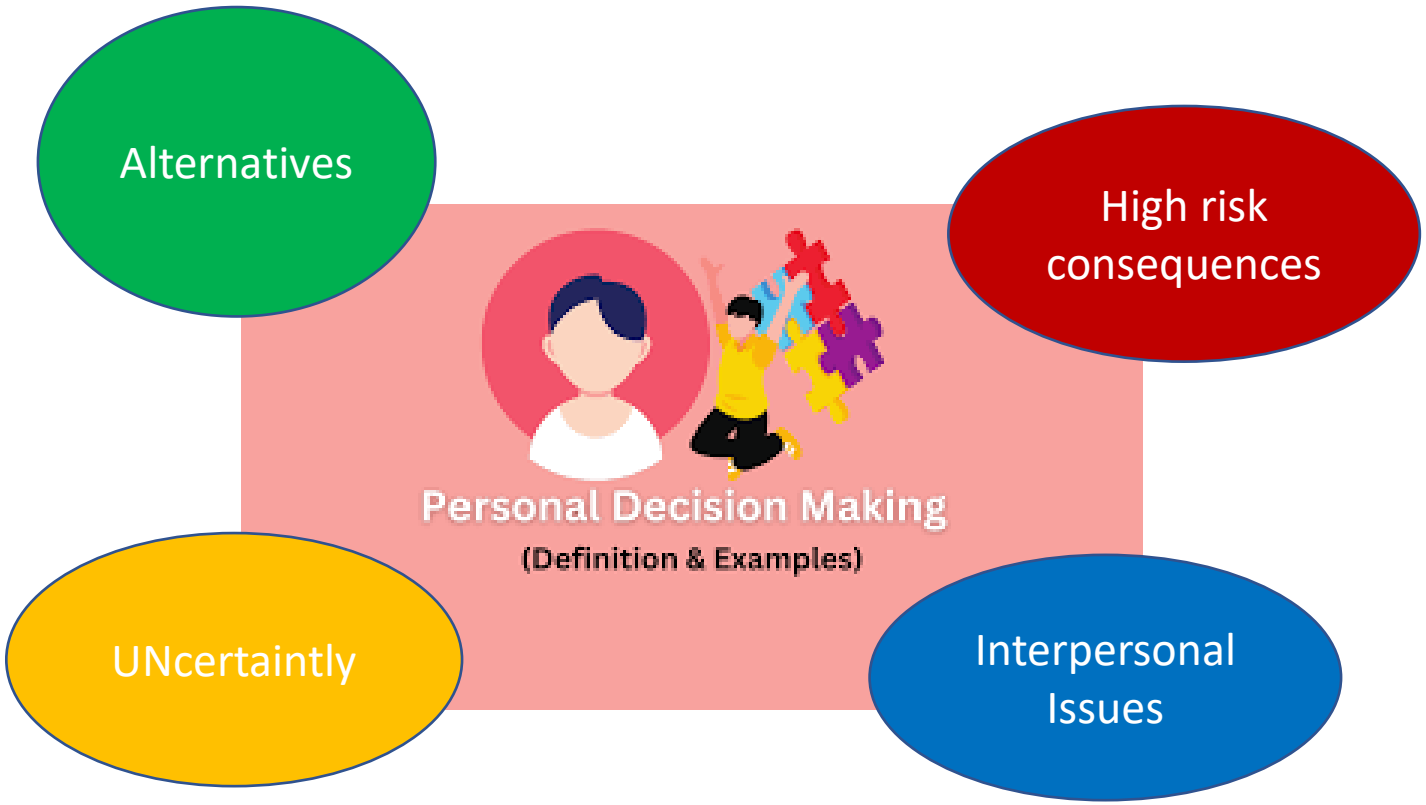
Ovary	183	22.10 (194)	33.27 (142)	0.67 (0.50—0.89)	—11.17	33.6
Bladder & kidney	188—189	17.64 (159)	20.25 (88)	0.87 (0.61—1.23)	—2.61	12.9
Central nervous system & pituitary	191,1943	5.73 (51)	6.95 (32)	0.76 (0.42—1.36)	—1.22	17.5
Thyroid	193	2.42 (22)	2.28 (10)	1.02 (0.37—2.74)	0.14	
Site unknown	199	23.61 (212)	28.22 (122)	0.84 (0.63—1.13)	—4.61	16.3
Lymphatic & hematopoietic	200—208	31.90 (281)	43.18 (189)	0.74 (0.58—0.94)	—11.28	26.1
Other cancers		37.25 (336)	38.95 (166)	0.96 (0.75—1.23)	1.49	
Main gynecologic	180,182,183	56.51 (503)	74.31 (312)	0.76 (0.63—0.91)	—17.80	24.0
Any cancer	140—209	542.44 (4661)	566.09 (2341)	0.96 (0.90, 1.03)	—23.65	4.2

- NO evidence of new cancer risks later in life
- No expose to long-term cancer harms
- Benefit from reductions of risk for many years

American Journal of Obstetrics & Gynecology JUNE 2017

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 73 / No. 3
August 8, 2024

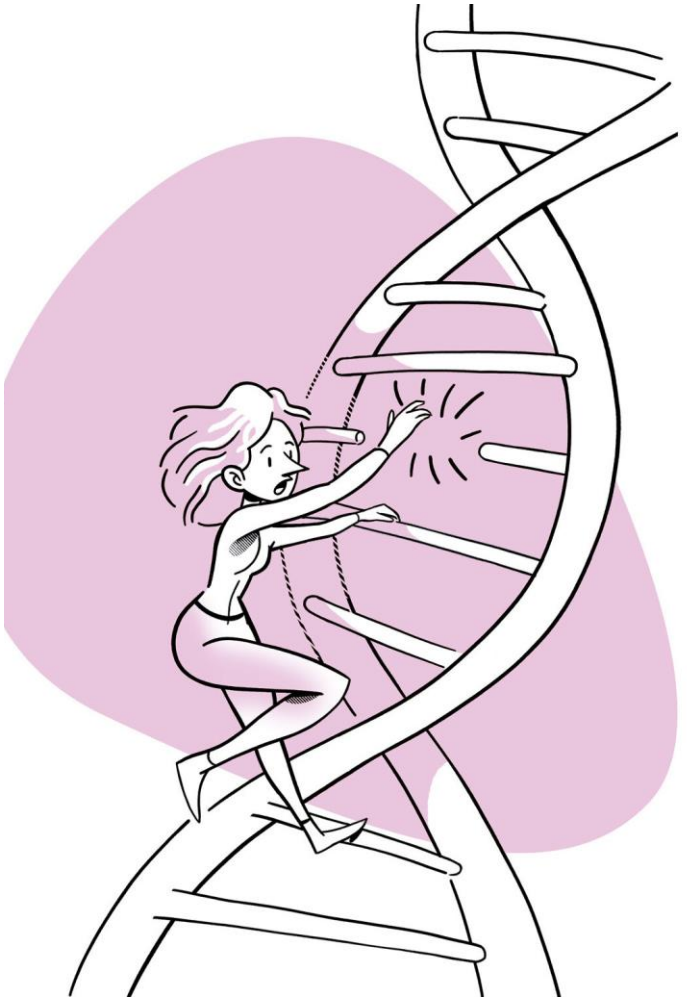
U.S. Selected Practice Recommendations for Contraceptive Use, 2024



BOX 1. Using the *U.S. Medical Eligibility Criteria for Contraceptive Use* and *U.S. Selected Practice Recommendations for Contraceptive Use* recommendations to support contraceptive decision-making

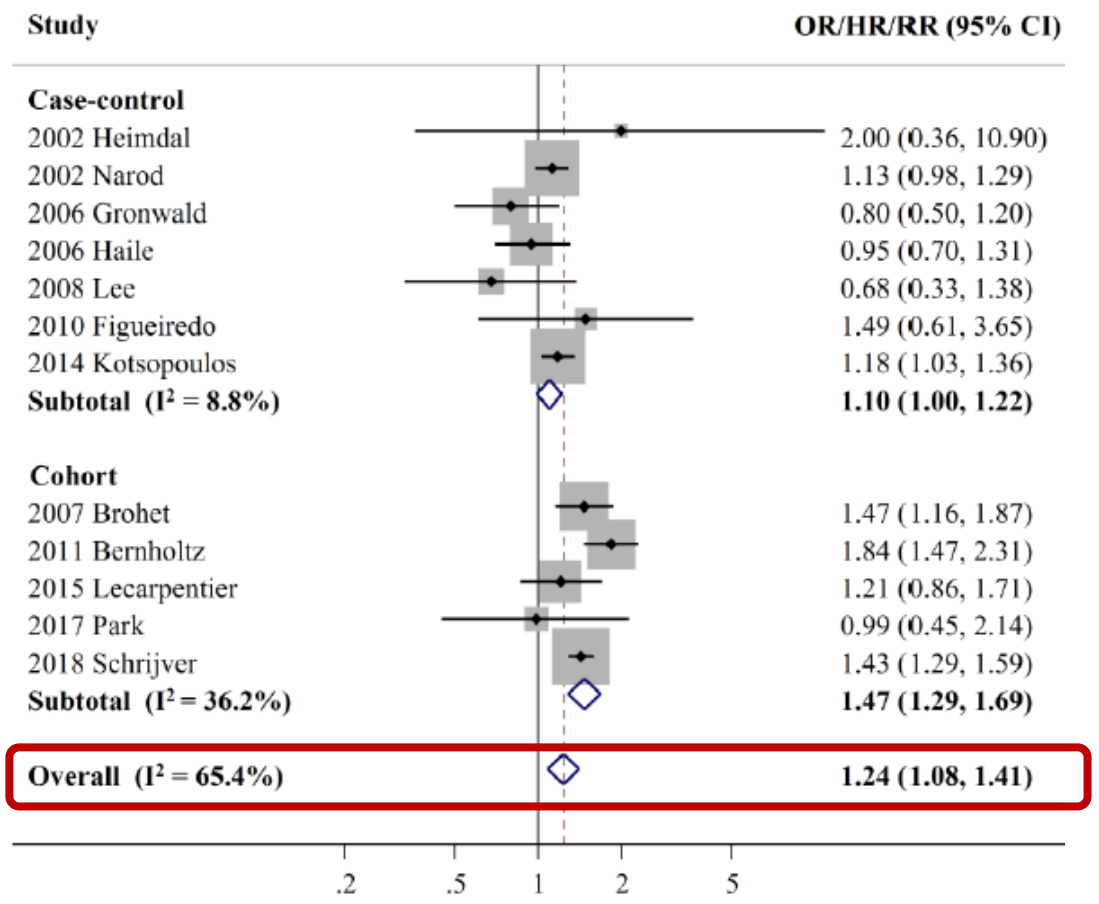
- CDC acknowledges the paramount importance of personal autonomy in contraceptive decision-making.
- Persons should have equitable access to the full range of contraceptive methods.
- Contraceptive services should be offered in a noncoercive manner that supports a person's values, goals, and reproductive autonomy.
- Shared decision-making and person-centered approaches recognize the expertise of both the health care provider and the person.
- A person-centered approach to contraceptive decision-making
  - prioritizes a person's preferences and reproductive autonomy rather than a singular focus on pregnancy prevention,
  - respects the person as the main decision-maker in contraceptive decisions, and
  - includes respecting the decision not to use contraception or to discontinue contraceptive method use.
- U.S. MEC and U.S. SPR recommendations can be used by health care providers to support persons in contraceptive decision-making.
- U.S. MEC and U.S. SPR recommendations can be used by health care providers to remove unnecessary medical barriers to accessing and using contraception.

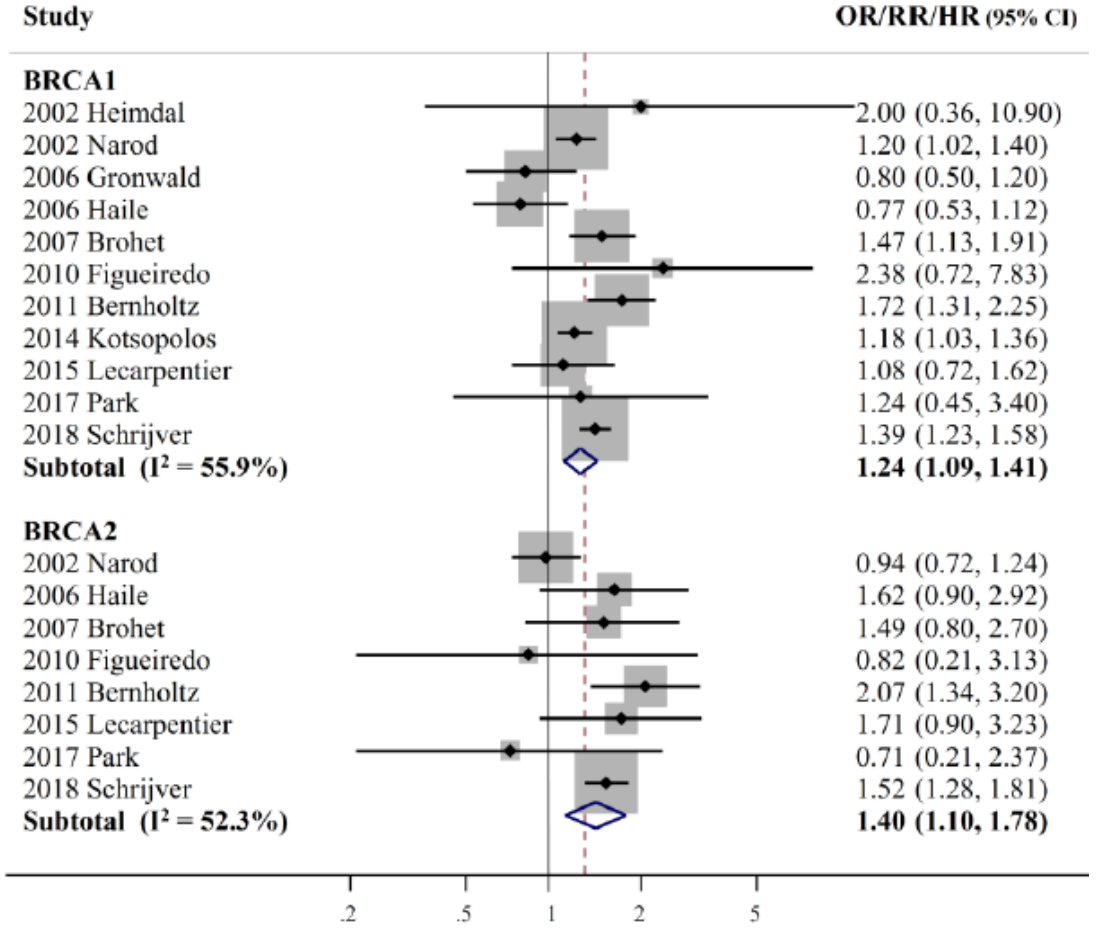
- ✓ Controindicata
- ✓ Indicata per prevenzione
- ✓ Decision personal making



Oral contraceptives and risk of breast cancer and ovarian cancer in women with a *BRCA1* or *BRCA2* mutation: A meta-analysis of observational studies

12 studi entro 2021





Aumentato rischio nelle utilizzatrici

Indipendentemente da BRCAm

Park et al , 2020

Oral contraceptives and risk of breast cancer and ovarian cancer in women with a *BRCA1* or *BRCA2* mutation: A meta-analysis of observational studies

12 studi entro 2021

OC DURATION	OR/RR/HR (95% CI)
Any BRCA	
≤ 5 years	1.13 (1.00-1.29)
> 5 years	1.29 (1.11-1.50)
BRCA 1	
≤ 5 years	1.12 (0.98-1.27)
> 5 years	1.40 (1.26-1.57)
BRCA 2	
≤ 5 years	1.18 (0.95-1.48)
> 5 years	1.49 (1.15-1.93)

✓Indipendentemente da BRCAm

✓ Incremento relativo all'utilizzo sopra i 5 anni

Park et al , 2020

Archives of Gynecology and Obstetrics (2020) 301:875–885
https://doi.org/10.1007/s00404-020-05458-w

REVIEW

Use of oral contraceptives in *BRCA* mutation carriers and risk for ovarian and breast cancer: a systematic review

D. Huber[1] · S. Seitz[1] · K. Kast[2] · G. Emons[3] · O. Ortmann[1]

4 metanalisi
1 review
1 studio
1 studi di casi
1 studio retrospettico
1 studio di coorte prospettico caso controllo

Pasanisi et al. [20] Case-only study LOE 4	382 "genetic", 1333 "sporadic" cases	Borderline significant association Genetic cases: OR = 1.3; 95% CI 1.0–1.7 (p = 0.05) Highest association for OC start at 18–20 years: OR = 1.6; 95% CI 1.1–2.3 (p trend = 0.18) Duration of use not statistically significant (p = 0.32)
Iodice et al. [6] Meta-analysis LOE 2a Included studies Four case–control studies [14, 21, 25, 28] One retrospective cohort study [26]	Cases: 2154 *BRCA1*, 707 *BRCA2* Controls: 2280 *BRCA1*, 672 *BRCA2*	No significant association *BRCA1*: RR = 1.09; 95% CI 0.77–1.54 *BRCA2*: RR = 1.15; 95% CI 0.61–2.18 Combined: SRR = 1.33; 95% CI 0.88–1.45) No association with duration of use (p = 0,2)
Cibula et al. [11] Review LOE 2a Included studies Seven case–control studies [21, 25, 27, 28, 39, 41]	Cases: 2151 *BRCA1*, 862 *BRCA2*, 94 *BRCA1/2* (not further indicated, from [40]) Controls: 2121 *BRCA1*, 719 *BRCA2*	Mild to moderate increase in risk Further increase in risk when OC duration ≥ 4 years before FFT (BRCA1: HR = 1.49; 95% CI 1.05–2.11. BRCA 2: HR = 2.58; 95% CI 1.21–5.49)

Durata di utilizzo
Età giovanile di assunzione

Archives of Gynecology and Obstetrics (2020) 301:875–885
https://doi.org/10.1007/s00404-020-05458-w

REVIEW

Use of oral contraceptives in *BRCA* mutation carriers and risk for ovarian and breast cancer: a systematic review

D. Huber[1] · S. Seitz[1] · K. Kast[2] · G. Emons[3] · O. Ortmann[1]

4 metanalisi
1 review
1 studio
1 studi di casi
1 studio retrospettico
1 studio di coorte prospettico caso controllo

Study/study design/Oxford Center of Evidence-based Medicine (OCEBM) level of evidence (LOE)	Number	Results
Park et al. [34] Retrospective cohort study LOE 2b	Cases: 168 *BRCA1*, 109 *BRCA2* Controls: 54 *BRCA1*, 250 *BRCA2*	No significant association *BRCA1*: HR = 1.24; 95% CI 0.45–3.40 *BRCA2*: HR = 0.71; 95% CI 0.21–2.37
Schrijver et al. [35] Retrospective and prospective cohort study LOE 1b	Prospective cohort: Cases: 269 *BRCA1*, 157 *BRCA2* Controls: 2007 *BRCA1*, 1453 *BRCA2*	No association for *BRCA1* (HR = 1.08; 95% CI 0.75–1.5), increase in risk for *BRCA2* (HR = 1.75; 95% CI 1.03–2.9)
	Retrospective cohort, left-truncated: Cases: 1095 *BRCA1*, 752 *BRCA2* Controls: 2733 *BRCA1*, 1760 *BRCA2*	Increase in risk for *BRCA1* (HR = 1.26; 95% CI 1.06–1.51), no association for *BRCA2* (1.06; 95% CI 0.85–1.33)
	Retrospective full-cohort: Cases: 2525 *BRCA1*, 1548 *BRCA2* Controls: 3180 *BRCA1*, 1973 *BRCA2*	Increase in risk for *BRCA1* (HR = 1.39; 95% CI 1.23–1.58) and *BRCA2* (HR = 1.52; 95% CI 1.28–1.81) Inverse correlation with duration of use, especially before FFTP (*BRCA1*: both retrospective analyses, $p < 0.001$ and $p = 0.001$; *BRCA2*: full retrospective analysis, $p = 0.002$)

No associazione
Associazione solo BRCA 2

Nel complesso non può essere escluso il rischio di incremento di breast cancer - - _> COUNSELLING

Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing

Helena Jernström [a,*], Niklas Loman [a], Oskar T. Johannsson [b], Åke Borg [a], Håkan Olsson [a,c]

245 < 40 anni

- Early onset BC increase with Ocs use before 20 age + three times risk to be BRCA 1-2 m

(a) All women ($n = 140/372$) (cases/controls)			
Per year of OC use prior to age 20 years	1.17	(1.03–1.33)	0.01
Per year of OC use age 20 years or older	1.02	(0.98–1.07)	0.28
(b) (i) Cases and matched controls born in 1955 and later ($n = 88/151$) (cases/controls)			
Per year of OC use prior to age 20 years	1.31	(1.07–1.62)	0.01
Per year of OC use age 20 years or older	1.05	(0.97–1.14)	0.24
(ii) Cases and matched controls born in 1954 and earlier ($n = 52/134$) (cases/controls)			
Per year of OC use prior to age 20 years	0.95	(0.74–1.20)	0.65
Per year of OC use age 20 years or older	1.03	(0.97–1.10)	0.34
(c) (i) Age at diagnosis 35 years or younger ($n = 43/116$) (cases/controls)			
Per year of OC use prior to age 20 years	1.53	(1.17–1.99)	0.002
Per year of OC use age 20 years or older	1.04	(0.93–1.16)	0.51
(ii) Age at diagnosis 36 years or older ($n = 97/256$) (cases/controls)			
Per year of OC use prior to age 20 years	1.06	(0.91–1.24)	0.45
Per year of OC use age 20 years or older	1.03	(0.98–1.07)	0.26

- The effect of early OC use was limited to women diagnosed prior to age 36 years

European Journal of Cancer 41 (2005) 2312–2320

Hormonal Contraception and Breast Cancer Risk for Carriers of Germline Mutations in *BRCA1* and *BRCA2*

Kelly-Anne Phillips, MD, MBBS, FRACP, FAHMS[1,2,3]; Joanne Kotsopoulos, PhD[4,5]; Susan M. Domchek, MD[6,7]; Mary Beth Terry, PhD[8,9]; James A. Chamberlain, PhD[10]; Julie K. Bassett, PhD[10]; Amber M. Aeilts, MS, LGC[11]; Irene L. Andrulis, PhD[12,13]; Saundra S. Buys, MD[14]; Wanda Cui, MBBS, BMEDSCI[1,2]; Mary B. Daly, MD, PhD[15]; Andrea F. Eisen, MD, FRCPC[16,17]; William D. Foulkes, MBBS, PhD[18]; Michael L. Friedlander, PhD[19,20]; Jacek Gronwald, MD[21]; John L. Hopper, PhD[3]; Esther M. John, PhD, MSPH[22,23,24]; Beth Y. Karlan, MD[25,26]; Raymond H. Kim, MD, PhD[27,28]; Allison W. Kurian, MD, MSc[22,23,24]; Jan Lubinski, MD, PhD[21]; Kelly Metcalfe, PhD, RN, FAAN, FCAHS[4,29]; Katherine L. Nathanson, MD[6,7,30]; Christian F. Singer, MD, MPH[31]; Melissa C. Southey, PhD, Grad Dip Law, FHGSA, FFSc (RCPA)[10,32,33]; Heather Symecko, MPH[6]; Nadine Tung, MD[34]; Steven A. Narod, MD, FRCPC, FRSC[4,5]; and Roger L. Milne, PhD[3,10,33]; for the Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer, the Risk Factor Analysis of Hereditary Breast and Ovarian Cancer Study, the Basser Center University of Pennsylvania Registry, and the Breast Cancer Family Registry

4 studi prospettici di coorte BRCA1 e BRCA 2

- ✓ 191 BRRCA 1 e BRCA2 mutation carriers developed BC during median follow-up of 5.9 and 5.6 years, respectively
- ✓ 3,882 BRCA1 (53%) and 1,509 BRCA2 (71%) had ever used hormonal contraceptives for at least 1 year

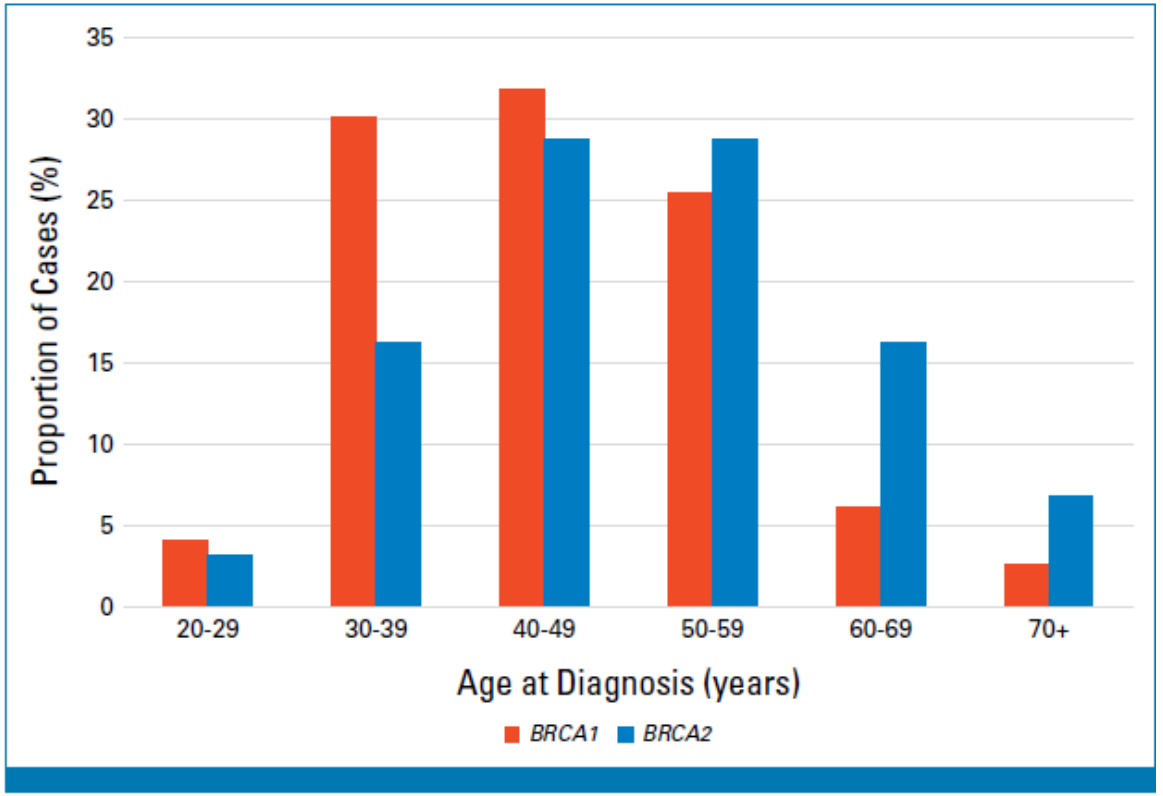


FIG 2. Age at breast cancer diagnosis of 488 *BRCA1* and 191 *BRCA2* mutation carriers.

J Clin Oncol 43:422-431

BRCA 1 aumentato rischio di BC
(non significativo se passato ed almeno 1 anno)

BRCA 1

TABLE 2. Associations Between Hormonal Contraception Use and Breast Cancer Risk for Carriers of a *BRCA1* Mutation

Hormonal Contraceptive Use	Person-Years	Cases, No.	Cases per 1,000 Person-Years	HR[a]	95% CI	*P*
Ever use						
Never used	12,365	201	16.3	1 (ref)		
Ever used	13,409	287	21.4	1.29	1.04 to 1.60	.02
Current or past use						
Never used	12,365	201	16.3	1 (ref)		
Current use[b]	2,629	43	16.4	1.40	0.94 to 2.08	.10
Past use: 1-5 years before	2,747	45	16.4	1.16	0.80 to 1.69	.4
Past use: 6-10 years before	2,412	59	24.5	1.40	0.99 to 1.97	.05
Past use >10 years before	5,621	140	24.9	1.27	0.98 to 1.63	.07
Cumulative duration of use[c]						
Cumulative duration, per year	25,774	488	18.9	1.03	1.00 to 1.06	.03
Age at first use[c]						
Younger age, per year	25,774	488	18.9	1.01	0.99 to 1.04	.4
Use before first birth[c]						
No use before first birth	15,927	278	17.5	1 (ref)		
Used before first birth	9,847	210	21.3	1.23	0.89 to 1.70	.2

ùBRCA 2 non associato aumentato rischio di BC

BRCA 2

TABLE 3. Associations Between Hormonal Contraception Use and Breast Cancer (BC) Risk for Carriers of a *BRCA2* Mutation

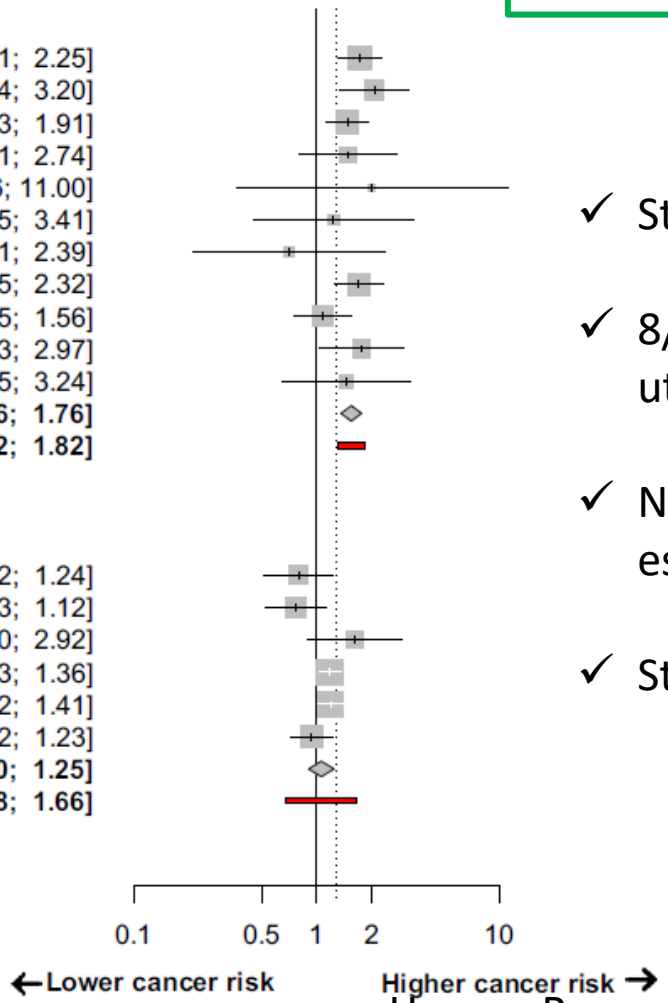
Hormonal Contraceptive Use	Person-Years	Cases, No.	Cases per 1,000 Person-Years	HR[a]	95% CI	*P*
Ever use						
Never used	2,872	51	17.8	1 (ref)		
Ever used	7,057	140	19.8	1.07	0.73 to 1.57	.7
Current or past use						
Never used	2,873	51	17.8	1 (ref)		
Current use[b]	1,165	11	9.4	0.70	0.33 to 1.47	.3
Past use: 1-5 years before	1,168	14	12.0	0.80	0.40 to 1.61	.5
Past use: 6-10 years before	1,041	20	19.2	1.08	0.57 to 2.05	.8
Past use >10 years before	3,682	95	25.8	1.15	0.77 to 1.70	.5
Cumulative duration of use[c]						
Cumulative duration, per year	9,929	191	19.2	0.99	0.96 to 1.03	.6
Age at first use[c]						
Younger age, per year	9,929	191	19.2	0.99	0.95 to 1.03	.5
Use before first birth[c]						
No use before first birth	4,096	80	19.5	1 (ref)		
Used before first birth	5,833	111	19.0	1.16	0.64 to 2.12	.6

Metanalisi di 7 studi (7454 donne)
Metanalisi di 4 studi (9056 donne)

Contraceptives and cancer risks in *BRCA1/2* pathogenic variant carriers: a systematic review and meta-analysis

Majke H.D. van Bommel[1,*], Joanna IntHout[2], Guus Veldmate[3], C. Marleen Kets[4], Joanne A. de Hullu[1], Anne M. van Altena[1], and Marline G. Harmsen[1]

Author, year	N	BRCA	Contra-ceptive	Ratio	95% CI
HR					
Bernholtz, 2011	638	BRCA1	OCP	1.72	[1.31; 2.25]
Bernholtz, 2011	250	BRCA2	OCP	2.07	[1.34; 3.20]
Brohet, 2007	1181	BRCA1	OCP	1.47	[1.13; 1.91]
Brohet, 2007	412	BRCA2	OCP	1.49	[0.81; 2.74]
Heimdal, 2002	98	BRCA1	OCP	2.00	[0.36; 11.00]
Park, 2017	222	BRCA1	OCP	1.24	[0.45; 3.41]
Park, 2017	359	BRCA2	OCP	0.71	[0.21; 2.39]
Rieder, 2016	366	BRCA1/2	OCP	1.70	[1.25; 2.32]
Schrijver, 2018	2276	BRCA1	OCP	1.08	[0.75; 1.56]
Schrijver, 2018	1610	BRCA2	OCP	1.75	[1.03; 2.97]
Toss, 2017	113	BRCA1/2	OCP	1.45	[0.65; 3.24]
Random−effects model	**7525**			**1.55**	**[1.36; 1.76]**
Prediction Interval					**[1.32; 1.82]**
Heterogeneity: I^2 = 0% [0%; 60%], τ^2 = < 0.01					
OR					
Gronwald, 2006	696	BRCA1	OCP	0.80	[0.52; 1.24]
Haile, 2006	497	BRCA1	OCP	0.77	[0.53; 1.12]
Haile, 2006	307	BRCA2	OCP	1.62	[0.90; 2.92]
Kotsopoulos, 2014	4984	BRCA1	OCP	1.18	[1.03; 1.36]
Narod, 2002	1962	BRCA1	OCP	1.20	[1.02; 1.41]
Narod, 2002	660	BRCA2	OCP	0.94	[0.72; 1.23]
Random−effects model	**9106**			**1.06**	**[0.90; 1.25]**
Prediction Interval					**[0.68; 1.66]**
Heterogeneity: I^2 = 52% [0%; 81%], τ^2 = 0.02					



- ✓ Studi solo con COC (tempi e tipologie diverse)
- ✓ 8/11 studi descrivono correlazione con tempo di utilizzo
- ✓ NO differenze di rischio tra BRCA1/2 negli studi esaminati
- ✓ Studi > 10 o < 10 anni no differenze di rischio

Human Reproduction Update, Vol.29, No.2, pp. 197–217, 2023

Metanalisi di 7 studi (7454 donne)
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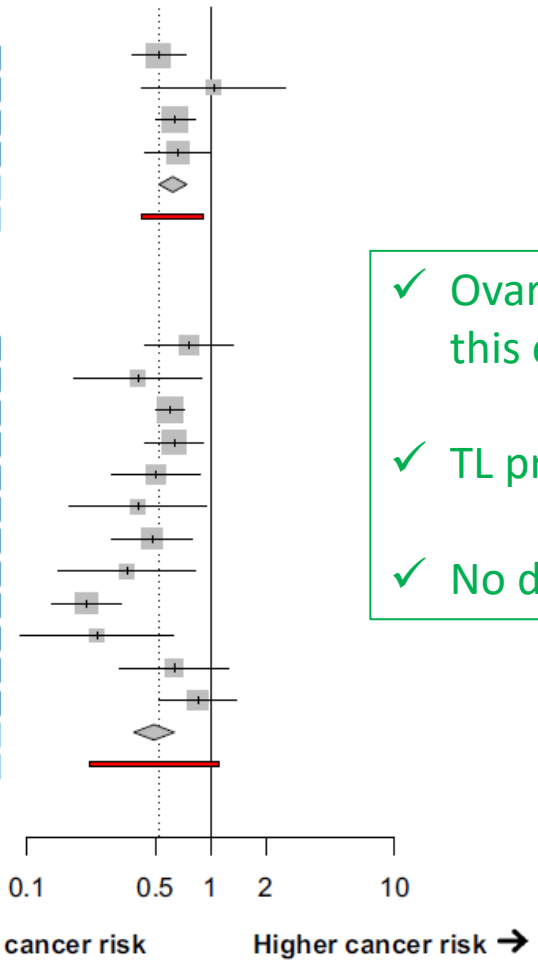
Author, year	N	BRCA	Contra-ceptive	Ratio	95% CI
HR					
Antoniou, 2009	2281	BRCA1	OCP	0.52	[0.37; 0.73]
Antoniou, 2009	1038	BRCA2	OCP	1.04	[0.42; 2.56]
Schrijver, 2021	4818	BRCA1	OCP	0.64	[0.50; 0.81]
Schrijver, 2021	2844	BRCA2	OCP	0.66	[0.43; 1.01]
Random-effects model	**10981**			**0.62**	**[0.52; 0.74]**
Prediction Interval					**[0.42; 0.91]**
Heterogeneity: I^2 = 0% [0%; 85%], τ^2 = < 0.01					
OR					
Ferris, 2014	639	BRCA1/2	OCP	0.76	[0.44; 1.31]
Gronwald, 2006	300	BRCA1	OCP	0.40	[0.18; 0.89]
Kotsopoulos, 2015	5386	BRCA1	OCP	0.60	[0.50; 0.71]
Kotsopoulos, 2015	1180	BRCA2	OCP	0.63	[0.44; 0.91]
Narod, 1998	229	BRCA1	OCP	0.50	[0.29; 0.87]
Narod, 1998	31	BRCA2	OCP	0.40	[0.17; 0.94]
Narod, 2001	346	BRCA1	OCP	0.48	[0.29; 0.80]
Narod, 2001	118	BRCA2	OCP	0.35	[0.15; 0.82]
Perri, 2015	718	BRCA1	OCP	0.21	[0.14; 0.32]
Perri, 2015	331	BRCA2	OCP	0.24	[0.09; 0.62]
Vicus, 2010	661	BRCA1	OCP	0.63	[0.32; 1.25]
Whittemore, 2004	451	BRCA1/2	OCP	0.85	[0.52; 1.38]
Random-effects model	**10390**			**0.49**	**[0.38; 0.63]**
Prediction Interval					**[0.22; 1.11]**
Heterogeneity: I^2 = 64% [34%; 81%], τ^2 = 0.12					



- ✓ Ovarian cancer risk was lower among OCP users, but this effect vanishes after cessation of use.
- ✓ TL protects against ovarian cancer
- ✓ No data are available for other kinds of contraceptives

Human Reproduction Update, Vol.29, No.2, pp. 197–217, 2023

Indicata per prevenzione ?....

- ✓ COC porta ad una riduzione del rischio di OC anche nelle BRCAm. Non è escludibile un incremento di rischio nel BC

  Huber et al ,2020

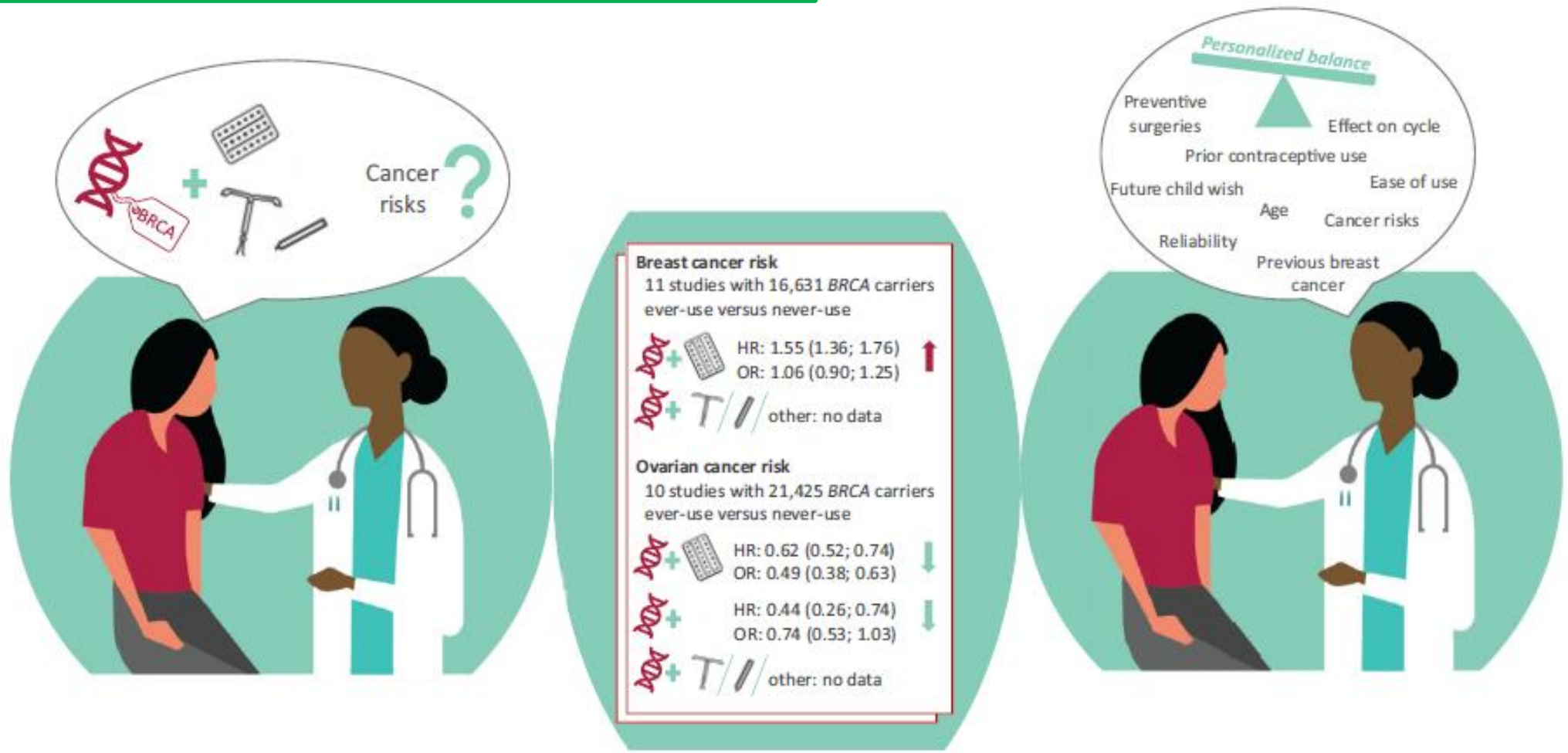
- ✓ Insufficienti evidenze raccomandano l'uso dei COC come chemioprevenzione nelle BRCA a meno che non la utilizzano come contraccezione

  Mooman et al,2013

Contraceptives and cancer risks in *BRCA1/2* pathogenic variant carriers: a systematic review and meta-analysis

Majke H.D. van Bommel [1,*], Joanna IntHout [2], Guus Veldmate [3], C. Marleen Kets [4], Joanne A. de Hullu [1], Anne M. van Altena [1], and Marline G. Harmsen [1]

Counselling of BRCA1/2-PV carriers should be personalized



Review

Oral contraception use in *BRCA* gene mutation carriers: information for counselling in routine clinical practice

Chiara Cassani[1,*], Francesca Zanellini[1], Cristina Angela Camnasio[1], Diana Pettinato[1], Simona Secondino[2], Angelica Della Valle[3], Mario Urtis[4], Eloisa Arbustini[4], Silvia Martella[1,5,6], Arsenio Spinillo[1,5], Rossella Elena Nappi[5,6]

- ✓ Another issue to be considered is that germline mutations in BRCA suppressor genes have been associated over time with several malignancies, in addition to breast and ovarian cancers.
- ✓ The Breast Cancer Linkage Consortium and The Hereditary Breast Cancer Study Group showed an **increased risk for endometrial cancer in BRCA1** mutated women
- ✓ Recently, Oh et al. in their systematic review (18 studies) and meta-analysis (14 studies) found that the **risk of colorectal cancer is moderately elevated in BRCA1** (OR = 1.49, 95% CI = 1.19 to 1.85, $p < 0.001$), regardless of study design, specific type of cancer, method of detection, or age.

✓ **OC may offer a protective benefit against endometrial and colorectal malignancies**

Counselling of BRCA1/2-PV carriers should be personalized

European Journal of Gynaecological Oncology, 2021

Guidelines ……..

	Country, society	Guideline	Year	Recommendations/summary	Conclusion
1	Slovakia, SAGO	Guidelines for complex genetic analysis of hereditary breast ovarian cancer syndrome in Slovak population	2015	– Hormonal contraception is not necessarily contraindicated in carriers of a mutation; however, the benefits need to be considered.	Not contra-indicated
2	The Netherlands, NVOG	Erfelijk en familiair ovariumcarcinoom (in English: Hereditary and familial ovarian carcinoma)	2015	– No reason to advise against OCP in healthy women with a *BRCA1/2* mutation aged 25 years or below – Data regarding LR-IUD and the risk of breast cancer in healthy *BRCA1/2* mutation carriers is lacking, therefore no statement can be made on the safety of these IUDs in this specific group – There is some data showing that the use of LR-IUD after breast cancer does not increase the risk of recurrence of breast cancer.	Not contra-indicated
3	USA, AGOC	US Medical Eligibility Criteria for Contraceptive Use	2016	– Evidence does not suggest that the increased risk for breast cancer among women with either a family history of breast cancer or breast cancer susceptibility genes is modified by the use of combined oral contraceptives.	Not contra-indicated
4	Spain, SEGO	Clinical guidelines in hereditary breast and ovarian cancer	2016	– Oral contraceptives in *BRCA1/2* mutation carriers can reduce the risk of ovarian cancer by 50%, with the benefit being greater with longer duration of treatment. Their use is not contraindicated, although there is a possibility of an increased risk of breast cancer.	Not contra-indicated
5	Canada, SOGC	Canadian Contraception Consensus	2017	The use of combined oral contraception in *BRCA1/2* carriers is controversial but appears to be associated with a decreased risk of ovarian cancer and no increase in the risk of breast cancer – Women with a history of breast cancer >5 years ago: benefit for expert consultation prior to advising against contraceptive use – In general: adequate counselling prior to OCP initiation to ensure an informed choice and improve adherence and continuation	Ambivalent, counsel

Guidelines ……..

6	United Kingdom, NICE*	Surveillance proposal for *BRCA*	2017	– Women <35 years with a family history of breast cancer: in keeping with general health advice on the use of the OCP – Women >35 years with a family history of breast cancer: inform on an increased breast cancer risk associated with taking the OCP, and that their absolute risk increases with age – *BRCA1* carriers: conflicting effects of a potential increased risk of breast cancer under the age of 40 years and the lifetime protection against ovarian cancer risk from taking the OCP should be discussed – The OCP should not be prescribed purely for prevention of cancer	Ambivalent, counsel
7	USA, ACOG	Clinical management guidelines for Obstetrician-Gynecologists: Hereditary Breast and Ovarian Cancer Syndrome	2017	– Given the magnitude of the potential benefits (e.g. ovarian and endometrial cancer risk reduction, pregnancy, prevention, cycle regulation), it is appropriate for women with mutations in *BRCA1* or *BRCA2* to use oral contraceptives if indicated, and use for cancer prophylaxis is reasonable. Although there have been conflicting reports in the literature on the effect of oral contraceptives on breast cancer risk. – In high-risk women who are undergoing tubal sterilization for contraception, bilateral salpingectomy followed by future oophorectomy may be a reasonable option to offer, but ovarian cancer risk reduction remains under evaluation.	Not contra-indicated
8	Canada, SOGC	Gynaecologic management of hereditary breast and ovarian cancer	2018	– Combined hormonal contraceptive use is an effective method of chemoprevention for ovarian/tubal/peritoneal cancer in the general population and women with *BRCA1/2*. – The use of OCP in young *BRCA1* variant carriers should be individualized, taking into account the risks and benefits.	Ambivalent, individualize
Collaborative societies					
13	WHO	Medical eligibility criteria for contraceptive use	2015	Women with a family history of cancer or with breast cancer susceptibility genes (such as *BRCA1* and *BRCA2*): – Combined oral contraceptive, combined contraceptive patch, vaginal ring or injectable contraceptive: no restriction for use	Not contra-indicated
14	EMSO	Prevention and screening in *BRCA* mutation carriers	2016	– The use of the OCP may be considered as a risk-reducing measure for ovarian cancer. It should however be noted that there are conflicting data whether OCP increases breast cancer risk among *BRCA1/2* carriers	Not contra-indicated

Guidelines ……..

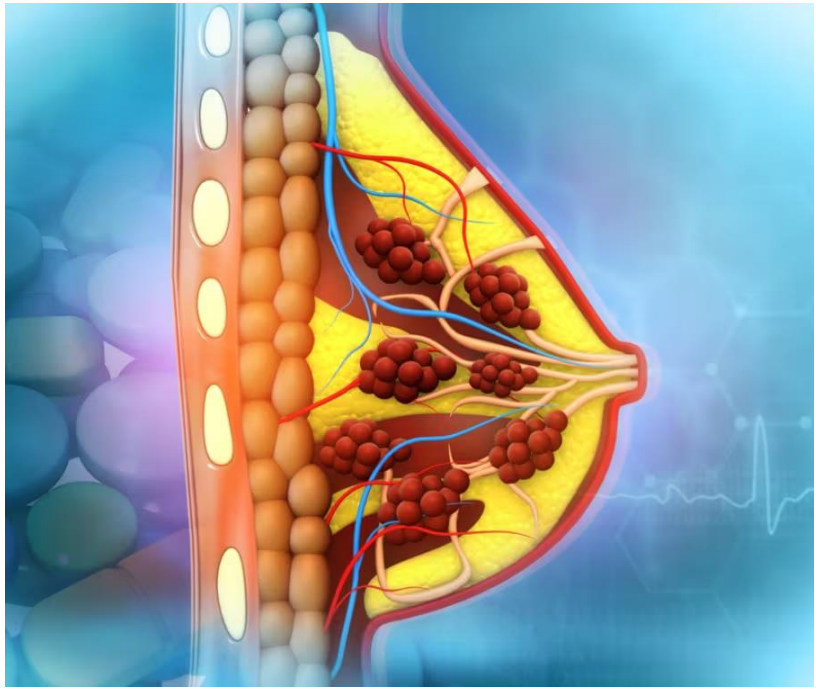
	Country, society	Guideline	Year	Recommendations/summary	Conclusion
9	United Kingdom, FSRH	Guideline-combined-hormonal-contraception	2019	– Amongst *BRCA* carriers, use of OCPs is associated with reduced risk of ovarian cancer with use, proportional to the duration of use. The evidence is stronger for *BRCA1* carriers but exists for both *BRCA1* and *BRCA2*. This advantage would need to be weighed against the potential increased risk of breast cancer. – Women with a *BRCA* mutation should be advised that current use of combined hormonal contraception is associated with a small increased risk of breast cancer which reduces with time after stopping combined hormonal contraception.	Ambivalent, counsel
10	United Kingdom, FSRH	UK Medical Eligibility Criteria (UKMEC) for contraceptive use	2019	Carriers of a known gene mutations associated with breast cancer (e.g. *BRCA1/BRCA2):* – Copper IUD: no restriction for use – LR-IUD, progestogen-only-implant, medroxyprogesterone acetate, progestogen-only-pill, combined hormonal contraception: the advantages generally outweigh the theoretical or proven risks	Not contra-indicated
11	USA, NCCN	Genetic/familial high-risk assessment: Breast and ovarian cancer	2019	– The use of oral contraceptives significantly reduced the risk of ovarian cancer by approximately 50% for both the *BRCA1* and *BRCA2* mutation carriers. Studies on the effects of oral contraceptive use on breast cancer risk among *BRCA1/2* mutation carriers have reported conflicting data.	No advice reported
12	The Netherlands, NHG*	Anticonceptie (in English: Contraception)	2020	– *BRCA* ≥35 years: absolute contra-indication for hormonal contraceptives – *BRCA* 25-35 years: relative contra-indication for hormonal contraceptives – BRCA <25 years: no contra-indication for hormonal contraceptives	Contra-indicated, depending on age

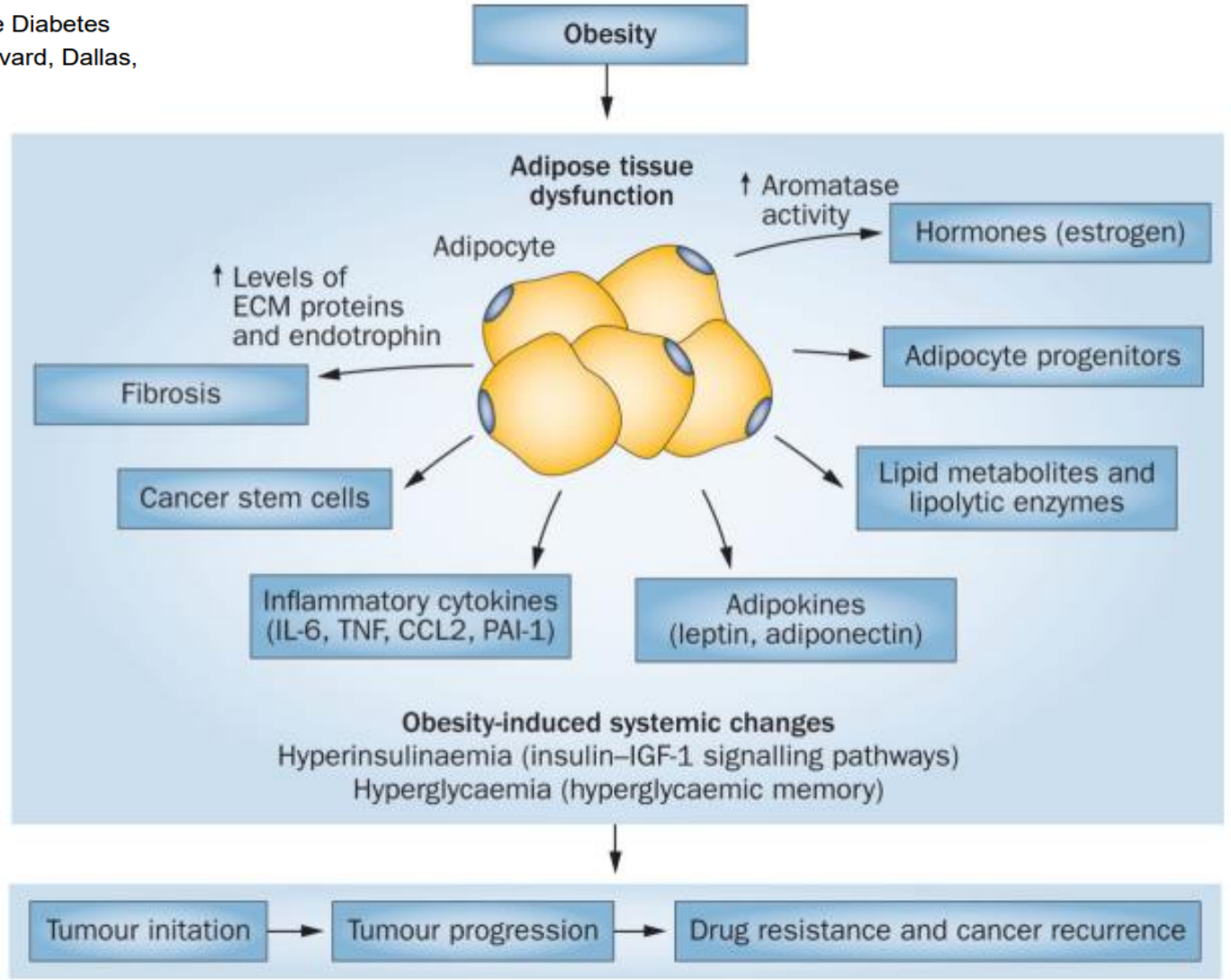
Nat Rev Endocrinol. 2014 August ; 10(8): 455–465. doi:10.1038/nrendo.2014.94.

Obesity and cancer—mechanisms underlying tumour progression and recurrence

Jiyoung Park[#], **Thomas S. Morley**[#], **Min Kim**, **Deborah J. Clegg**, and **Philipp E. Scherer**
Department of Biological Sciences, School of Life Sciences, Ulsan National Institute of Science and Technology, 50 UNIST Street, Ulsan 689–798, South Korea (J.P.). Touchstone Diabetes Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA (T.S.M., M.K., D.J.C., P.E.S.).

Infiammazione , sindrome metabolica e tumori ….





BRCA1-
BRCA2

Obesità

Fattori
Ambientali

Fattori
epigenetici

Vantaggi
Contraccettivi

Paura
oncologica

Temi aperti di approfondimento :

- Valutazione dell'impatto delle nuove molecole estrogeniche e progestiniche sul rischio nelle BRCAm
- Fattori di rischio associati (ambientali – epigenetici – stili di vita – alimentazione)
- Studi differenti per BRCA1 e BRCA 2
- Impatto della RRSO e successiva terapia su queste donne