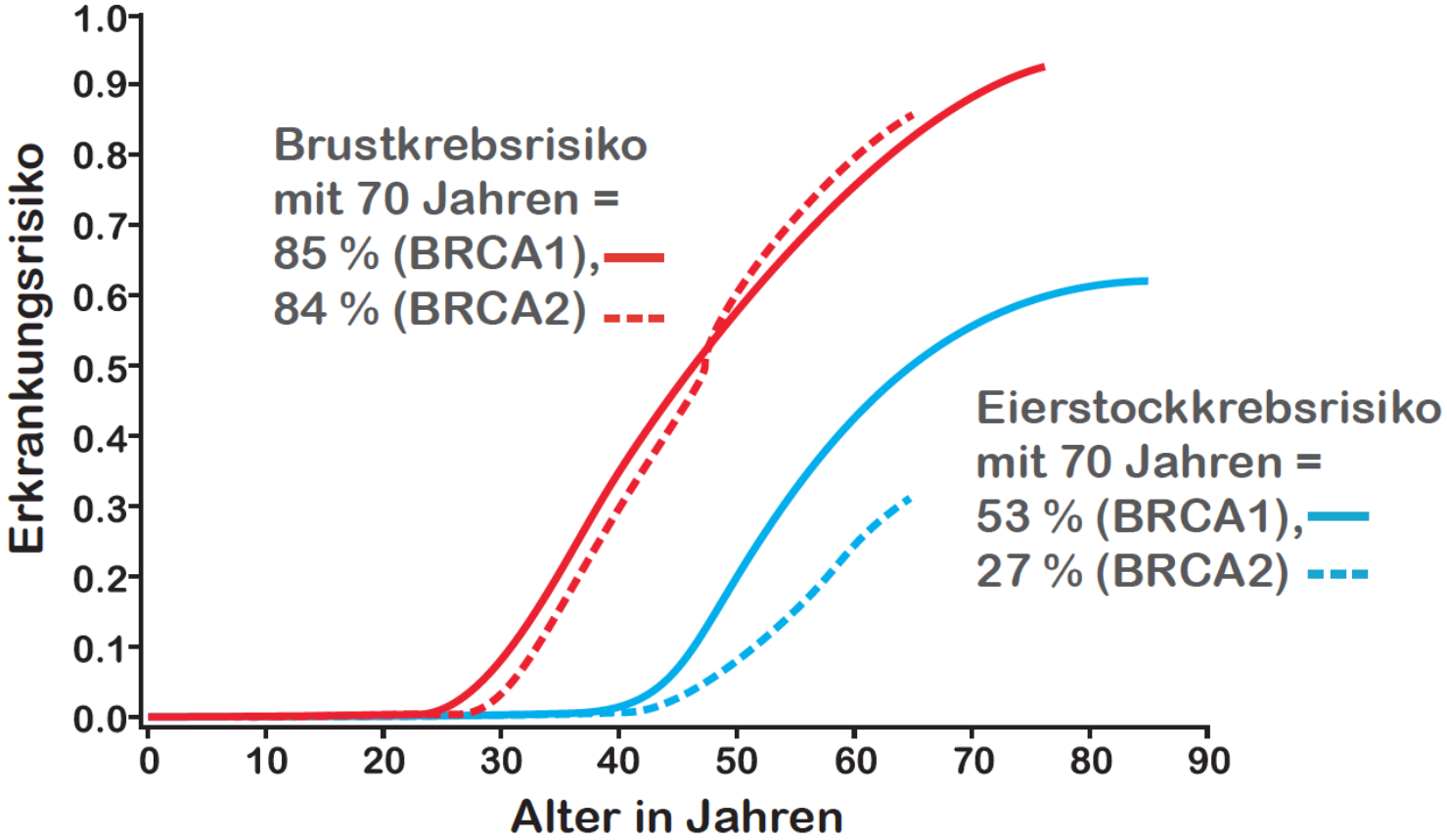
Prophylaktische bilaterale Adnexexstirpation

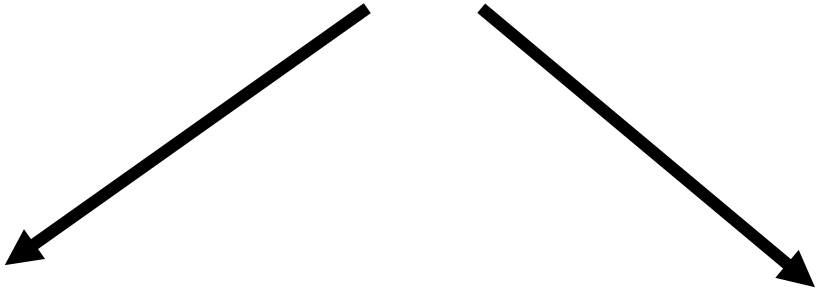
Assoc. Prof. Priv.-Doz. Dr. Christoph Grimm
Abteilung für allgemeine Gynäkologie und gynäkologische Onkologie

BRCA Erkrankungsrisiko



Procedere

Hochrisikopatientin



Früherkennung=
Screening

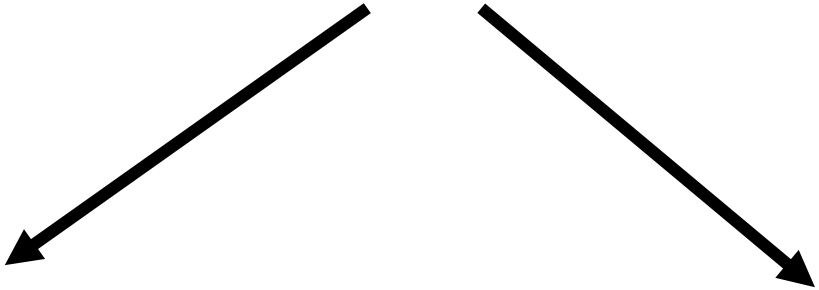
Ziel: Senkung der Mortalität

Vorsorge=
Prävention

Ziel: Senkung der Inzidenz
und infolge Mortalität

Procedere

Hochrisikopatientin



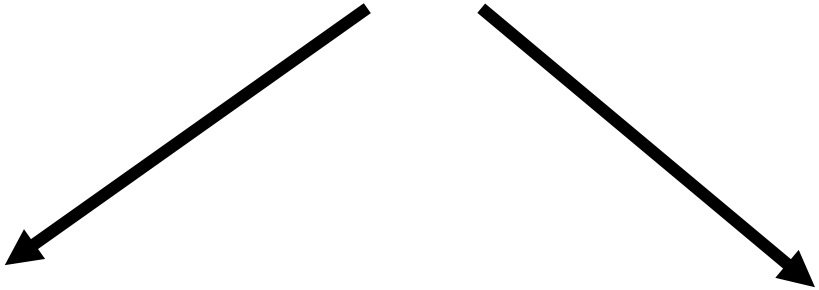
Früherkennung= Screening

Vorsorge= Prävention

Gut bei Mamma, schlecht bei Ovar (TVUS + CA-125)

Procedere

Hochrisikopatientin



Früherkennung=
Screening

Vorsorge=
Prävention

Chemoprävention: OC
Operative Prävention

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Oral Contraceptives and Risk of Ovarian Cancer and Breast Cancer Among High-Risk Women: A Systematic Review and Meta-Analysis

Chemoprävention - Orale Kontrazeptive

6476 BRCA 1/2 Mutationsträgerinnen

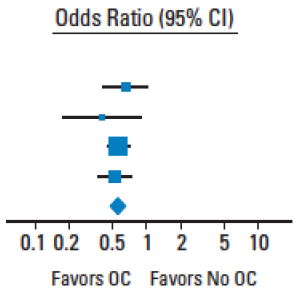
Inzidenz von Ovarialkarzinom und Mammakarzinom?

Moorman et al., JCO 2013

Ovarialkarzinom

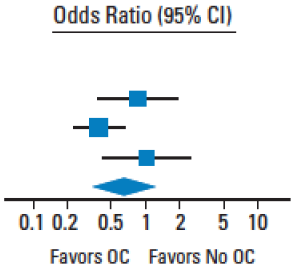
BRCA 1

	Odds Ratio	Lower Limit	Upper Limit
Whittemore I, 2004	0.650	0.410	1.030
Gronwald, 2006	0.400	0.180	0.889
McLaughlin, 2007	0.560	0.446	0.703
Antoniou, 2009	0.520	0.370	0.730
	0.552	0.466	0.655



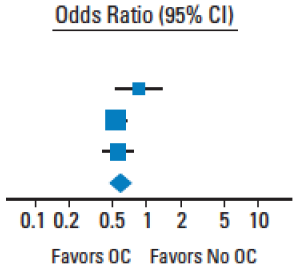
BRCA 2

	Odds Ratio	Lower Limit	Upper Limit
Whittemore II, 2004	0.860	0.380	1.948
McLaughlin, 2007	0.390	0.230	0.661
Antoniou, 2009	1.040	0.423	2.558
	0.649	0.339	1.244



BRCA 1/2

	Odds Ratio	Lower Limit	Upper Limit
Whittemore, 2004	0.850	0.523	1.381
McLaughlin, 2007	0.529	0.429	0.652
Antoniou, 2009	0.550	0.399	0.758
	0.582	0.464	0.730



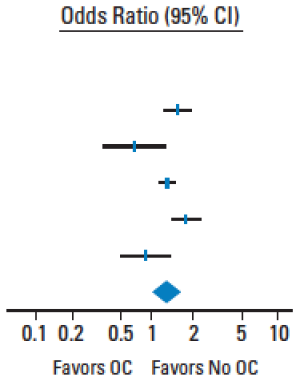
OR: 0.58
95%CI (0.46-

Fig 2 …en oral contraceptives and ovarian cancer among (A) *BRCA1* mutation carriers, (B) *BRCA2* mutation carriers, and (C) *BRCA1* and *BRCA2* mutation carriers combined. There was no significant heterogeneity in these analyses. (A) Q-value of 1.24 for 3 *df*, $P = .743$. (B) Q-value of 4.68 for 2 *df*, $P = .096$. (C) Q-value of 3.12 for 2 *df*, $P = .210$. OC, oral contraceptive.

Mammakarzinom

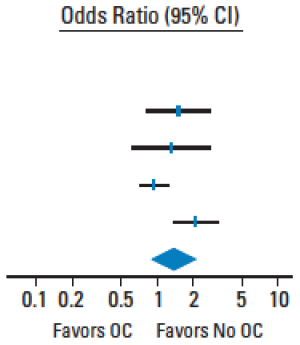
BRCA 1

	Odds Ratio	Lower Limit	Upper Limit
Brohet, 2007	1.470	1.131	1.911
Haile, 2006	0.640	0.352	1.165
Narod, 2002	1.200	1.024	1.406
Bernholtz, 2011	1.715	1.307	2.251
Gronwald, 2006	0.800	0.500	1.280
	1.191	0.916	1.548



BRCA 2

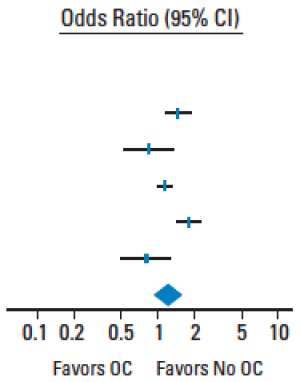
	Odds Ratio	Lower Limit	Upper Limit
Brohet, 2007	1.490	0.811	2.737
Haile, 2006	1.290	0.606	2.744
Narod, 2002	0.940	0.716	1.234
Bernholtz, 2011	2.070	1.339	3.201
	1.364	0.888	2.097



BRCA 1/2

	Odds Ratio	Lower Limit	Upper Limit
Brohet, 2007	1.473	1.158	1.874
Haile, 2006	0.839	0.525	1.341
Narod, 2002	1.128	0.984	1.293
Bernholtz, 2011	1.808	1.435	2.277
Gronw			

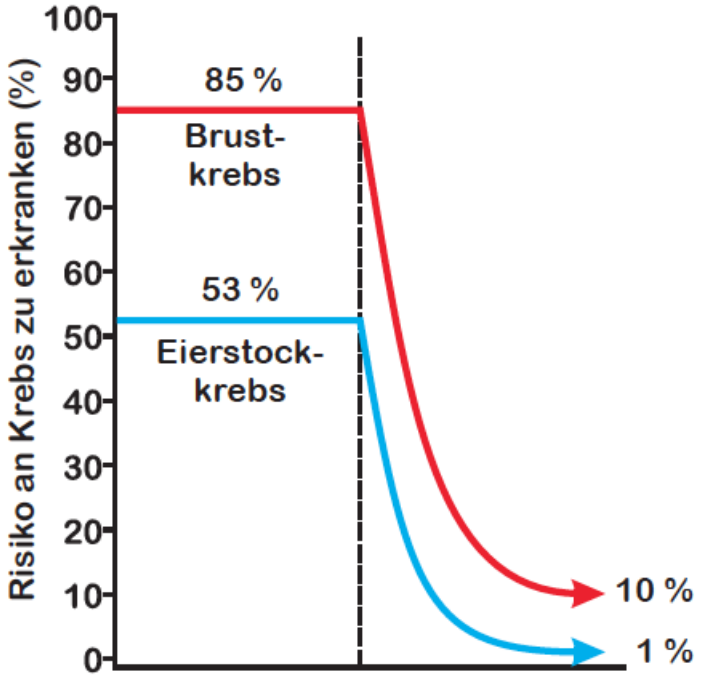
OR: 1.2 (n.s.)
95%CI (0.93-



Moorman et al., JCO 2013

Vorbeugende Operationen

- Vorbeugende Entfernung des Brust-gewebes (Prophylaktische Mastektomie)
- Vorbeugende Entfernung der Eierstöcke (Prophylaktische Ovarektomie)



pBSO: Mortalitätsreduktion!

Variable	No. of Patients	*BRCA1*			*BRCA2*			All Patients		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age group at study entry, years										
≤ 40	2,104	0.27	0.15 to 0.48	< .001	0.44	0.17 to 1.09	.08	0.30	0.19 to 0.49	< .001
41-50	1,906	0.23	0.16 to 0.33	< .001	0.29	0.14 to 0.59	< .001	0.24	0.17 to 0.33	< .001
51-60	1,189	0.28	0.19 to 0.43	< .001	0.19	0.08 to 0.43	< .001	0.27	0.18 to 0.38	< .001
≥ 61	584	0.43	0.25 to 0.71	.001	0.89	0.33 to 2.43	.84	0.49	0.31 to 0.76	.002
Total	5,783	0.30	0.24 to 0.38	< .001	0.33	0.22 to 0.50	< .001	0.31	0.26 to 0.38	< .001
Previous breast cancer										
Yes	2,561	0.31	0.24 to 0.39	< .001	0.34	0.22 to 0.52	< .001	0.32	0.26 to 0.39	< .001
No	2,633	0.21	0.12 to 0.37	< .001	0.67	0.08 to 5.35	.70	0.23	0.13 to 0.39	< .001

Finch, Singer, et al, JCO 2014

Operatives Management und Histologie

CAVEATS bei OP:

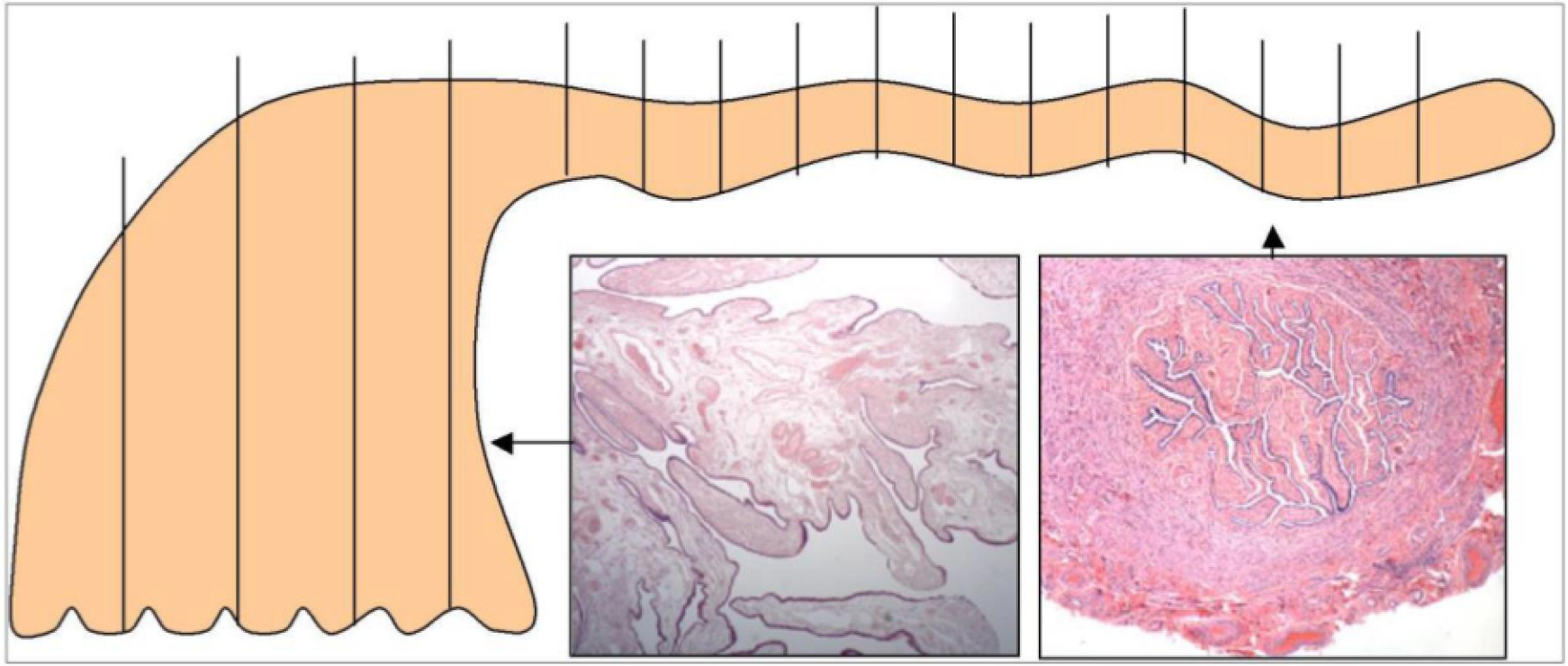
- Sorgfältiger Rundum-Blick;
- immer intraoperative Zytologie;
- sorgfältige histologische Aufarbeitung mittels SEEFIM-Protokoll (Risiko für okkultes OvCA und STICS!)

9% okkulte Ovarialkarzinome, davon 2/3 intraoperativ unauffällig

Finch, Singer, JCO 2014

SEE-FIM

sectioning and extensively examining the fimbriated ends



Folgen

- Osteoporose
- Sexualität
- Wechselbeschwerden

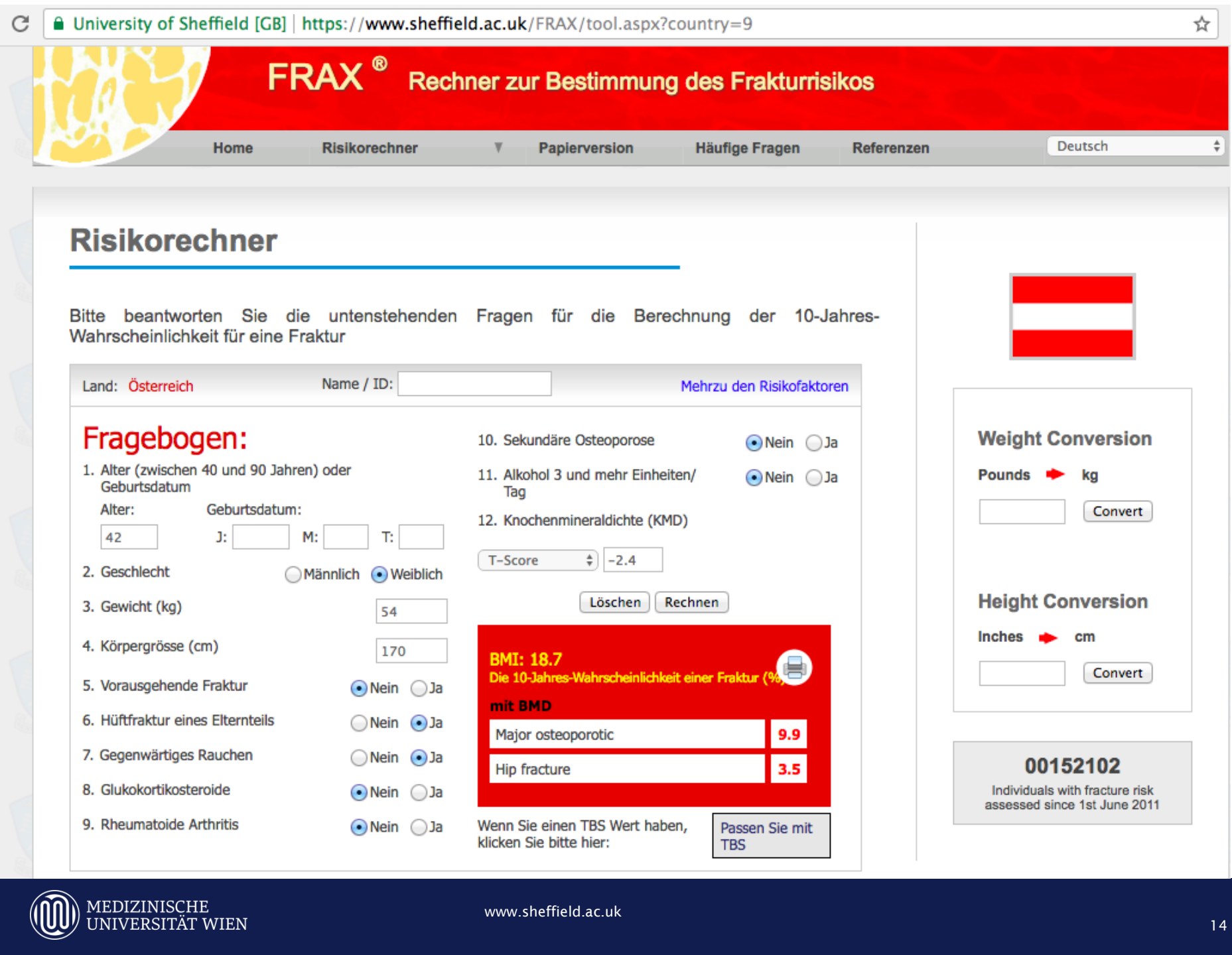
Osteoporose nach pBSO

- Heterogene Daten

Osteopenie	40-55%
Osteoporose	6-12%
Frakturen	4% (keine Erhöhung gegenüber Kontrollpopulation)

- Knochendichtemessung postoperativ: 36-75 %
- Knochendichtemessung: Basis + 1/2 Jahre postoperativ bzw. risikoadaptiert

Fakkert et al, EJC 2015
Garcia et al., Gynecol Oncol 2015


University of Sheffield [GB] | https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9
FRAX® Rechner zur Bestimmung des Frakturrisikos
Home
Risikorechner
Papierversion
Häufige Fragen
Referenzen
Deutsch
Risikorechner
Bitte beantworten Sie die untenstehenden Fragen für die Berechnung der 10-Jahres-Wahrscheinlichkeit für eine Fraktur
Land: Österreich
Name / ID:
Mehrzu den Risikofaktoren
Fragebogen:
1. Alter (zwischen 40 und 90 Jahren) oder Geburtsdatum
Alter: 42
Geburtsdatum: J: M: T:
2. Geschlecht Männlich Weiblich
3. Gewicht (kg) 54
4. Körpergrösse (cm) 170
5. Vorausgehende Fraktur Nein Ja
6. Hüftfraktur eines Elternteils Nein Ja
7. Gegenwärtiges Rauchen Nein Ja
8. Glukokortikosteroide Nein Ja
9. Rheumatoide Arthritis Nein Ja
10. Sekundäre Osteoporose Nein Ja
11. Alkohol 3 und mehr Einheiten/ Tag Nein Ja
12. Knochenmineraldichte (KMD)
T-Score -2.4
Löschen Rechnen
BMI: 18.7
Die 10-Jahres-Wahrscheinlichkeit einer Fraktur (%)
mit BMD
Major osteoporotic 9.9
Hip fracture 3.5
Wenn Sie einen TBS Wert haben, klicken Sie bitte hier:
Passen Sie mit TBS
Weight Conversion
Pounds kg
Convert
Height Conversion
Inches cm
Convert
00152102
Individuals with fracture risk assessed since 1st June 2011

Sexuelles Empfinden nach pBSO

- Sexuelle Dysfunktion 74%
- Red. Sexuelles Verlangen 73%
- Sex. Zufriedenheit 41%
- Dyspareunie 28%
- Wunsch nach mehr Information 59%

=> Topisches Östrogen: deutliche Besserung!

Tucker et al, Gynecol Oncol 2016, Campfield et al Fam. Cancer 2011

Wechselbeschwerden-HRT

- Wirksamkeit gBRCAm
- Safety
- Beginn (sofort postOP vs bei Symptomen)?
- Einflussfaktoren:
  - HE ja/nein
  - MammCA ja/nein
  - Mastektomie ja/nein
- 44-59% nehmen HRT nach pBSO ein

Finch et al 201, Gyneco Oncol., Vermeulen et al 2017 Euro. Journal of Cancer

Endokrine Symptome nach pBSO

Symptom	T1 HRT users	T1 HRT Non users	T1 GS	T3 HRT users	T3 HRT Non users	T3 GS
Hitzewallung	0%	0%	1%	8%	42%	5%
Kaltes Schwitzen	4%	0%	3%	4%	39%	7%
Nachtschweiß	7%	0%	7%	8%	39%	12%
Verlust Interesse an Sex	0%	0%	5%	0%	28%	4%

GS= gynäkologisches Screening, T1=präoperativ/ vor dem Screening, T3= 9 Monate postoperativ/ 12 Monate post Screeningstart

Vermeulen et al 2017 Euro. Journal of Cancer

Sicherheit der HRT

N=462 BRCA Mutationsträgerinnen ohne BC

pBSO : n=239

Table 3. Breast Cancer Risk Reduction After BPO Stratified by Postsurgical HRT Use

Variable		Total Sample			BPO Before Age 50		
		No.	HR	95% CI*	No.	HR	95% CI*
No surgery	No HRT	286	1.0	—	286	1.0	—
BPO	No HRT	62	0.38	0.09 to 1.59	50	0.59	0.14 to 2.52
BPO	Any HRT	93	0.37	0.14 to 0.96	89	0.30	0.11 to 0.85
BPO	E2 only	50	0.44	0.12 to 1.61	50	0.44	0.12 to 1.61
BPO	PROG ± E2	34	0.43	0.07 to 2.68	34	0.43	0.07 to 2.68

Abbreviations: BPO, bilateral prophylactic oophorectomy; HRT, hormone replacement therapy; HR, hazard ratio; E2, estrogen; PROG, progesterone.
*Adjusted for birth year, *BRCA1* versus *BRCA2*, center of ascertainment, and parity.

Rebbeck TR, Domchek S, JCO 2005

Beginn HRT

	Retrospektive Studie			Prospektive Studie		
Symptom	HRT users 77	HRT Non users 87	GS 286	HRT Users 26	HRT Non users 27	GS 93
Hitzewallung	20%	41%	2%	8%	42%	5%
Kaltes Schwitzen	23%	38%	2%	4%	39%	7%
Nachtschweiß	25%	39%	7%	8%	39%	12%
Verlust Interesse an Sex	16%	22%	4%	0%	28%	4%

GS= gynäkologisches Screening

HRT

- Hohes Risiko für BC : Mamma intakt
  - BRCA1m: HRT (Kombinationstherapie ohne HE, Östrogen Monotherapie bei St.p. HE)
  - BRCA2m: weniger Daten, HRT (vielleicht eher zurückhaltender)
- Mittleres Risiko für BC: St.p. Mastektomie
  - Kombinationstherapie ohne HE, Östrogen Monotherapie bei St.p. HE)
- St.p. Mamma CA:
  - HRT kontraindiziert
  - SSRI gegen vasomotorische Symptome
  - Lokale Östrogentherapie?

Finch et al, Women`s Health 2012

Lösung: prophTubektomie?

Testing Strategy	Estimated No. With Breast Cancer (% Risk Reduction Compared With Prophylactic [Bilateral] Salpingectomy at Age 40 y Alone)	Estimated No. With Ovarian Cancer (% Risk Reduction Compared With Prophylactic [Bilateral] Salpingectomy at Age 40 y alone)	Estimated No. of Deaths Attributed to Cardiovascular Disease
BRCA1 (n=700)			
Prophylactic (bilateral) salpingectomy at age 40 y	274	123	0
Prophylactic salpingectomy at age 40 y, prophylactic oophorectomy at age 50 y	273 (↓0.4%)	105 (↓14.6%)	0
Bilateral salpingo-oophorectomy at age 40 y	212 (↓22.6%)	95 (↓22.8%)	5
BRCA2 (n=1,600)			
Prophylactic (bilateral) salpingectomy at age 40 y	549	122	0
Prophylactic salpingectomy at age 40 y, prophylactic oophorectomy at age 50 y	543 (↓1.1%)	106 (↓13.1%)	0
Bilateral salpingo-oophorectomy at age 40 y	331 (↓39.7%)	97 (↓20.5%)	10

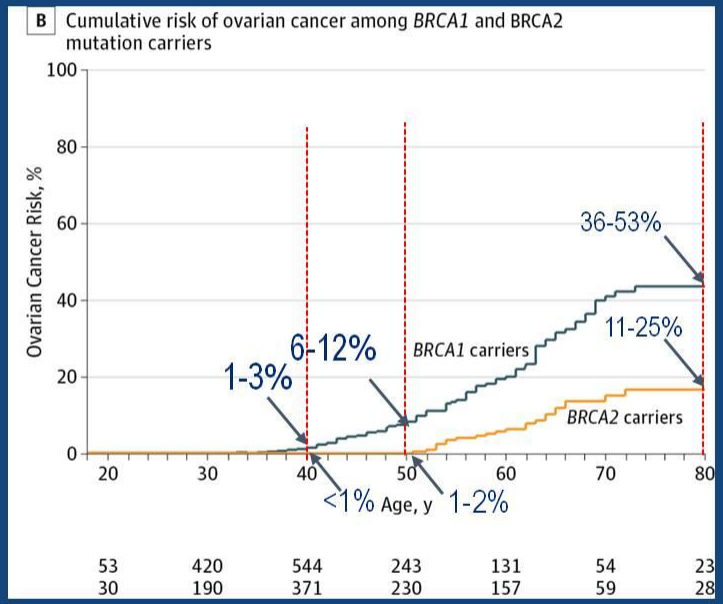
Kwon JS, Obs Gyn 2013

Synchrone Hysterektomie?

PRO	CONTRA
Tamoxifen Therapie	Höhere Morbidität
Hormonersatztherapie	Längerer Spitalsaufenthalt
Blutungen, Myome, etc	Komplexerer Eingriff

ProphBSO: News

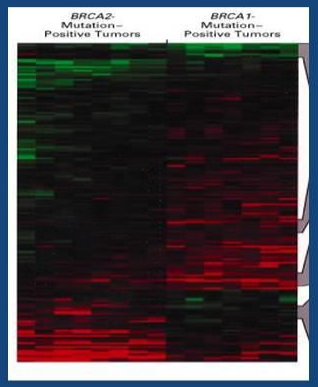
Cumulative Risks for Gynecologic Cancer in Carriers of *BRCA* Mutations (Prospective Cohort of 9856 Mutation Carriers)



Kuchenbaeker KB, et al. *JAMA*. 2017; 317:2402-16

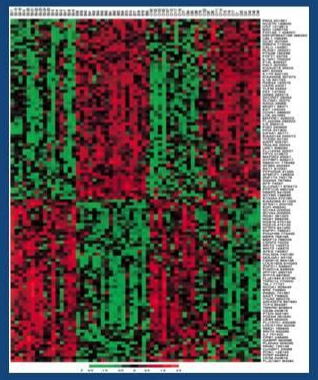
Mutations in *BRCA1* and *BRCA2* Cause Distinct Cancer Susceptibility Syndromes

- Breast Cancer
  - *BRCA1*: 10-24% ER positive
  - *BRCA2*: 65-79% ER positive
- Ovarian Cancer
  - *BRCA1*: 34-46% risk (to age 70)
  - *BRCA2*: 10-27% risk (to age 70)



Breast

Hedenfalk I, et al. NEJM 2002



Ovary

Jazaeri A, et al. JNCI 2002

Results Stratified by Mutation Status

					RRSO Follow-up from Time of Oophorectomy	
	Women Electing RRSO	Breast Cancers after RRSO	Women Electing Surveillance	Breast Cancers during Surveillance	Hazard Ratio	95% CI
BRCA1 and BRCA2	303	19	294	28	0.53	0.29 - 0.96
BRCA1	190	15	178	19	0.61	0.30 - 1.22
BRCA2	113	4	116	9	0.28	0.08 - 0.92

Results Treating RRSO as a Time-Dependent Covariate

					RRSO Follow-up from Time of Oophorectomy		RRSO Treated as a Time-Dependent Covariate	
	Women Electing RRSO	Breast Cancers after RRSO	Women Electing Surveillance	Breast Cancers during Surveillance	Hazard Ratio	95% CI	Hazard Ratio	95% CI
BRCA1 and BRCA2	303	19	294	28	0.53	0.29 - 0.96	0.57	0.31 - 1.05
BRCA1	190	15	178	19	0.61	0.30 - 1.22	0.68	0.33 - 1.38
BRCA2	113	4	116	9	0.28	0.08 - 0.92	0.30	0.09 - 1.00

HR for development of Breast Cancer following RRSO from Heemskerk-Gerritsen et al.

BRCA1: HR=1.21 (95% CI: 0.72 – 2.06)
BRCA2: HR=0.54 (95% CI: 0.17 – 1.66)

Study	Methods	HR for development of breast cancer following RRSO in BRCA2 mutation carriers
Kauff et al. JCO 2008 (re-analysis)	-RRSO treated as time-dependent covariate -F/U started from latest of ascertainment or genetic testing	HR = 0.30 (95% CI 0.09 - 1.00)
Heemskirk-Gerritsen et al. JNCI 2015	-RRSO treated as time-dependent covariate -F/U started from latest of ascertainment or genetic testing	HR = 0.54 (95% CI 0.17 - 1.66)
Kotsopoulus et al. JNCI 2017	-RRSO treated as time-dependent covariate -F/U started from latest of ascertainment or genetic testing	HR = 0.65 (95% CI 0.37 - 1.16)
Kotsopoulus et al. JNCI 2017 (limiting analysis to association with breast cancer diagnosed prior to age 50)	-RRSO treated as time-dependent covariate -F/U started from latest of ascertainment or genetic testing	HR = 0.18 (95% CI 0.05 - 0.63)

Zusammenfassung

- Nutzen der prophylaktischen Salpingoophorektomie

  OC Risiko 90% ↓

  Gesamtüberleben 70% ↑

- Differenz BRCA1m vs BRCA2m
  - Zeitpunkt für pBSO
  - +/- HE ??
  - Protektive Effekt auf MammaCA
- 2-zeitig??

  BS nach abgeschlossener Familienplanung

  BO postmenopausal

- Folgen
  - Vor OP besprechen!!, gezielte Therapie, HRT wenn notwendig

DKG
KREBSGESELLSCHAFT

Zertifiziertes
Gynäkologisches
Krebszentrum

MEDIZINISCHE
UNIVERSITÄT WIEN

Früherkennungsprogramm

Art der Untersuchung	Ab 18 LJ	Ab 25 LJ	Ab 35 LJ	Bei Bedarf
Gynäkologische Untersuchung	1 x jährlich			
Ärztliche Brustuntersuchung	1 x jährlich			
Brustultraschall				x
Mammografie			1 x jährlich	
Brust MRT		1 x jährlich		
Vaginalultraschall			**1 x jährlich**	
Tumormarker			**1 x jährlich**	

Outcome

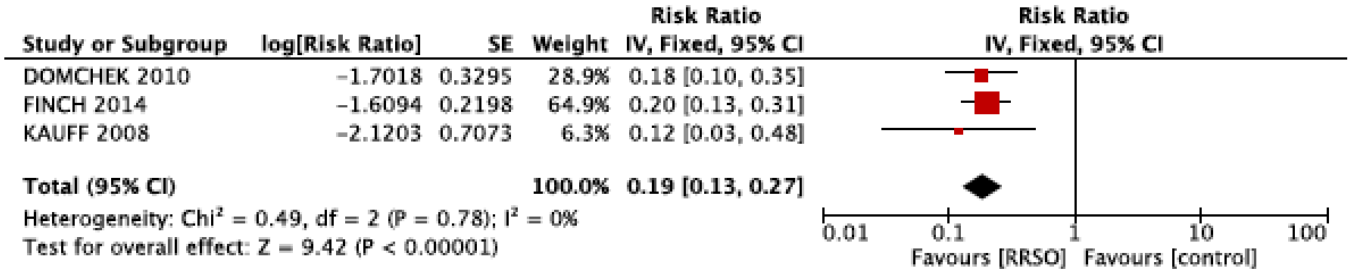


Figure 2 Forest plots of relative risk (RR) estimates for risk reduction of ovarian cancer associated with risk-reducing salpingo-oophorectomy in the overall population of BRCA 1 and BRCA 2 mutation carriers.

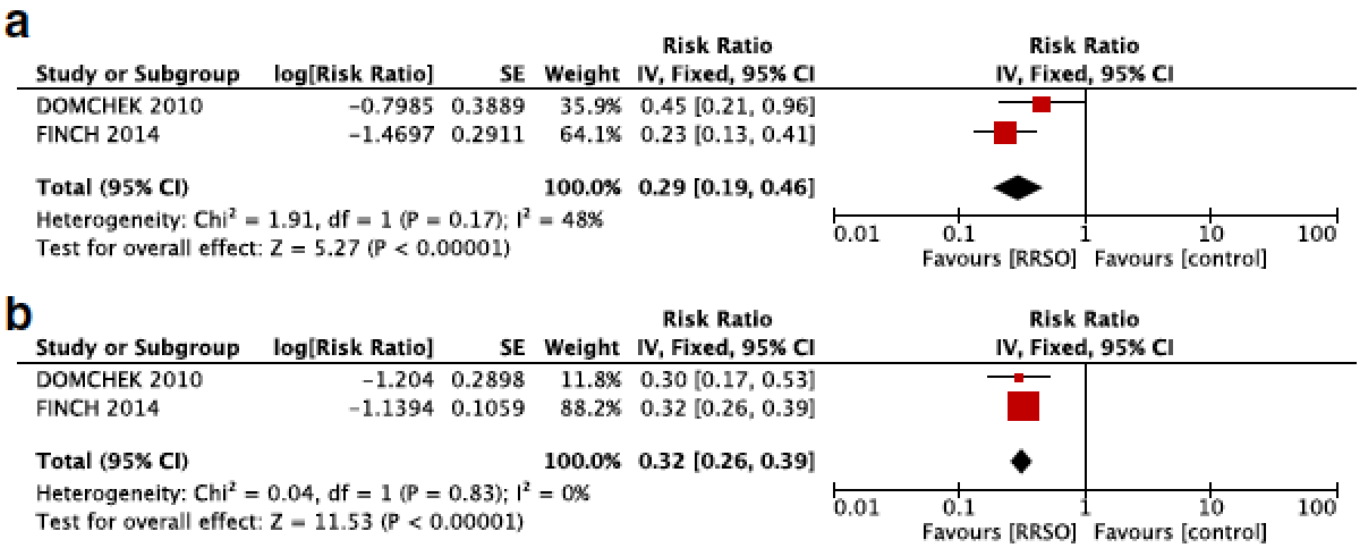


Figure 4 Forest plots of relative risk (RR) estimates for all-causes mortality associated with risk-reducing salpingo-oophorectomy in BRCA 1 and BRCA 2 mutation carriers without prior (a) and with prior breast cancer (b).

Prophylaktische bilaterale rrBSO

- **80-96%** Risikoreduktion für Ovarialkarzinom
- **30-75%** Risikoreduktion für Mammakarzinom (BRCA1 ***UND*** 2!), spätere Erkrankung
- Verbesserung des erkrankungsspezifischen Überlebens
- Verbesserung des Gesamtüberleben
- In Ö: **46% rrBSO** - Durchschnittsalter 44 Jahre
- Auch HE ansprechen
- Nutzen nimmt mit dem Alter ab

Rebbeck TR et al, N Engl J Med 2002, Domchek SM, JAMA 2010
Meijers-Heijboer, NEJM 2001
Hartmann, Lancet 2000

Chemoprävention?

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Oral Contraceptives and Risk of Ovarian Cancer and Breast Cancer Among High-Risk Women: A Systematic Review and Meta-Analysis

Orale Kontrazeptive

6476 BRCA 1/2 Mutationsträgerinnen

Inzidenz von Ovarialkarzinom und Mammakarzinom?

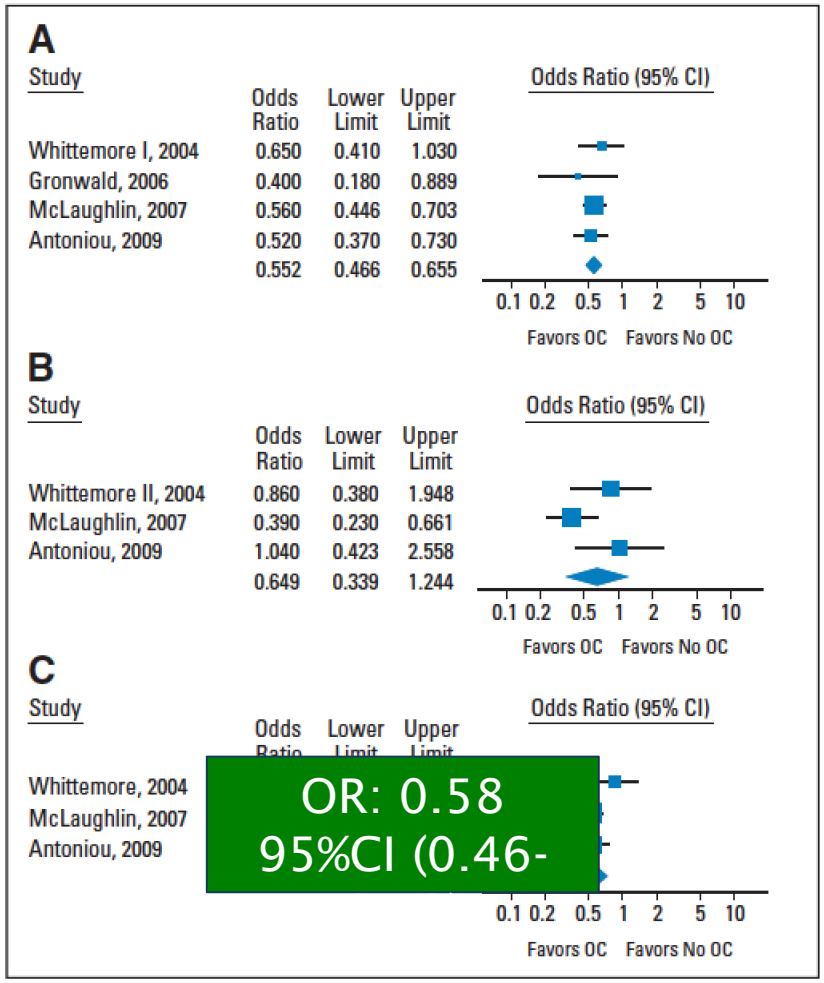
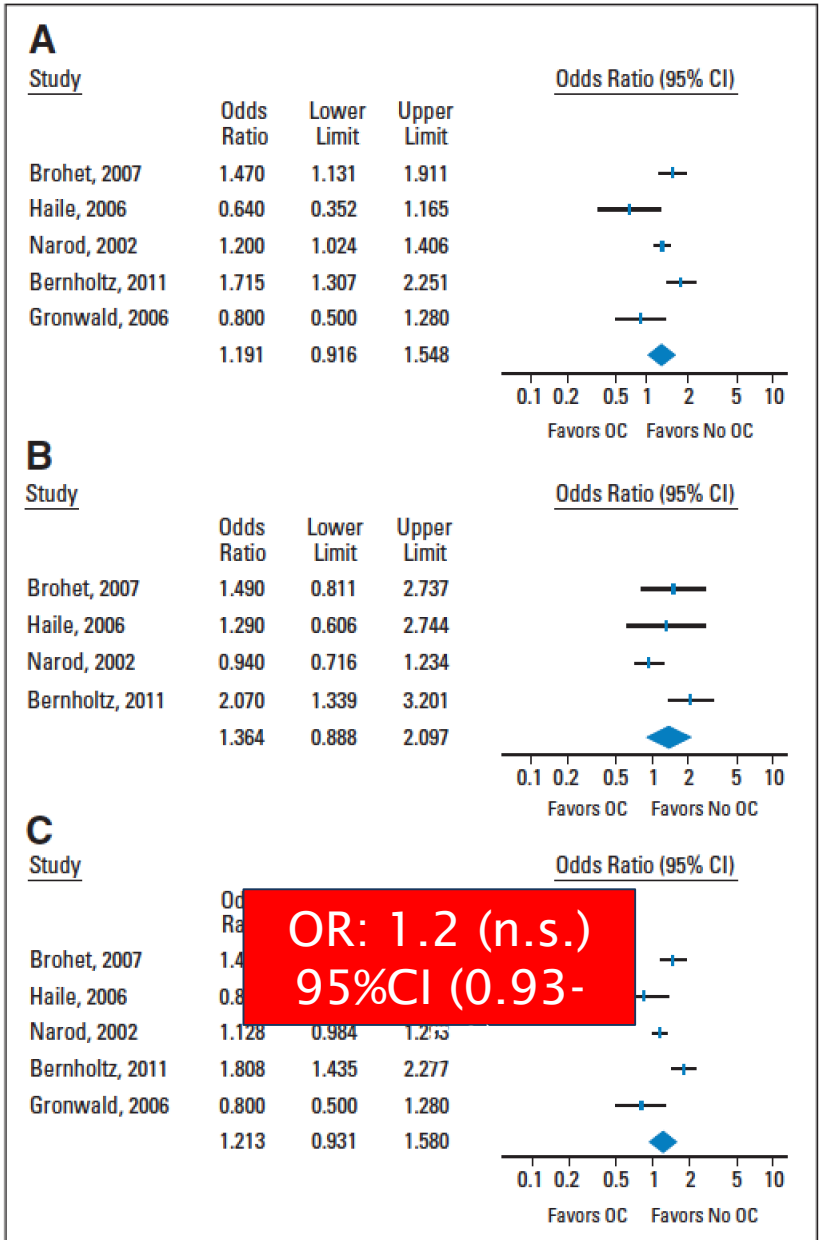


Fig 2. Forest plots for associations between oral contraceptives and ovarian cancer among (A) *BRCA1* mutation carriers, (B) *BRCA2* mutation carriers, and (C) *BRCA1* and *BRCA2* mutation carriers combined. There was no significant heterogeneity in these analyses. (A) Q-value of 1.24 for 3 *df*, $P = .743$. (B) Q-value of 4.68 for 2 *df*, $P = .096$. (C) Q-value of 3.12 for 2 *df*, $P = .210$. OC, oral contraceptive.



	United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS)
Studiendesign	Prospektive, Single-Arm CAVE: kein RCT
Teilnehmerinnen	3563 mit BRCA 1/2 Mutation oder belasteter Familienanamnese
Screening Strategie	Studienphase I: TVUS und CA125 jährlich Studienphase II: zusätzlich CA125 seriell alle 4 Monate + ROCA
CA 125 Interpretation	35 kU/l cut-off
Ergebnisse	Sensitivität 67-100% (OC)
Einfluss auf Outcome	30.8% (Phase I) und 42% (Phase II) Stadium I/II OC R0 nach OC OP: 62% vs 92%
Interpretation	Serielle CA 125 Messungen alle 4 Monate sensitiver, Screening im High-Risk Kollektiv nicht vergleichbar mit rrBSO
Status	Abgeschlossen