Klinische Studien bei MutationsträgerInnen

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Was sind klinische Studien?

- Untersuchungen, die Antworten auf wissenschaftliche Fragen geben und bessere Möglichkeiten zur Behandlung oder Prävention von Krankheiten erforschen sollen
- Finden mit freiwilligen Teilnehmern statt
- Unterscheiden sich in ihrem Studiendesign
- Zwei Haupttypen:
  - **Beobachtungsstudien** (z.B. Fall-Kontroll-, Kohorten-, Querschnittstudien)
    - Studienteilnehmerinnen bekommen keine studienbezogene Behandlung
    - Studienteilnehmerinnen werden in ihrer normalen Lebensführung beobachtet
  - **Interventionsstudie** (z.B. Randomisierte kontrollierte Studie)
    - Ein Teil der Teilnehmerinnen bekommt eine Behandlung („Intervention“) und ein anderer Teil der Teilnehmer bekommt keine Behandlung („Controls“)
    - die in einer kontrollierten, standardisierten und stark überwachten Umgebung durchgeführt werden
    - Nach einem Zeitintervall untersucht man den Effekt zwischen Interventions- und Kontrollgruppe

Warum sind klinische Studien so wichtig?

- Um herauszufinden, ob eine neue Behandlungsmöglichkeit sicher und wirksam ist
- Die Prävention, Erkennung und Behandlung von Krankheiten zu verbessern

Fragestellungen

- Einfluss von Lebensstil auf Penetranz
- Einfluss von genetischen Co-faktoren auf Penetranz
- Etablierung von polygenomischen Risiko-Scores
- Reklassifikation von UVs
- Therapeutische Studien
- Prophylaktische Studien
- Lebensqualität und Unterstützungsbedarf bei BRCA Mutationsträgern

Beobachtungsstudien

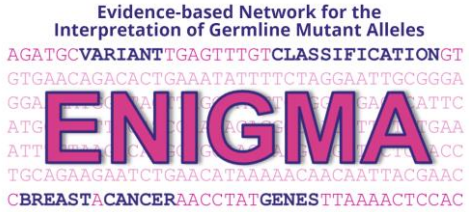
The International BRCA1/2 Carrier Cohort Study

- Initiiert im Jahr 1997 bei IARC, France
- 15 Studienzentrum aus Europa und Großbritannien

- **Ziel**
  1. Alters-, geschlechts- und mutationsspezifisches Krebsrisikos bei BRCA1/2 Mutationsträgern
  2. Einfluß von Lifestyle- und genetische Faktoren auf das Krebsrisiko
  3. Wirksamkeit von prophylaktischen Operationen und Früherkennungsmaßnahmen

The Consortium of Investigators of Modifiers of BRCA1/2

- Gegründet 2005 (Australien)
- >80 verschiedenen Gruppen aus Europa, Nord- und Südamerika, Asien und Afrika
- **Ziel**
  - Identifizierung genetischer Modifier, die das Krebsrisiko in BRCA Mutationsträgern beeinflussen
- Erfasst Genotyp- und Phänotypdaten z.B. Alter bei der Diagnose, Geschlecht, Familienanamnase usw.
- Bis heute:
  - phänotypdaten = ca. 80.000 weibliche und männliche BRCA1- und BRCA2-Mutationsträger
  - genotypisierte Daten = ca. 43.000
  - mit weiteren 25.000, die dieses Jahr genotypisiert werden sollen
- >70 Publikationen



- Internationales Konsortium (NCI finanziert)
- Gegründet 2009 (Australien)
- **Ziel**:
  - Klassifizierung der unklaren Veränderungen (unclassified variants)
  - Bereitstellung eines Rahmens für ein gemeinsames Vokabular in der klinischen Berichterstattung
- 30 Publikationen

Confluence

Uncovering breast cancer genetics

- Spin-off Projekt von CIMBA (2020) (NCI finanziert)
- Ein Multi-Konsortium Brustkrebs-GWAS-Projekt
- **Ziel**:
  - Entdeckung von Suszeptibilitäts-Loci und Erweiterung des Wissens über die Ätiologie von Brustkrebs insgesamt und nach Subtypen
  - Entwicklung von polygenen Risiko-Scores und deren Integration mit bekannten Risikofaktoren für eine personalisierte Brustkrebs-Risikobewertung
  - Entdeckung von Loci für die Brustkrebsprognose

Untersuchung des Therapieerfolges, der Lebensqualität und des Unterstützungsbedarfs von HochrisikopatientInnen

- **Ziele**
  - Therapieergebnisse weiblicher, erkrankter BRCA Trägerinnen zu evaluieren und zu vergleichen
  - Unterstützungsbedarf und Lebensqualität erkrankter Hochrisiko-PatientInnen zu identifizieren und zu evaluieren
  - Lebensqualität, Krebssorgen bzw. Progredienzangst zwischen gesunden und erkrankten Hochrisiko-PatientInnen zu vergleichen
- 400 Männer und Frauen rekrutieren
- Pilot study → response rate 56%

Ander Studien

- BRCA-assoziierter metastasierter Brustkrebs und PARP-Therapie (Pfizer finanziert)
- Brustkrebs-Hirnmetastasen
- BRCA-assoziierter Prostatakrebs
- Tumorspektrum und Familienanamnese bei Männern mit BRCA1/2-Mutation oder VUS
- Kontralaterales Brustkrebsrisiko bei Frauen mit BRCA1/2-MutationTrends
- Trends in der Inanspruchnahme von prophylaktischen Operationen bei Frauen mit einer BRCA1/2-Mutation

Einschlußkriterien

Männer und Frauen

- Gesund oder erkrankt
- Alter >18 Jahre
- Teilnahme an genetischer Beratung bzw. genetischer Testung
- Mutationsträger (BRCA1/2 oder anderen Brust- und Eierstockkrebs-Risiko-Genen)
- DNA-Probe vorhanden und Histopathologie-Daten, falls erkrankt
- Phänotyp-Daten verfügbar
- Unterschriebene Einverständniserklärung

Datenerhebung

Für alle Studien zusammen erfassen wir:

- Phänotyp-Daten
- Histopathologie-Daten (aus Pathologiebefunden)
- DNA-Proben (als Teil der Routineversorgung)
- Lebensstil und hormonelle Risikofaktoren (mit Hilfe von Fragebögen)
  - Baseline-Fragebogen zusammen mit Aufklärungsunterlagen
  - Follow-up-Fragebogen alle zwei Jahre
- Lebensqualität und Unterstützungsbedarf Faktoren (mit Hilfe von Fragebögen)
- Therapie- und Outcome-Daten

Clinical Trials

BRCA-P

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, International Phase 3 Study to determine the Preventive Effect of Denosumab on Breast Cancer in Women carrying a BRCA1 Germline Mutation

Conducted in:

Austria, United States of America, Australia, United Kingdom, Israel, Spain, Germany

Ziele

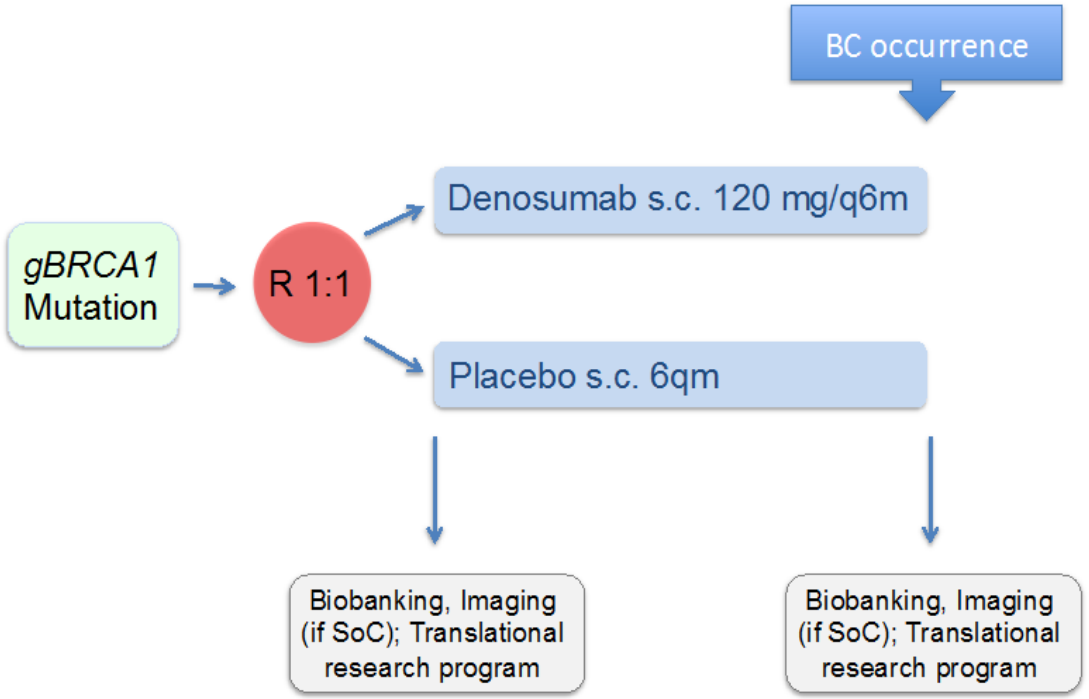
Primäres Ziel

Untersucht ob Denosumab eine sichere und wirksame Option zur Brustkrebsprävention ist

Sekundäre Ziele

- Untersucht, ob Denosumab das Risiko für Eierstockkrebs oder andere Krebserkrankungen reduziert,
- bewertet die Auswirkungen auf die Knochengesundheit, Nebenwirkungen und biologische Marker sowie die von Patienten berichtete Ergebnisse

Trial Design



- Sample size
  - 2918 patients from 7 countries
  - 1:1 randomized and blinded
  - Austria: 5 sites activated; 44 randomized participants
- Treatment arms
  - Arm A (Experimental): Denosumab 120mg s.c., q6m
  - Arm B (Placebo): Placebo s.c. q6m
- Daily calcium and vitamin D supplements highly recommended

Inclusion Criteria

- **Women**:
  - With a confirmed *BRCA1* germline mutation
  - Age between 25 and 55 years
  - No evidence of breast cancer by mammography or MRI within last 6 months
  - No clinical evidence of ovarian cancer
  - Negative pregnancy test in women of childbearing potential
  - No preventive breast surgery planned during the study period
  - ECOG performance status of 0 or 1
  - Ability to provide informed consent prior to start of study

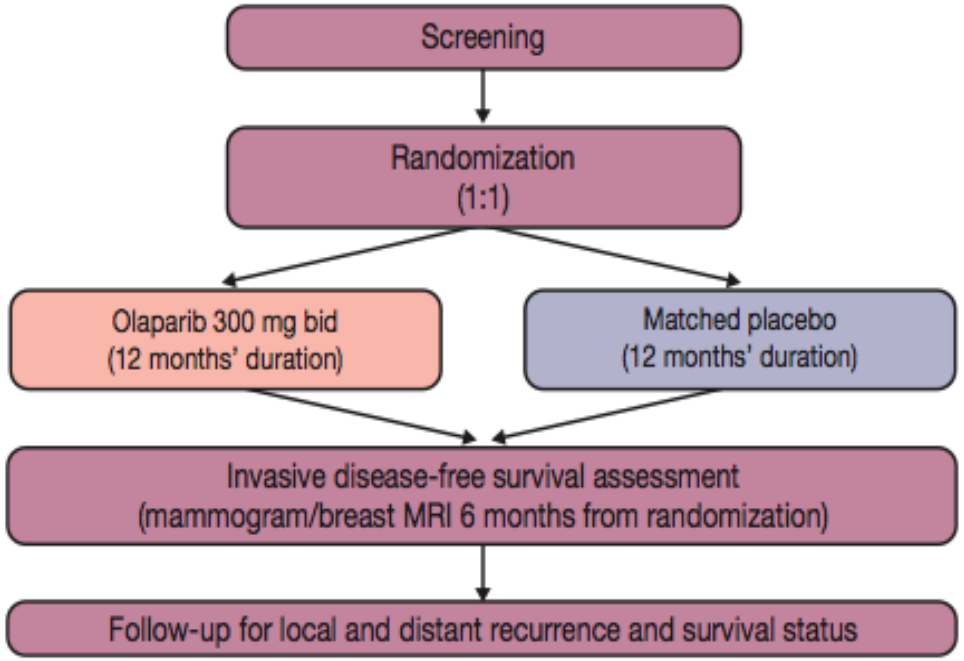
Exclusion Criteria

- Prior bilateral mastectomy
- History of breast cancer and/or ovarian cancer, including fallopian and peritoneal cancer
- History of other invasive cancer, except basal/squamous cell skin cancer or carcinoma in situ of the cervix or stage 1 papillary/follicular thyroid cancer
- Pregnant or lactating women (within last 2 months)
- Unwillingness to use contraception during and within 5 months after cessation of denosumab therapy
- Hypocalcemia or serum calcium <2.0mmol/L (8.0mg/dL)
- Prior use of denosumab
- Prior history or current evidence of osteonecrosis or osteomyelitis of the jaw, or active dental/jaw condition which requires oral surgery including tooth extraction within 3 months of enrolment
- Concurrent treatment with biphosphonate or anti-angiogenic agent
- Use of tamoxifen, raloxifene or aromatase inhibitor (HRT is permitted)

COMPLETED

OlympiA
Olaparib in adjuvant BRCAm breast cancer

Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer



- **Ziel**: Untersucht ob Olaparib den adjuvant Outcome verbessert
- Rekrutierung ca. 4 Jahre (2014-2019)
- 1,836 gBRCA-mutierte Frauen mit HER2-negativem Brustkrebs nahmen teil
- Prim Endpunkt: invasive Disease Free Survival (iDFS) d.h. Rezidiv oder neuer Krebs
- Presseaussendung (17.02.2021) Zwischenanalyse: Olaparib verbessert das adjuvante Outcome

Teilnahme an einer klinischen Studie

Wie kann man teilnehmen?

- **Mindestkriterien**:
  - 18+ Jahre
  - Unterschriebene Einwilligungserklärung

- Alle durchgeführten Studien, die Einwilligungserklärung und die verwendeten Fragebögen wurden von der Ethikkommission genehmigt (EK votum 2190/2019)

Publikationen

2020

JAMA Oncology | Original Investigation JAMA Oncol. 2020;6(8):1218-1230

Characterization of the Cancer Spectrum in Men With Germline *BRCA1* and *BRCA2* Pathogenic Variants

Results From the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)

Valentina Silvestri, PhD; Goska Leslie, MEng; Daniel R. Barnes, PhD; and the CIMBA Group

IMPORTANCE The limited data on cancer phenotypes in men with germline *BRCA1* and *BRCA2* pathogenic variants (PVs) have hampered the development of evidence-based recommendations for early cancer detection and risk reduction in this population.

OBJECTIVE To compare the cancer spectrum and frequencies between male *BRCA1* and *BRCA2* PV carriers.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of 6902 men, including 3651 *BRCA1* and 3251 *BRCA2* PV carriers, older than 18 years recruited from cancer genetics clinics from 1966 to 2017 by 53 study groups in 33 countries worldwide collaborating through the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Clinical data and pathologic characteristics were collected.

MAIN OUTCOMES AND MEASURES *BRCA1/2* status was the outcome in a logistic regression, and cancer diagnoses were the independent predictors. All odds ratios (ORs) were adjusted for age, country of origin, and calendar year of the first interview.

RESULTS Among the 6902 men in the study (median [range] age, 51.6 [18-100] years), 1634 cancers were diagnosed in 1376 men (19.9%), the majority (922 of 1,376 [67%]) being *BRCA2* PV carriers. Being affected by any cancer was associated with a higher probability of being a *BRCA2*, rather than a *BRCA1*, PV carrier (OR, 3.23; 95% CI, 2.81-3.70; $P < .001$), as well as developing 2 (OR, 7.97; 95% CI, 5.47-11.60; $P < .001$) and 3 (OR, 19.60; 95% CI, 4.64-82.89; $P < .001$) primary tumors. A higher frequency of breast (OR, 5.47; 95% CI, 4.06-7.37; $P < .001$) and prostate (OR, 1.39; 95% CI, 1.09-1.78; $P = .008$) cancers was associated with a higher probability of being a *BRCA2* PV carrier. Among cancers other than breast and prostate, pancreatic cancer was associated with a higher probability (OR, 3.00; 95% CI, 1.55-5.81; $P = .001$) and colorectal cancer with a lower probability (OR, 0.47; 95% CI, 0.29-0.78; $P = .003$) of being a *BRCA2* PV carrier.

CONCLUSIONS AND RELEVANCE Significant differences in the cancer spectrum were observed in male *BRCA2*, compared with *BRCA1*, PV carriers. These data may inform future recommendations for surveillance of *BRCA1/2*-associated cancers and guide future prospective studies for estimating cancer risks in men with *BRCA1/2* PVs.

Cancer Epidemiol Biomarkers Prev 2020;29:368–78

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION | RESEARCH ARTICLE

Alcohol Consumption, Cigarette Smoking, and Risk of Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers: Results from The BRCA1 and BRCA2 Cohort Consortium

Hongyan Li[1], Mary Beth Terry[2,3], Antonis C. Antoniou[4], Kelly-Anne Phillips[5,6,7], Karin Kast[8,9,10], Thea M. Mooij[11], Christoph Engel[12]; Catherine Noguès[13], Dominique Stoppa-Lyonnet[14,15], Christine Lasset[16], Pascaline Berthet[17], Veronique Mari[18], Olivier Caron[19]; for the GENEPSO study; Daniel Barrowdale[4], Debra Frost[4], Carole Brewer[20], D. Gareth Evans[21], Louise Izatt[22], Lucy Side[23], Lisa Walker[24], Marc Tischkowitz[25], Mark T. Rogers[26], Mary E. Porteous[27], Katie Snape[28]; for the EMBRACE study; Hanne E.J. Meijers-Heijboer[29], Johan J.P. Gille[29], Marinus J. Blok[30], Nicoline Hoogerbrugge[31]; for the HEBON Investigators; Mary B. Daly[32], Irene L. Andrulis[33,34], Saundra S. Buys[35], Esther M. John[36]; Sue-Anne McLachlan[37,38], Michael Friedlander[39,40]; for the kConFab Investigators; Yen Y. Tan[41], Ana Osorio[42], Trinidad Caldes[43], Anna Jakubowska[44,45], Jacques Simard[46], Christian F. Singer[41], Edith Olah[47], Marie Navratilova[48], Lenka Foretova[48], Anne-Marie Gerdes[49], Marie-José Roos-Blom[11], Brita Arver[50,51], Håkan Olsson[51], Rita K. Schmutzler[52,53], John L. Hopper[5], Roger L. Milne[5,54,55], Douglas F. Easton[4,56], Flora E. Van Leeuwen[11], Matti A. Rookus[11], Nadine Andrieu[57,58,59,60], and David E. Goldgar[1,61]

ABSTRACT

Background: Tobacco smoking and alcohol consumption have been intensively studied in the general population to assess their effects on the risk of breast cancer, but very few studies have examined these effects in *BRCA1* and *BRCA2* mutation carriers. Given the high breast cancer risk for mutation carriers and the importance of *BRCA1* and *BRCA2* in DNA repair, better evidence on the associations of these lifestyle factors with breast cancer risk is essential.

Methods: Using a large international pooled cohort of *BRCA1* and *BRCA2* mutation carriers, we conducted retrospective (5,707 *BRCA1* mutation carriers and 3,525 *BRCA2* mutation carriers) and prospective (2,276 *BRCA1* mutation carriers and 1,610 *BRCA2* mutation carriers) analyses of alcohol and tobacco consumption using Cox proportional hazards models.

Results: For both *BRCA1* and *BRCA2* mutation carriers, none of the smoking-related variables was associated with breast cancer risk, except smoking for more than 5 years before a first full-term pregnancy (FFTP) when compared with parous women who never smoked. For *BRCA1* mutation carriers, the HR from retrospective analysis (HR_R) was 1.19 [95% confidence interval (CI), 1.02–1.39] and the HR from prospective analysis (HR_P) was 1.36 (95% CI, 0.99–1.87). For *BRCA2* mutation carriers, smoking for more than 5 years before an FFTP showed an association of a similar magnitude, but the confidence limits were wider (HR_R = 1.25; 95% CI, 1.01–1.55 and HR_P = 1.30; 95% CI, 0.83–2.01). For both carrier groups, alcohol consumption was not associated with breast cancer risk.

Conclusions: The finding that smoking during the prereproductive years increases breast cancer risk for mutation carriers warrants further investigation.

Impact: This is the largest prospective study of *BRCA* mutation carriers to assess these important risk factors.

Barnes et al. Genetics in Medicine volume 22, pages1653–1666(2020)

ARTICLE Genetics inMedicine

Open

Polygenic risk scores and breast and epithelial ovarian cancer risks for carriers of *BRCA1* and *BRCA2* pathogenic variants

A full list of authors and their affiliations appears at the end of the paper.

Purpose: We assessed the associations between population-based polygenic risk scores (PRS) for breast (BC) or epithelial ovarian cancer (EOC) with cancer risks for *BRCA1* and *BRCA2* pathogenic variant carriers.

Methods: Retrospective cohort data on 18,935 *BRCA1* and 12,339 *BRCA2* female pathogenic variant carriers of European ancestry were available. Three versions of a 313 single-nucleotide polymorphism (SNP) BC PRS were evaluated based on whether they predict overall, estrogen receptor (ER)–negative, or ER-positive BC, and two PRS for overall or high-grade serous EOC. Associations were validated in a prospective cohort.

Results: The ER-negative PRS showed the strongest association with BC risk for *BRCA1* carriers (hazard ratio [HR] per standard deviation = 1.29 [95% CI 1.25–1.33], $P = 3\times10^{-72}$). For *BRCA2*, the strongest association was with overall BC PRS (HR = 1.31 [95% CI 1.27–1.36], $P = 7\times10^{-50}$). HR estimates decreased significantly with age and there was evidence for differences in associations by predicted variant effects on protein expression. The HR estimates were smaller than general population estimates. The high-grade serous PRS yielded the strongest associations with EOC risk for *BRCA1* (HR = 1.32 [95% CI 1.25–1.40], $P = 3\times10^{-22}$) and *BRCA2* (HR = 1.44 [95% CI 1.30–1.60], $P = 4\times10^{-12}$) carriers. The associations in the prospective cohort were similar.

Conclusion: Population-based PRS are strongly associated with BC and EOC risks for *BRCA1/2* carriers and predict substantial absolute risk differences for women at PRS distribution extremes.

Genetics in Medicine (2020) 22:1653–1666; https://doi.org/10.1038/s41436-020-0862-x

Key words: *BRCA1/2*; breast cancer; ovarian cancer; PRS; genetics

Patel et al. Cancer Res 2020;80:624–38

Association of Genomic Domains in *BRCA1* and *BRCA2* with Prostate Cancer Risk and Aggressiveness

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Abstract

Pathogenic sequence variants (PSV) in *BRCA1* or *BRCA2* (*BRCA1/2*) are associated with increased risk and severity of prostate cancer (PCa). We evaluated whether PSVs in *BRCA1/2* were associated with risk of overall PCa or high grade (Gleason 8+) PCa using an international sample of 65 *BRCA1* and 171 *BRCA2* male PSV carriers with PCa, and 3,388 *BRCA1* and 2,880 *BRCA2* male PSV carriers without PCa. PSVs in the 3' region of *BRCA2* (c.7914+) were significantly associated with elevated risk of PCa compared with reference bin c.1001-c.7913 (HR=1.78, 95%CI: 1.25–2.52, p=0.001), as well as elevated risk of Gleason 8+ PCa (HR=3.11, 95%CI: 1.63–5.95, p=0.001). c.756-c.1000 was also associated with elevated PCa risk (HR=2.83, 95%CI: 1.71–4.68, p=0.00004) and elevated risk of Gleason 8+ PCa (HR=4.95, 95%CI: 2.12–11.54, p=0.0002). No genotype-phenotype associations were detected for PSVs in *BRCA1*. These results demonstrate that specific *BRCA2* PSVs may be associated with elevated risk of developing aggressive PCa.

Mavaddat et al. Breast Cancer Research (2020) 22:8
https://doi.org/10.1186/s13058-020-1247-4

Breast Cancer Research

RESEARCH ARTICLE Open Access

Risk-reducing salpingo-oophorectomy, natural menopause, and breast cancer risk: an international prospective cohort of *BRCA1* and *BRCA2* mutation carriers

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Abstract

Background: The effect of risk-reducing salpingo-oophorectomy (RRSO) on breast cancer risk for *BRCA1* and *BRCA2* mutation carriers is uncertain. Retrospective analyses have suggested a protective effect but may be substantially biased. Prospective studies have had limited power, particularly for *BRCA2* mutation carriers. Further, previous studies have not considered the effect of RRSO in the context of natural menopause.

Methods: A multi-centre prospective cohort of 2272 *BRCA1* and 1605 *BRCA2* mutation carriers was followed for a mean of 5.4 and 4.9 years, respectively; 426 women developed incident breast cancer. RRSO was modelled as a time-dependent covariate in Cox regression, and its effect assessed in premenopausal and postmenopausal women.

Results: There was no association between RRSO and breast cancer for *BRCA1* (HR = 1.23; 95% CI 0.94–1.61) or *BRCA2* (HR = 0.88; 95% CI 0.62–1.24) mutation carriers. For *BRCA2* mutation carriers, HRs were 0.68 (95% CI 0.40–1.15) and 1.07 (95% CI 0.69–1.64) for RRSO carried out before or after age 45 years, respectively. The HR for *BRCA2* mutation carriers decreased with increasing time since RRSO (HR = 0.51; 95% CI 0.26–0.99 for 5 years or longer after RRSO). Estimates for premenopausal women were similar.
(Continued on next page)

OXFORD

JNCI Cancer Spectrum (2018) 00(0): pky023

doi: 10.1093/jncics/pky023
Article

ARTICLE

Oral Contraceptive Use and Breast Cancer Risk: Retrospective and Prospective Analyses From a BRCA1 and BRCA2 Mutation Carrier Cohort Study

Lieske H. Schrijver, Håkan Olsson, Kelly-Anne Phillips, Mary Beth Terry, David E. Goldgar, Karin Kast, Christoph Engel, Thea M. Mooij, Julian Adlard, Daniel Barrowdale, Rosemarie Davidson, Ros Eeles, Steve Ellis, D. Gareth Evans, Debra Frost, Louise Izatt, Mary E. Porteous, Lucy E. Side, Lisa Walker, Pascaline Berthet, Valérie Bonadona, Dominique Leroux, Emmanuelle Mouret-Fourme, Laurence Venat-Bouvet, Saundra S. Buys, Melissa C. Southey, Esther M. John, Wendy K. Chung, Mary B. Daly, Anita Bane, Christi J. van Asperen, Encarna B. Gómez Garcia, Marian J. E. Mourits, Marie-José Roos-Blom, Michael L. Friedlander, Sue-Anne McLachlan, Christian F. Singer, Lenka Foretova, Anne-Marie Gerdes, Trinidad Caldes, Edith Olah, Anna Jakubowska, Catherine Noguès, Nadine Andrieu, Douglas F. Easton, Flora E. van Leeuwen, John L. Hopper, Roger L. Milne, Antonis C. Antoniou, Matti A. Rookus; on behalf of EMBRACE, GENEPSO, BCFR, HEBON, kConFab, and IBCCS

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Abstract

Background: For BRCA1 and BRCA2 mutation carriers, the association between oral contraceptive preparation (OCP) use and breast cancer (BC) risk is still unclear.
Methods: Breast camcer risk associations were estimated from OCP data on 6030 BRCA1 and 3809 BRCA2 mutation carriers using age-dependent Cox regression, stratified by study and birth cohort. Prospective, left-truncated retrospective and full-cohort retrospective analyses were performed.
Results: For BRCA1 mutation carriers, OCP use was not associated with BC risk in prospective analyses (hazard ratio [HR] = 1.08, 95% confidence interval [CI] = 0.75 to 1.56), but in the left-truncated and full-cohort retrospective analyses, risks were increased by 26% (95% CI = 6% to 51%) and 39% (95% CI = 23% to 58%), respectively. For BRCA2 mutation carriers, OCP use was associated with BC risk in prospective analyses (HR = 1.75, 95% CI = 1.03 to 2.97), but retrospective analyses were inconsistent (left-truncated:

An wen kann ich mich wenden?

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Prüfungsfragen

Fragen 1

Klinische Studien unterscheiden sich in ihrem Studiendesign. Welcher Studientyp bewertet die Wirksamkeit der Behandlungsintervention in einer stark überwachten Umgebung und in der Regel unter stark ausgewählten Patientenstichproben? (2 richtige Antworten)

A. Prospektive Kohortenstudie

B. Querschnittstudie

C. Randomisierte kontrollierte Studie

D. Fall-Kontroll-Studie

E. Kontrollierte Interventionsstudie

Fragen 2

Ein Mutationsträger möchte an einer Forschungsstudie teilnehmen. Welche der folgenden Kriterien sind die Mindestteilnahmekriterien? (2 richtige Antworten)

A. Familienanamnase

B. Alter >18J

C. DNA-probe

D. Histopathologie-Daten

E. Einwilligungserklärung

Fragen 3

Welches Dokument ist zwingend notwendig, um Teilnehmer in klinische Studien einzuschreiben?

A. Studienprotokoll

B. Fallbericht-Formular

C. Prüfarzt-Broschüre

D. Einwilligungserklärung

E. Konformitätserklärung