Kontracepcija u žena liječenih zbog raka

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- *Opcije očuvanja plodnosti*
- *Planiranje obitelji*
- *Nedostatak informacija i smjernica o izboru kontracepcijskih metoda u žena s rakom*

Varijable povezane sa zabrinutošću o plodnosti u žena mlađih od 41 godina u žena s rakom dojke (n = 657)

- *Mlađa životna dob u trenutku dijagnoze*
- *Stupanj edukacije*
- *Neudate*
- *"Full time" posao*
- *Redoviti menstruacijski ciklusi*
- *Prethodne trudnoće/ živorođeni*
- *Do sada nije pokušala zanijeti*
- *Bez pobačaja*
- *Prethodno liječenje neplodnosti*
- *Strah od recidiva u trenutku postavljanja dijagnoze*

- *57% - koje su moje kontracepcijske opcije?*

C. Gracia and T.K. Woodruff (eds.), Oncofertility Medical Practice: 149 Clinical Issues and Implementation, DOI 10.1007/978-1-4419-9425-7_11, © Springer Science+Business Media New York 2012

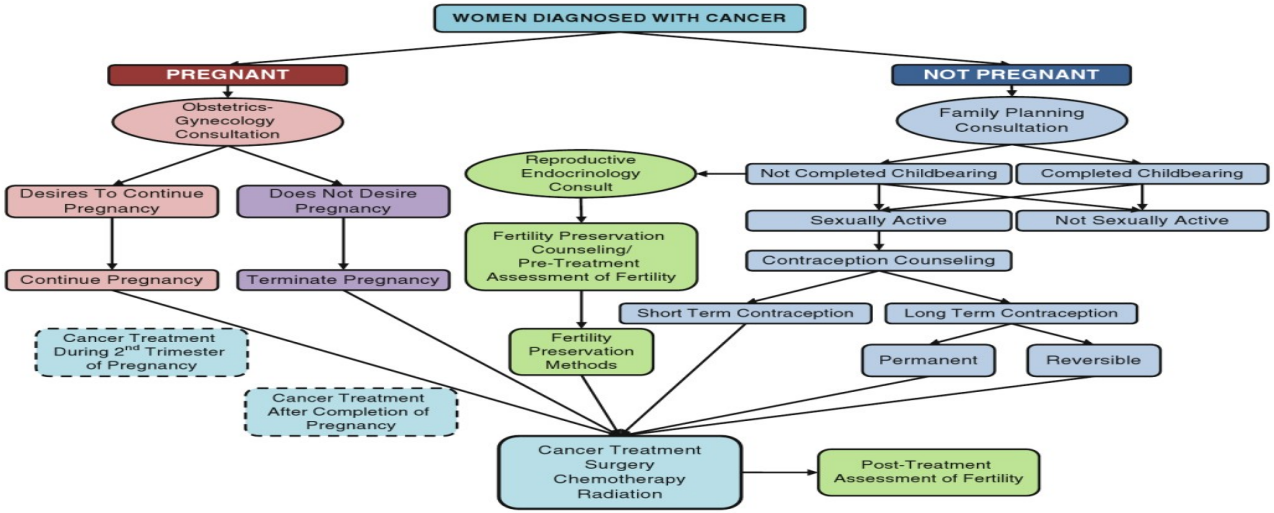


Fig. 14.1 Engendering reproductive health in oncologic survivorship algorithm

to cancer survivors, who do not often share sexual health concerns with their oncology team [8]. Leading organizations have guidelines to assist the oncology team navigating reproductive health issues. Many gynecologic and family planning providers and organizations can offer assistance and guidance. While the expectations of an oncology team may not be to provide contraceptive management, offering the appropriate referrals for reproductive health issues would be a feasible option.

Engendering Reproductive Health in Oncologic Survivorship (EROS) Algorithm

A simple tool, the EROS Algorithm (Fig. 14.1), can aid providers caring for cancer survivors to expediently optimize available and appropriate reproductive health care. The Cook County Health and Hospitals System Minority-Based Community Clinical Oncology Program (MBCCOP) in conjunction with the Division of Family Planning developed the algorithm to aid in the navigation of reproductive health management in newly diagnosed breast cancer survivors. In a pilot of this model, 100 % of women received reproductive health management consistent with the reproductive health interests of the women studied [103].

In this algorithm, cancer patients are initially thought of in terms of current pregnancy status. Currently pregnant patients are referred to an obstetrician for options counseling to discuss delaying treatment or termination. Women who are not pregnant (or after delivery/abortion) are further stratified by future childbearing interests. If women desire future pregnancy or are unsure of future childbearing interests, referral to fertility preservation specialists is advised. For all non-pregnant women, including those desiring future pregnancy and those who have completed childbearing, referral to a family planning specialist for oncocontraception counseling should be offered.

Contraception. 2007;75:305–10. Patel AA, Mini S, Sutaria RP, Schoenhage MB, Patel AR, Radeke EK, et al. Reproductive health issues in women with cancer.

SOCIETY of FAMILY PLANNING
research, education, and leadership

Contraception 86 (2012) 191 – 198

Clinical Guidelines

Cancer and contraception

Release date May 2012
SFP Guideline #20121

Abstract

As a result of advances in cancer diagnosis and treatment, young women within the reproductive-aged group are now more likely to survive cancer. Reproductive-aged women with cancer may be interested in deferring pregnancy either temporarily or permanently at cancer diagnosis, during therapy or after treatment. Currently, there are limited guidelines to aide clinicians in managing the contraceptive needs in this special population. After reviewing the evidence regarding the safety and efficacy of available methods of contraception for women who have been diagnosed with cancer, the Society of Family Planning recommends that women of childbearing age who are being treated for cancer avoid combined hormonal contraceptive methods (containing estrogen and progestin) when possible because they may further increase the risk of venous thromboembolism (VTE) (Level A). The copper T380A intrauterine device, a highly effective, reversible, long-acting, hormone-free method, should be considered the first-line contraceptive option for women with a history of breast cancer (Level A), although for women being treated with tamoxifen, the levonorgestrel-containing intrauterine system (IUS) which decreases endometrial proliferation may be preferable (Level B). Women who develop anemia may benefit from use of a progestin-containing contraceptive (Level A). Women who develop osteopenia or osteoporosis following chemotherapy should avoid the progestin-only contraceptive injection (Level B).

More information is needed in many areas. There are insufficient data to evaluate the risk of VTE when progestin-only contraceptives are used by women at high risk of VTE. Information is also needed on whether the levonorgestrel-containing IUS affects the risk of breast cancer recurrence and whether hormonal contraceptives affect the risk of breast cancer among women who have received chest wall, or "mantle field," radiation. Finally, studies of the safety and effectiveness of IUS use by women who are immunosuppressed and studies of whether progestin-only contraceptives affect the risk of fracture among cancer survivors or, more generally, women with osteopenia would be useful.

Keywords: Contraception; Cancer

Pitanja i preporuke

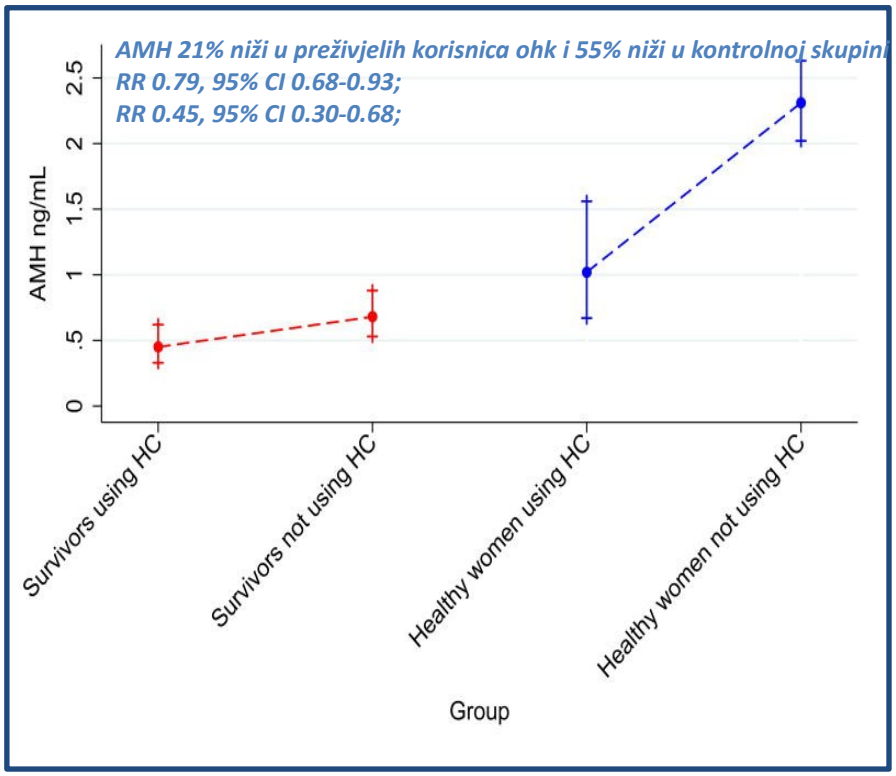
1. Procjena fertilnosti . Da li je potrebna kontracepcija ?

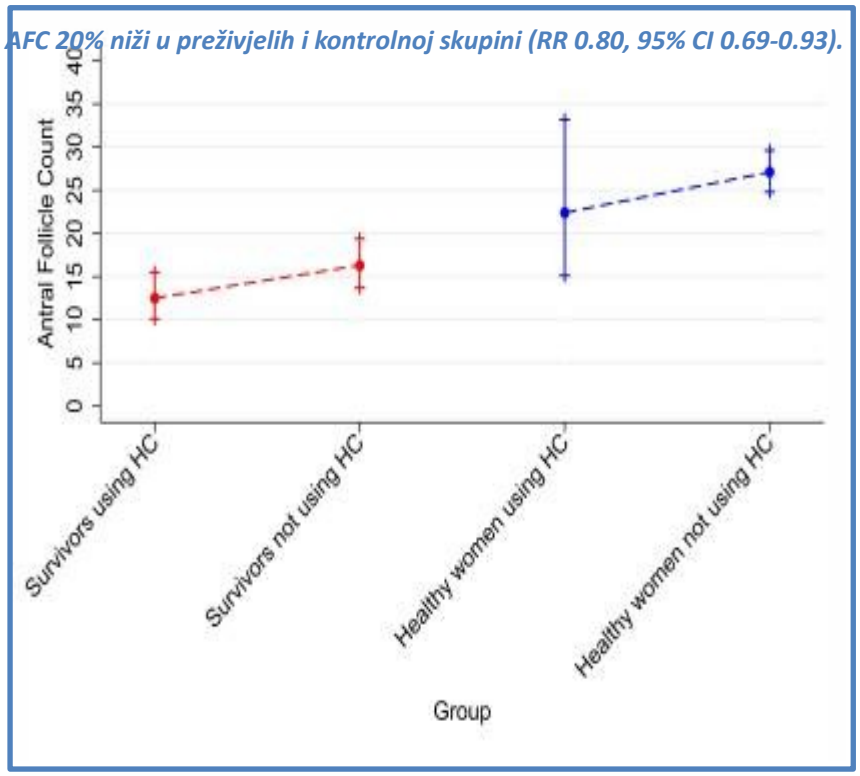
- AMH
- AFC
  - Utjecaj OHK na markere ovarijske rezerve – nepromjenjeni ili …
- FSH
  - varijabilnost tijekom menstruacijskog ciklusa
  - Ograničeno klinička korist tijekom primjene OHK

Amenoreja

- amenoreja kemoterapija -53%-89%,
- reverzibilna u žena ispod 40 godine

- Inhibin





- *Ukupno 249 žena (126 Ca survivors, 123 zdrava žene; prosječna dob 25.5) praćene 2.15 godina*
- *AMH – individualno – 17-35% niži, AFC 11% niži*

- ***AMH i AFC značajno manji u žena nedavno izloženih OHK.***
- ***AMH i AFC - oprez pri interpretaciji nalaza***

Johnson NL. Fertil Steril. 2014 Sep; 102(3): 774–781.e3. Published online 2014 Jun 14.

Pitanja i preporuke

2. Kontracepijski izbor ovisan o tipu karcinoma

- Kontroverze i zabrinutost primjene egzogenih hormona u žena oboljelih od raka dojke
  - Hormonski aktivni tumori (rak dojke)
  - E+P OHK- povećavaju rizik recidiva
  - Estrogenski i progesteronski receptori – rast tumora i prognoza
  - Nejasna uloga progestina
  - Animalni modeli – potiču rast i metastaze
  - Oralni MPA – benefit kemoterapijskog učinka
  - U općoj populaciji – progestini ne povećava rizik raka dojke

Cooper T380 A IUD

LEVONORGESTREL IUS

- Liječene tamoksifenom
- Kontraceptivni i endometrijski efekt

- Nema endometrijske proliferacije
- Nema potrebe za analizom vaginalnog krvarenja
- Nema rizika recidiva raka dojke

Kontracepcijske metode u oboljelih od raka

Autor	Kontraceptivna metoda	Populacija	Dizajn i ishod	Nalaz
Trinh XB (2008) [45]	Levonorgestrel-IUD	Breast cancer survivors	Case control study of breast cancer recurrence	increased recurrence among women with a levonorgestrel-IUD at time of diagnosis
Kesim MD (2008)[71]	Levonorgestrel-IUD	Breast cancer patients taking tamoxifen	Cohort followed for 36 months for lipid and endometrial changes	Improvement of endometrium, no effect on lipids
Chan SS (2007)[39]	Levonorgestrel-IUD	Breast cancer patients taking tamoxifen	Cohort followed for 12 months for endometrial changes	Improvement of endometrium
Gardner FJ (2000)[40]	Levonorgestrel-IUD	Breast cancer patients taking tamoxifen	Cohort followed for 12 months for endometrial changes	Improvement of endometrium
Kloke O (1999)[57]	Medroxy-progesterone acetate	Advanced breast cancer responding to induction chemotherapy	Randomized phase III trial of time to cancer progression and overall survival	Increased time to cancer progression, no effect on overall survival

Schwarz EB. J Gen Intern Med 2009;24:401-8.

Maternički uložak – visoko učinkovita i reverzibilna kontracepcija

LEVONORGESTREL IUS

- *Tamoksifen*
- *Nehormonski tumori*
- *Kontrole (MR, CT)*
- *Imunosupresija*
- *Ne povećava rizik zgrušavanja /osteoporoze*
- *5 godina*
- *Smanjuje grčeve*
- *Smanjuje menstruacijska krvarenja/rizik anemije*
- *Iregularni obrazac krvarenja*
- *Smanjuje endometrijsku proliferaciju*
- *Rizik recidiva ?*
- *Longe term safety ?*

COOPER T380 A IUD

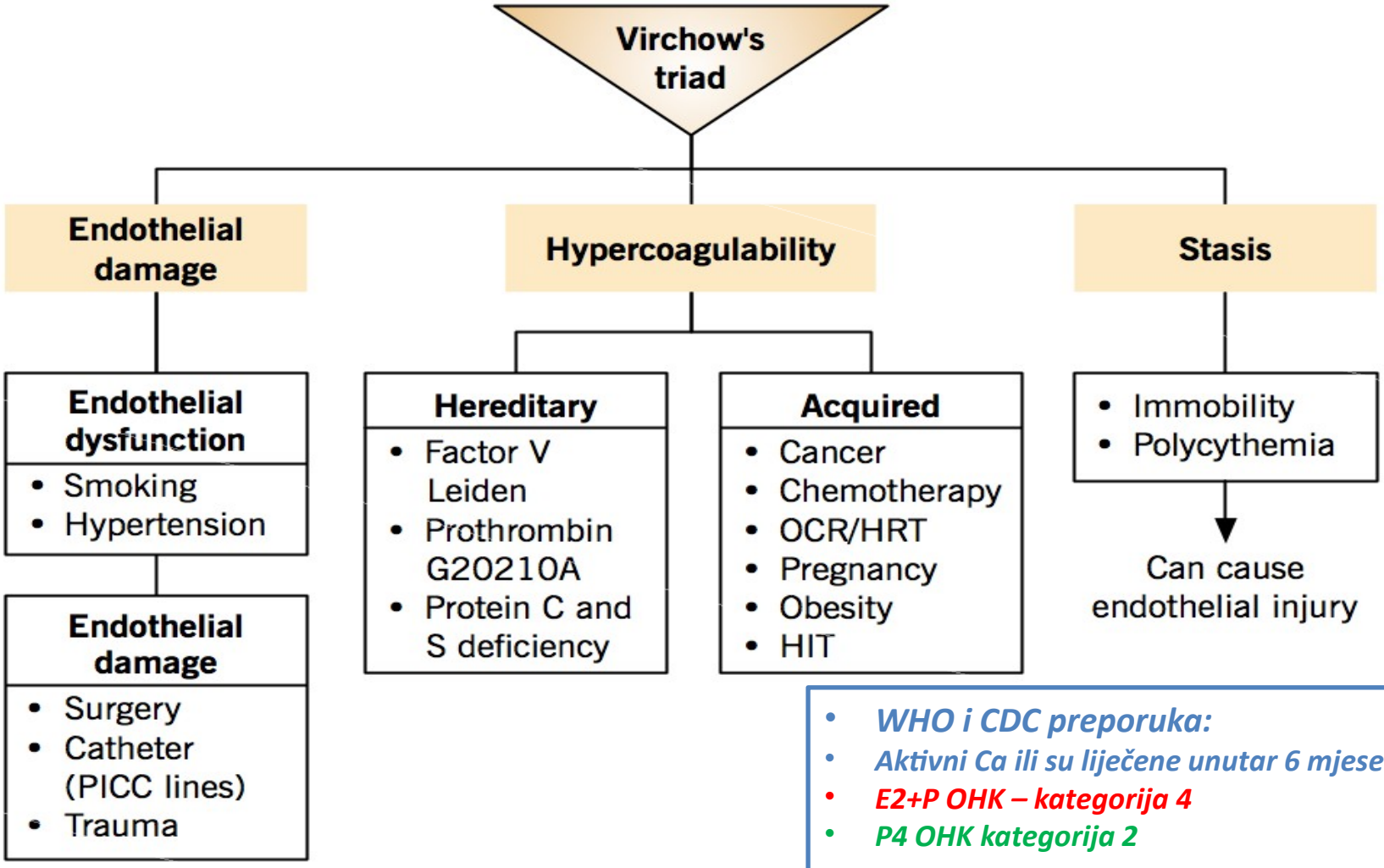
- *Poželjna opcija kod žena s hormonski aktivni tumorom 10 godina*
- *Menstruacijski grčevi i vaginalno krvarenje*

IMPLANTATI

- *3 godine*
- *Iregularna vaginalna krvarenja*
- *Nisu dostupni podaci za rizik raka/recidiva dojke*
- *Ne – za hormonski aktivne tumore ili torakalno zračenje*

Pitanja i preporuke

3. Povećani rizik za VTE i izbor kontracepcije



- *WHO i CDC preporuka:*
- *Aktivni Ca ili su liječene unutar 6 mjeseci*
- *E2+P OHK – kategorija 4*
- *P4 OHK kategorija 2*

WHO upute i klasifikacija medicinskih stanja za uporabu kontracepcije

1. ategorija
anje bez ograničenja za korištenje KOK
75-80%

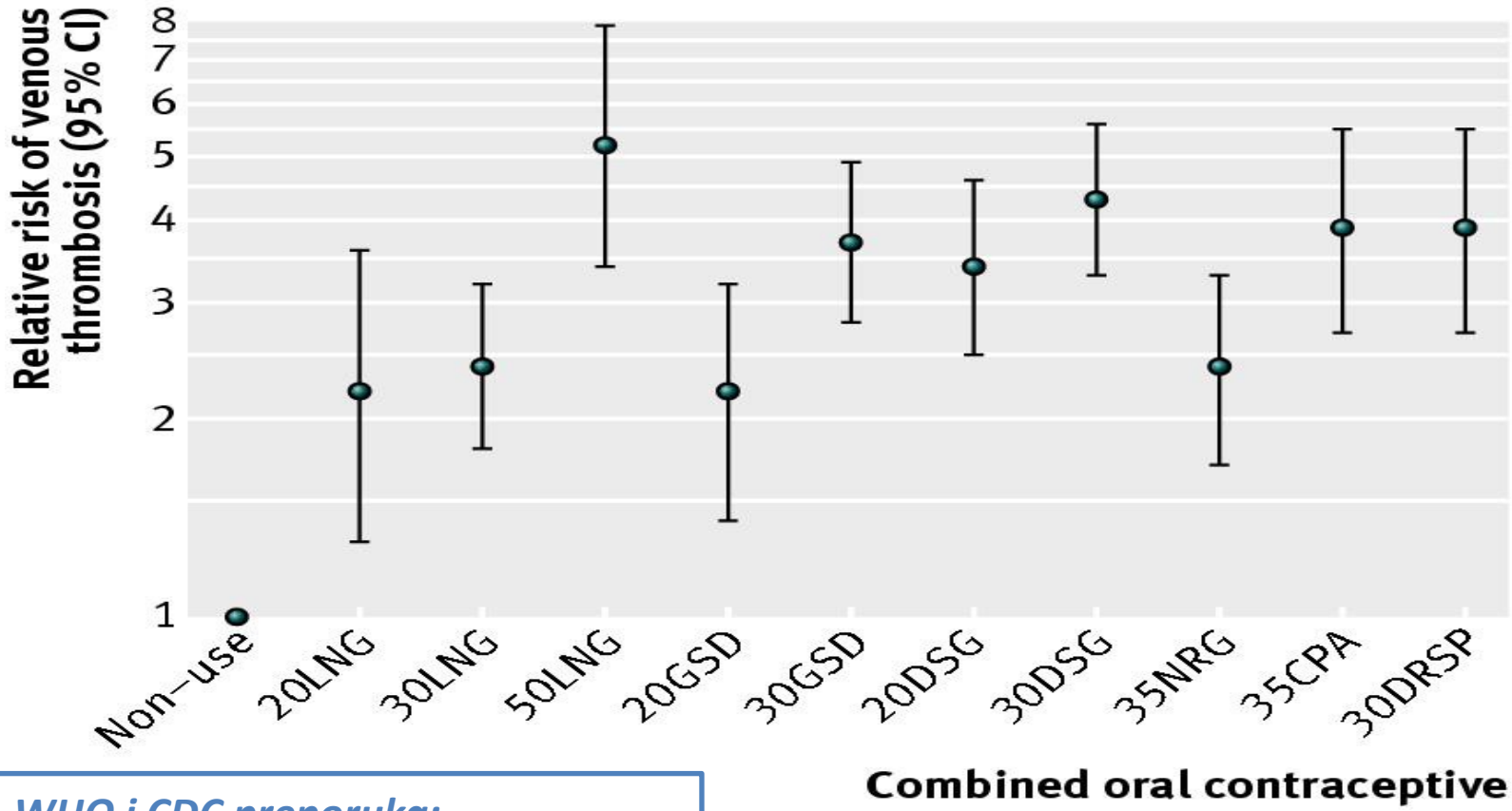
Kategorija
2. anja u kojih prednosti KOK nadmašuju
eoretski ili dokazani rizik
10-15%

Kategorija
3. anja u kojih teoretski ili dokazani rizici
admašuju prednosti KOK
7%

Kategorija
4. anja neprihvatljivog zdravstvenog rizika
z KOK
3%

Kombinirani oralni kontraceptivi : venska tromboza

50-80% viši od levonorgestrela



- ***WHO i CDC preporuka:***
- ***Aktivni Ca ili su liječene unutar 6 mjeseci***
- ***E2+P OHK – kategorija 4***
- ***P4 OHK kategorija 2***

Cochrane Database of Systematic Reviews
3 MAR 2014 DOI: 10.1002/14651858.CD010813.pub2
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010813.pub2/full#CD010813-fig-0004

Pitanja i preporuke

4. Komplikacije karcinoma i izbor kontraceptivne metode

ANEMIJA

Nekontracepcijski učinak
Sekundarna anemija – OoL, skraćeno preživljenje

Progesteronska kontracepcija
LEVONORGESTREL IUS
COOPER T 380 A
IMPLANTATI

OSTEOPOROZA

Komplikacija kemoterapije

DMPA rizik frakture
Implantati – BMD ulne i radijusa
LEVONORGESTREL IUS – nema negativan učinak na BMD
E kontraceptivi - ?

Pitanja i preporuke

4. Komplikacije karcinoma i izbor kontraceptivne metode

IMUNOSUPRESIJA | **TORAKALNO ZRAČENJE**

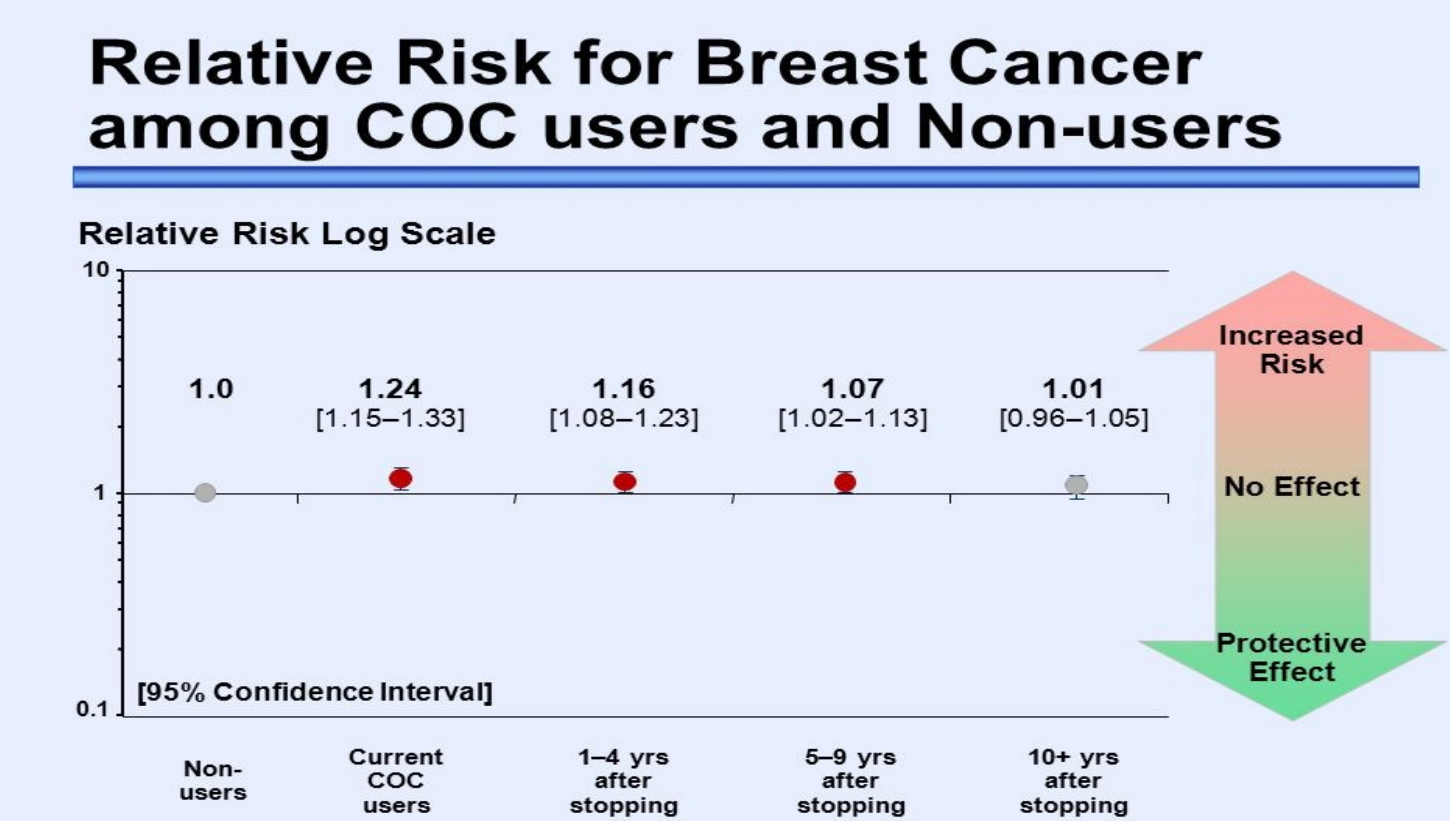
IUDs – sigurni (HIV pozitivni)
Bez PID i kontracepcijskog neuspjeha

Povećani rizik raka dojke

Cooper IUD T 380
LEVONORGESTREL IUS
E2+P4 OHK
PROGESTERONSKA KONTRACEPCIJA

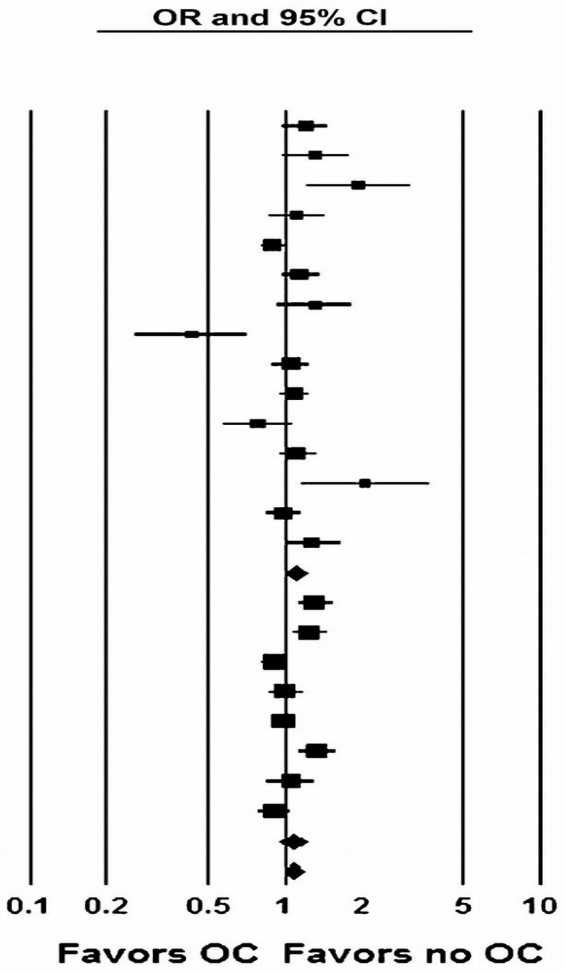
Pitanja i preporuke

5. Kontracepcija i rizik karcinoma ?



Relativni rizik OHK korisnice vs nekorisnice i incidencija raka dojke

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

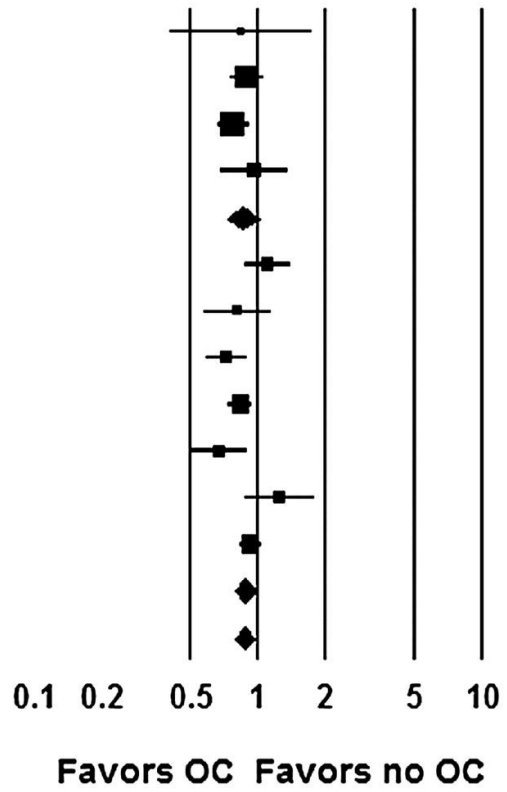


Jennifer M. Gierisch et al. Cancer Epidemiol Biomarkers Prev 2013;22:1931-1943

Korisnice vs nekorisnice OHK - kolorektalni karcinom.

- ***40-50%***

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



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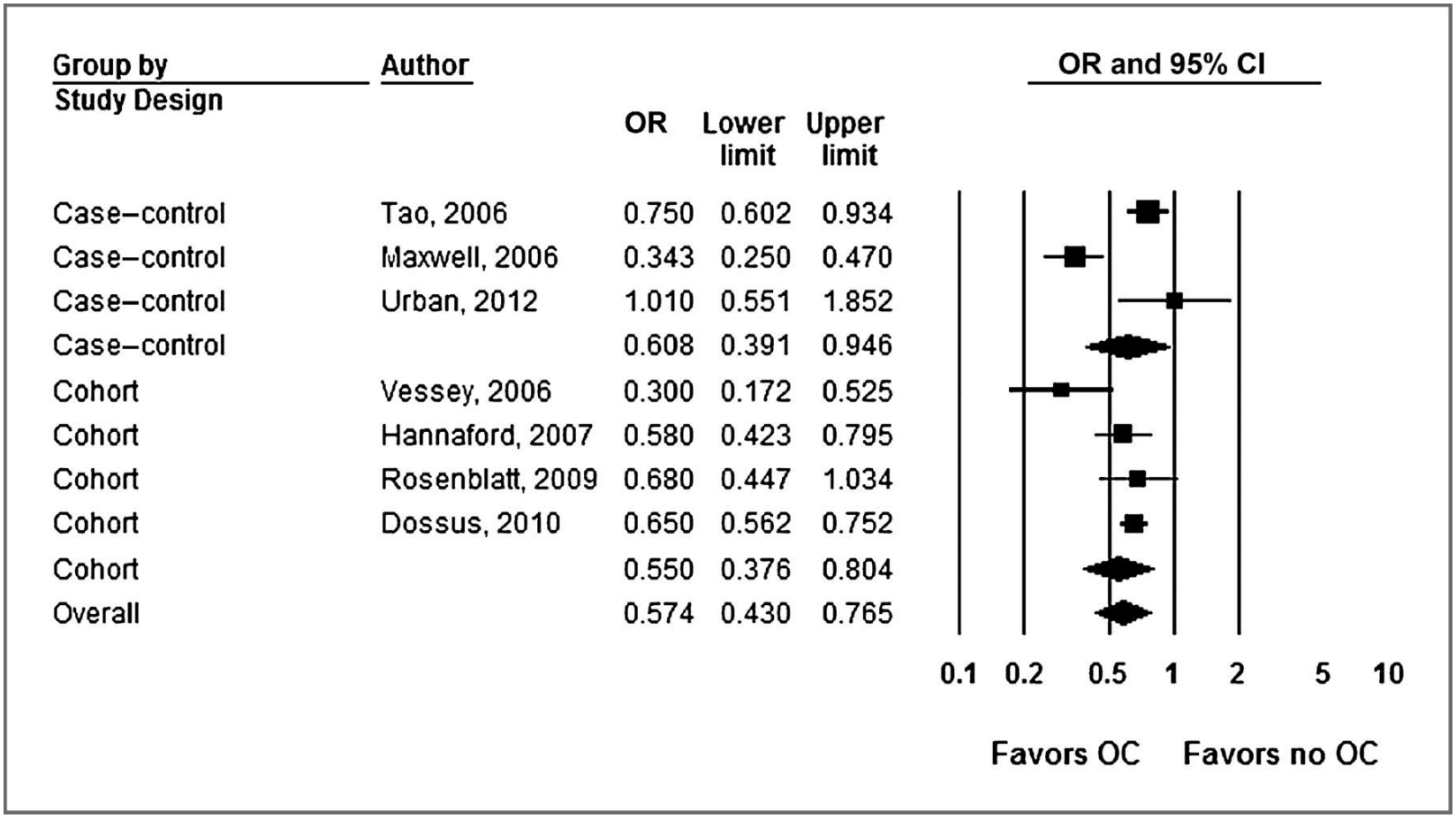
Korisnice vs nekorisnice OHK i incidencija endometrijskog karcinoma

50%



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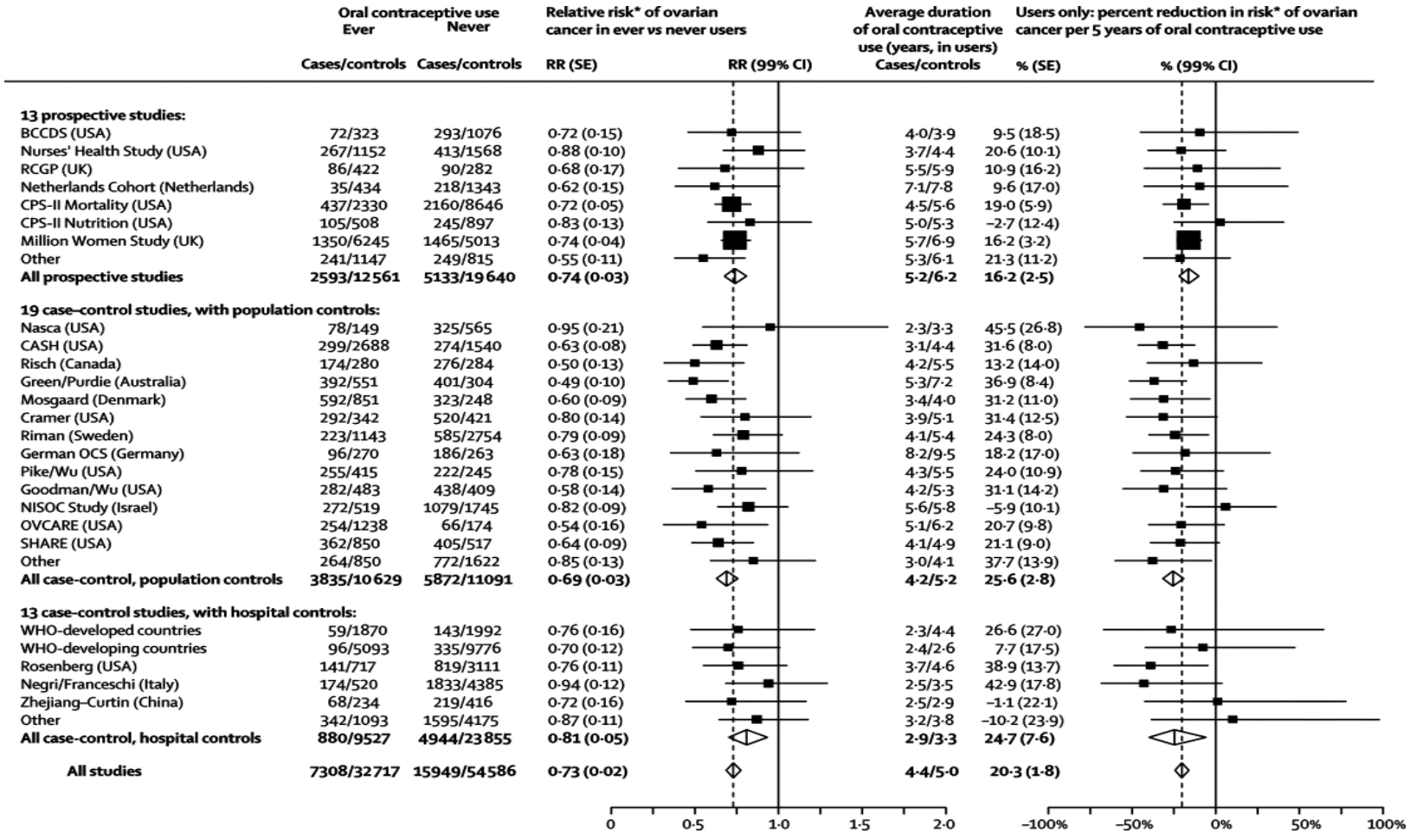
Korisnice vs nekorisnice OHK i rizik raka jajnika



Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23 257 women with ovarian cancer and 87 303 controls
Collaborative Group on Epidemiological Studies of Ovarian Cancer

Rizik karcinoma u korisnica hormonske kontracepcije

Studija	kontracepcija	Populacija	Dizajn i ishod	Nalaz
Beral V (2008)[51]	Oral contraceptives	General population	Case-control study of ovarian cancer	Reduced risk of ovarian cancer
Rosenblatt KA (2008)[54]	Oral contraceptives	Chinese textile workers	Cohort followed for 10 years for all and 12 site-specific cancers	No associations with risk of breast cancer or all cancers combined
Hannaford PC (2007)[50]	Oral contraceptives	General UK population	Large cohort study of all cancers	Less cancer of the large bowel, rectum, uterus, or ovaries
Wingo PA (2007) [53]	Oral contraceptives	General US population	Cohort and cancer registry study of breast cancer mortality	No effect
Collaborative Group on Hormonal Factors in Breast Cancer. (1996)[52]	Oral contraceptives	Women in 25 countries	Case control study of breast cancer	Small increase in relative risk of having breast cancer diagnosed
Vessey M (1989)[72]	Oral contraceptives	General UK population	20-year cohort study of breast, cervical, and ovarian cancer	No effect
Vessey M (1983)[59]	Oral contraceptives	General UK population	Case-control study of breast cancer diagnosis	No significant effect
Shapiro S (2000)[56]	Depomedroxy-progesterone acetate	South African women	Case-control study of breast cancer	No association
Backman T (2005)[60]	Levonorgestrel-IUD	General Finnish population	Incidence rates of breast cancer by IUD use in the Finnish Cancer Registry	No increased risk of breast cancer
International Collaborative Post-Marketing Surveillance of Norplant (2001)[47]	Norplant* contraceptive implant	Women in 8 developing countries	Post marketing surveillance, controlled cohort of all cancer	No increased risk

Schwarz EB. J Gen Intern Med 2009;24:401-8.

Pitanja i preporuke

6. Hitna kontracepcija – sigurni u žena s karcinomom ?

IUD cooper T 380 A – siguran i učinkovit

- ***WHO – nema medicinskog stanja u kojem rizici HK nadilaze njene dobrobiti***
- ***HK dostupna ženi sa dijagnosticiranim rakom dojke / liječenje***
- ***Primjena oralnih hitnih kontraceptiva u žena s (preboljelom) malignom bolešću nije ograničena bilo kakvim posebnim upozorenjem u dokumentaciji o lijekovima koju odobravaju nadležni regulatori.***

Casey PM. World J Clin Oncol 2014 October 10; 5(4): 693-704

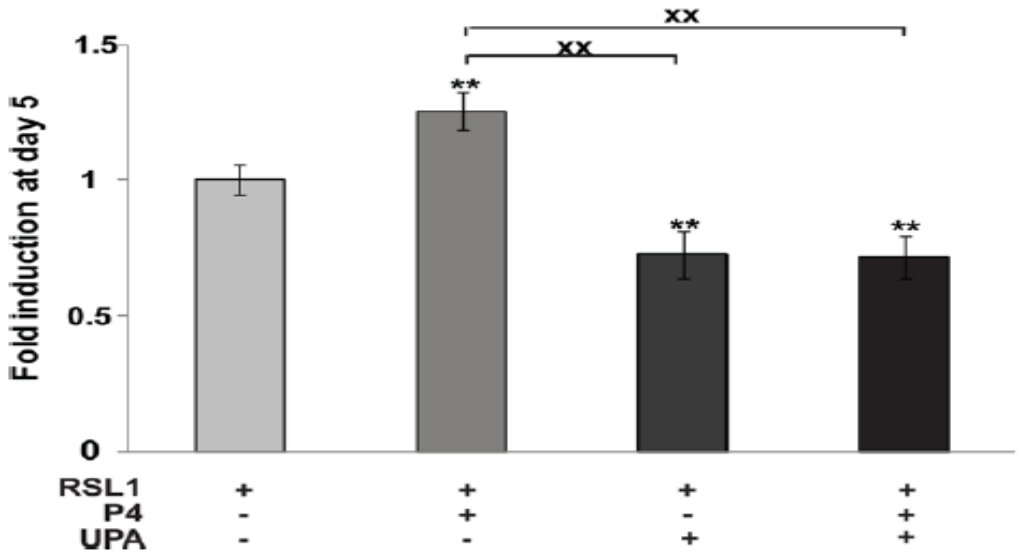


Fig 2. Ulipristal acetate (UPA) inhibits P4-dependent MDA-iPRA cell proliferation. MDA-iPRA cultured on 96-well plates, were treated with vehicle or P4 (1 nM) and/or UPA (1 μM) in fresh steroid-free medium containing DMSO or RSL1 (0.5 μM) on day 0, 2 and 4. Cell proliferation assays were performed using CellTiter96H AqueousOne Solution as described in Materials and Methods. The 490 nm absorbance was determined on day 1, 3 and 5. Data are expressed as fold induction compared to vehicle condition arbitrarily set at 1, and are means ± SEM from five independent cell cultures (n = 6 for each experiment). ** indicates $p<0.01$ compared to the vehicle-treated cells for each MDA-iPRA cell line while **xx** indicates $p<0.01$ compared to the P4-treated cells (non-parametric Mann Whitney t-tests).

doi:10.1371/journal.pone.0140795.g002

RESEARCH ARTICLE

Ulipristal Acetate Inhibits Progesterone Receptor Isoform A-Mediated Human Breast Cancer Proliferation and BCl_2-L_1 Expression

Nathalie Esber[1,2,3], Florian Le Billan[1,2], Michèle Resche-Rigon[3], Hugues Loosfelt[1,2], Marc Lombès[1,2,4], Nathalie Chabbert-Buffet[5,6]*

1 Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche-Scientifique 1185, Faculté de Médecine Paris Sud, Le Kremlin-Bicêtre, France, 2 Université Paris-Sud, Faculté de Médecine Paris Sud, Unité Mixte de Recherche-Scientifique 1185, Le Kremlin-Bicêtre, France, 3 HRA-Pharma, Paris, France, 4 Service d'Endocrinologie et des Maladies de la Reproduction, assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Le Kremlin Bicêtre, France, 5 Service de Gynécologie Obstétrique Médecine de la Reproduction, Hôpitaux Universitaires Est Parisien site Tenon, AP-HP, Paris, France, 6 Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche-Scientifique 938, Centre de Recherche Saint Antoine, Université Pierre et Marie Curie, Paris, France

- *UPA- inhibira staničnu proliferaciju*
- *Antiproliferacijski učinak UPA na zloćudne stanice raka dojke (protektivan učinak)*
- *Adjuvantna SPRM terapija*

Razina A – dobra i konzistentna znanstvena praksa

- *Kombinirana (E+P) OHK se ne preporuča za žene s aktivnim karcinomom ili manje od 6 mjeseci od završetka liječenja*

- *Rizik VTE*

- *žene s rakom dojke - Cooper T 380 IUD*

- *Žene s anemijom – levonorgestrel IUS*

Razina B – ograničeni ili nekonzistentni znanstveni dokazi

- *Žene s rakom dojke liječene tamoksifenom – levonorgestrel IUS*

  - *Smanjuje se rizik endometrijske patologije*
  - *Ne povećava rizik recidiva*

- *Žene – zračenja toraksa – kombinirano OHK NE*

- *Žene s osteopenijom i osteoporozom – izbjegavati POC*

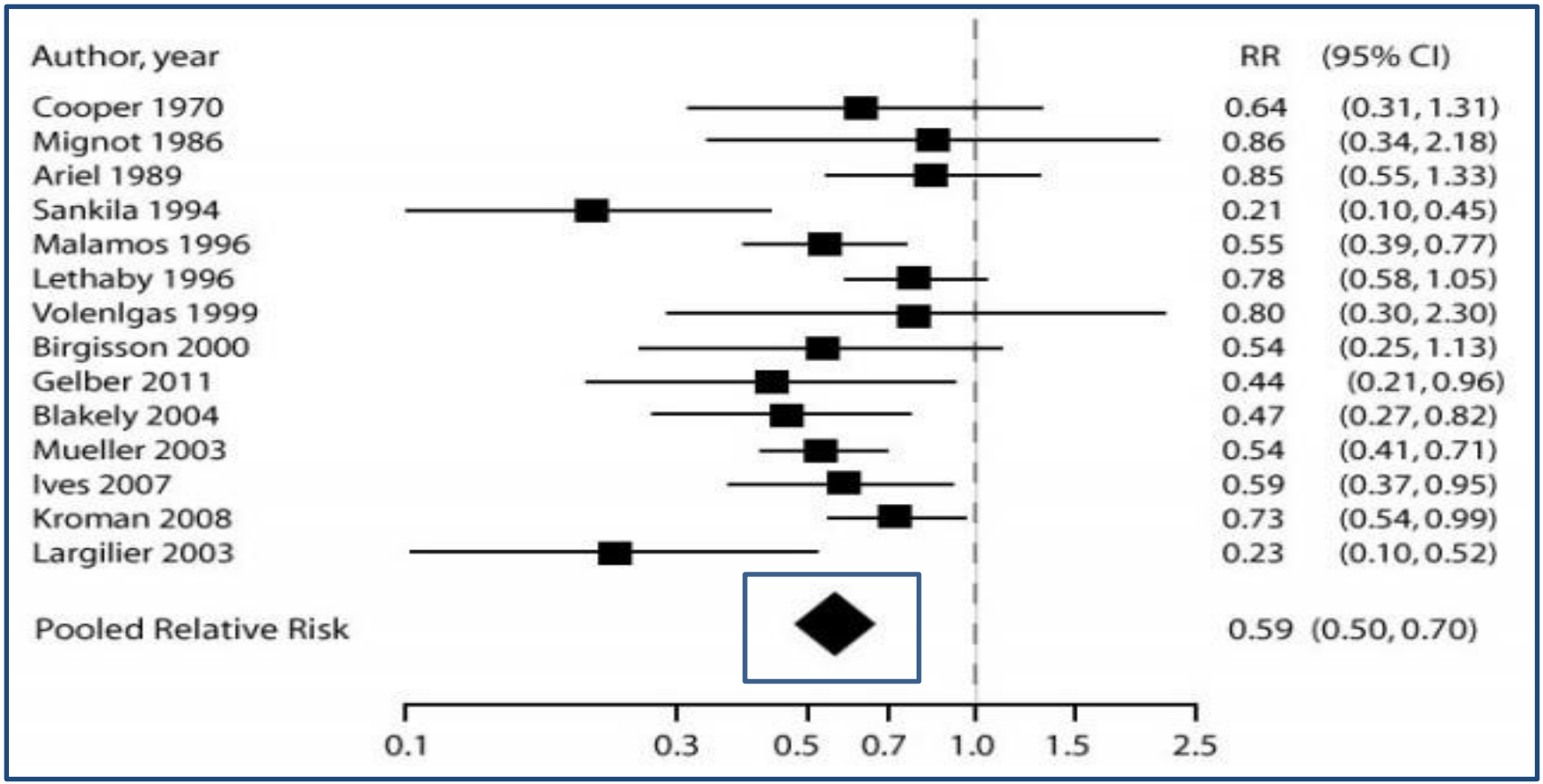
- *Žene s imunosupresijom – intrauterina kontracepcija DA*

- *Žena pod rizikom za rak dojke ili recidiv raka dojke - Hitna kontracepcija DA ako ne žele Cooper T 380 IUD*

Trudnoća i rak

- *Izbjeći trudnoću tijekom kemoterapije /zračenja zbog potencijalne teratogenosti*
- *Hormonski aktivni tumor – izbjeći trudnoću najmanje 3 godine od liječenja*
- *Nakon liječenja – nema rizika za opstetričke komplikacije ili da trudnoća povećava rizik recidiva*
- *Neki tipovi terapije (zračenja zdjelice i CNS-a, nealkilirajući agensi) – ne povećavaju rizik gubitka trudnoće i IUGR*

Sigurnost trudnoće nakon raka dojke



- "Healthly mother effects"

- Manji rizik ako je razmak > 2 g. zdravije žene koje su zanijele? preporučljivo > 5g. razmak

Overall survival analysis of women who became pregnant after cancer. Adapted from Azim HA, Jr., Santoro L, Pavlidis N, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer;47:74-83.

IZBOR KONTRACEPCIJSKE METODE

PERSONALIZIRANI PRISTUP

- *Dob pacijentice*
- *Tip karcinoma*
- *Ovarijska rezerva*
- *Komorbiditet*
- *Potencijalni nekontracepcijski učinak*
- *Neki kontraceptivi protektivni za neke vrste karcinoma*

- *NAJBOLJI KONTRACEPCIJSKI SAVJET*

- *OMOGUĆITI ŽENI DA SE TRUDNOĆA DOGODI U RAZDOBLJU OPTIMALNOG ZDRAVLJA*