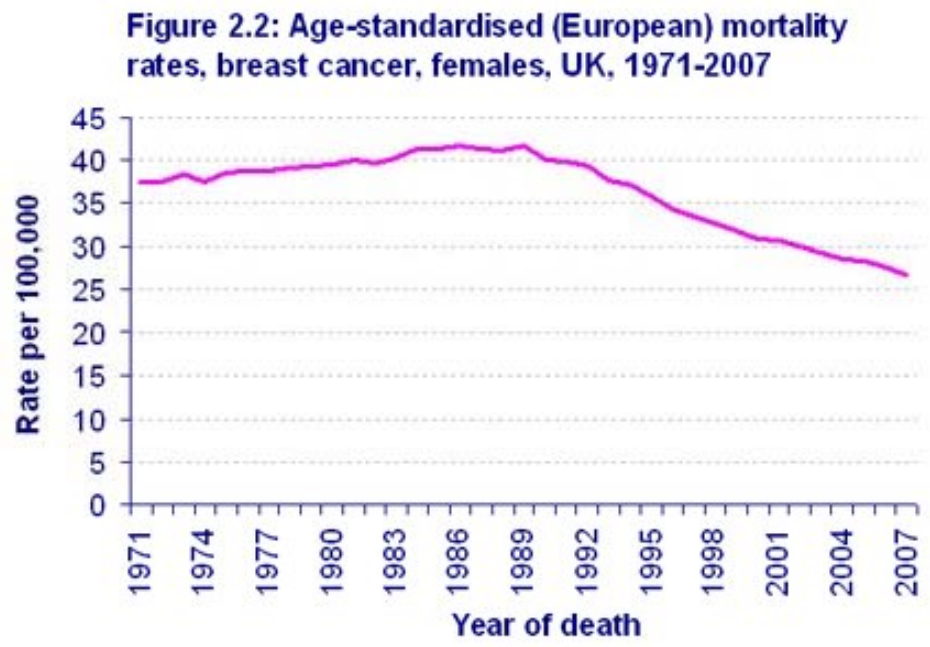
Pārmantotā vēža sindromu diagnostikas nozīme personalizētājā medicīnā

Prof. J. Gardovskis

Ievads

- Pēdējos 20 gadus vērojama krūts vēža mirstības samazināšanās
- Tomēr mirstības rādītāji joprojām augsti un nepieciešami jauni risinājumi



Ievads

- Vēža etioloģija un patoģenēze ir ļoti heterogēna un sarežģīta
- Esošās vēža morfoloģiski - molekulārās klasifikācijas sniedz nepilnīgu priekšstatu par dažādām vēža apkšgrupām, un to efektīvāko ārstēšanu
- Ģenētiski apstiprināti pārmantotā vēža gadījumi ir viena no perspektīvām individualizētās terapijas grupām

Ievads

Hum Mol Genet. 2011 May 19. [Epub ahead of print]

Low penetrance breast cancer susceptibility loci are associated with specific breast tumor subtypes: Findings from the Breast Cancer Association Consortium.

Broeks A, Schmidt MK, Sherman ME, Couch FJ, Hopper JL, Dite GS, Apicella C, Smith LD, Hammet F, Southey MC, Van 't Veer LJ, de Groot R, Smit VT, Fasching PA, Beckmann MW, Jud S, Ekici AB, Hartmann A, Hein A, Schulz-Wendtland R, Burwinkel B, Marme F, Schneeweiss A, Sinn HP, Sohn C, Tchatchou S, Bojesen SE, Nordestgaard BG, Flyger H, Orsted DD, Kaur-Knudsen D, Milne RL, Pérez JI, Zamora P, Rodríguez PM, Benítez J, Brauch H, Justenhoven C, Ko YD, Hamann U, Fischer HP, Brüning T, Pesch B, Chang-Claude J, Wang-Gohrke S, Bremer M, Karstens JH, Hillemanns P, Dörk T, Nevanlinna HA, Heikkinen T, Heikkilä P, Blomqvist C, Aittomäki K, Aaltonen K, Lindblom A, Margolin S, Mannermaa A, Kosma VM, Kauppinen JM, Kataja V, Auvinen P, Eskelinen M, Soini Y, Chenevix-Trench G, Spurdle AB, Beesley J, Chen X, Holland H, Lambrechts D, Claes B, Vandorpe T, Neven P, Wildiers H, Flesch-Janys D, Hein R, Löning T, Kosel M, Fredericksen ZS, Wang X, Giles GG, Baglietto L, Severi G, McLean C, Haiman CA, Henderson BE, Le Marchand L, Kolonel LN, Alnæs GG, Kristensen V, Børresen-Dale AL, Hunter DJ, Hankinson SE, Andrulis IL, Mulligan AM, O'Malley FP, Devilee P, Huijts P, Tollenaar RA, van Asperen CJ, Seynaeve C, Chanock SJ, Lissowska J, Brinton L, Peplonska B, Figueroa J, Yang XR, Hooning MJ, Hollestelle A, Oldenburg RA, Jager A, Kriege M, Ozturk B, van Leenders GJ, Hall P, Czene K, Humphreys K, Liu J, Cox A, Connley D, Cramp HE, Cross SS, Balasubramanian SP, Reed MW, Dunning AM, Easton DF, Humphreys MK, Caldas C, Lubinski J, Jakubowska A, Huzarski T, Byrski T, Cybulski C, Gorski B, Gronwald J, Brennan P, Sangrajrang S, Gaborieau V, Shen CY, Hsiung CN, Yu JC, Chen ST, Hsu GC, Hou MF, Huang CS, Anton-Culver H, Ziogas A, Pharoah PD, Garcia-Closas M.

Department of Experimental Therapy, The Netherlands Cancer Institute, Amsterdam, the Netherlands.

Abstract

Background: Breast cancers demonstrate substantial biological, clinical and etiologic heterogeneity. We investigated breast cancer risk associations of eight susceptibility loci identified in GWAS and two putative susceptibility loci in candidate genes in relation to specific breast tumor subtypes. Methods: Subtypes were defined by five markers (ER, PR, HER2, CK5/6, EGFR), and other pathological and clinical features. Analyses included up to 30,040 invasive breast cancer cases and 53,692 controls from 31 studies within the Breast Cancer Association Consortium. Results: We confirmed previous reports of stronger associations with ER+ than ER- tumors for six of the eight loci identified in GWAS: rs2981582 (10q26) (P-heterogeneity=6.1x10(-18)), rs3803662 (16q12) (P=3.7x10(-5)), rs13281615 (8q24) (P=0.002), rs13387042 (2q35) (P=0.006), rs4973768 (3p24) (P=0.003) and rs6504950 (17q23) (P=0.002). The two candidate loci, CASP8 (rs1045485, rs17468277) and TGFB1 (rs1982073), were most strongly related with the risk of PR negative tumors (P=5.1x10(-6) and P=4.1x10(-4), respectively), as previously suggested. Four of the eight loci identified in GWAS were associated with triple negative (TN) tumors (P≤0.016): (rs3803662 (16q12), rs889312 (5q11), rs3817198 (11p15), rs13387042 (2q35); however, only two of them (16q12 and 2q35) were associated with tumors with the core basal phenotype (P≤0.002). Conclusions: These analyses are consistent with different biological origins of breast cancers, and indicate that tumor stratification might help the identification and characterization of novel risk factors for breast cancer subtypes. This may eventually result in further improvements in prevention, early detection and treatment.

Biežākie ar vēža predispozīciju saistītie gēni

- BRCA1/2
- APC
- PTEN
- RET
- MLH1/MSH2/MSH6

BRCA1/2+

- **4-5%** no visiem krūts vēžiem Latvijā
  - 2000-2009
  - N-2546
  - (BRCA1+) 96 (3.77%; 95% Confidence Interval (CI) = 3.08 to 4.6)
  - (BRCA2+) 1%
- **10%** no visiem olnīcu vēžiem
- **2-3%** no visiem aizkuņģa dziedzera vēžiem
- **x%** no pārējo lokalizāciju vēžiem

- **Ideāls mērķis personalizētai terapijai**

BRCA1/2+

- Personalizētās terapijas medikamenti
  - Cisplatīns
  - PARP inhibitori
- Personalizētā ķirurģija
  - Mastektomija, arī tad, ja iespējama krūts saudzējoša operācija
  - Risku samazinošas operācijas
    - Mastektomija
      - Pretējās puses
        - » Ja pacientei krūts vēzis vienā pusē
      - Abpusēja
        - » Ja krūts vēzis nav vēl attīstījies
    - Adneksektomija

BRCA1/2+

Dtsch Arztebl Int. 2011 May;108(19):323-30. Epub 2011 May 13.

Hereditary breast and ovarian cancer: new genes, new treatments, new concepts.

Meindl A, Ditsch N, Kast K, Rhiem K, Schmutzler RK.

Abstract

BACKGROUND: Every year, 60 000 women in Germany are found to have breast cancer, and 9000 to have ovarian cancer. Familial clustering of carcinoma is seen in about 20% of cases.

METHODS: We selectively review relevant articles published up to December 2010 that were retrieved by a search in PubMed, and we also discuss findings from the experience of the German Consortium for Hereditary Breast and Ovarian Cancer.

RESULTS: High risk is conferred by the highly penetrant BRCA1 and BRCA2 genes as well as by other genes such as RAD51C. Genes for breast cancer that were originally designated as moderately penetrant display higher penetrance than previously thought in families with a hereditary predisposition. The role these genes play in DNA repair is thought to explain why tumors associated with them are sensitive to platin derivatives and PARP inhibitors. In carriers of BRCA1 and BRCA2, prophylactic bilateral mastectomy and adnexectomy significantly lowers the incidence of breast and ovarian cancer. Moreover, prophylactic adnexectomy also lowers the breast-and-ovarian-cancer-specific mortality, as well as the overall mortality. If a woman bearing a mutation develops cancer in one breast, her risk of developing cancer in the other breast depends on the particular gene that is mutated and on her age at the onset of disease.

CONCLUSION: About half of all monogenically determined carcinomas of the breast and ovary are due to a mutation in one or the other of the highly penetrant BRCA genes (BRCA1 and BRCA2). Women carrying a mutated gene have an 80% to 90% chance of developing breast cancer and a 20% to 50% chance of developing ovarian cancer. Other predisposing genes for breast and ovarian cancer have been identified. Clinicians should develop and implement evidence-based treatments on the basis of these new findings.

BRCA1/2+

Nat Rev Clin Oncol. 2010 Dec;7(12):702-7. Epub 2010 Oct 19.

BRCA mutations in the management of breast cancer: the state of the art.

Narod SA.

Womens College Research Institute, 790 Bay Street, Toronto, ON M5G 1N8, Canada. steven.narod@wchospital.ca

Abstract

Genetic testing for BRCA1 and BRCA2 mutations is gaining acceptance in clinical oncology worldwide and may help target unaffected high-risk women for prevention and for close surveillance. Annual screening with MRI seems to be an effective surveillance strategy, but the long term follow-up of women with small MRI-detected breast cancers is necessary to establish its ultimate value. Women with cancer and a BRCA mutation may benefit from tailored treatments, such as cisplatin or olaparib. The treatment goals for a woman with a BRCA-associated breast cancer should be to prevent recurrence of the initial cancer and to prevent second primary breast and ovarian cancers. Mutations in BRCA1 and BRCA2 are presented throughout the world and it is important that the benefits of genetic testing and of targeted therapies be extended to women who live outside of North America and Western Europe.

BRCA1/2+ un Cisplatīns

J Clin Oncol. 2010 Jan 20;28(3):375-9. Epub 2009 Dec 14.

Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy.

Byrski T, Gronwald J, Huzarski T, Grzybowska E, Budryk M, Stawicka M, Mierzwa T, Szwiec M, Wisniowski R, Siolek M, Dent R, Lubinski J, Narod S.

Department of Genetics andPathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland.

Abstract

PURPOSE: To estimate the rate of pathologic complete response (pCR) to neoadjuvant chemotherapy in BRCA1 mutation carriers according to chemotherapy regimen.

PATIENTS AND METHODS: From a registry of 6,903 patients, we identified 102 women who carried a BRCA1 founder mutation and who had been treated for breast cancer with neoadjuvant chemotherapy. Pathologic complete response was evaluated using standard criteria.

RESULTS: Twenty-four (24%) of the 102 BRCA1 mutation carriers experienced a pCR. The response rate varied widely with treatment: a pCR was observed in one (7%) of 14 women treated with cyclophospharnide, methotrexate, and fluorouracil (CMF), in two (8%) of 25 women treated with doxorubicin and docetaxel (AT), in 11 (22%) of 51 women treated with doxorubicin and cyclophosphamide (AC) or fluorouracil, doxorubicin, and cyclophosphamide (FAC), and in 10 (83%) of 12 women treated with cisplatin.

CONCLUSION: A low rate of pCR was observed in women with breast cancer and a BRCA1 mutation who were treated with AT or CMF. A high rate of pCR was seen after treatment with cisplatin. An intermediate rate of PCR was associated with AC or FAC. The relative benefits of AC and platinum therapy need to be confirmed through follow-up of this and other cohorts.

F1000 Biol Rep. 2010; 2: 10.
Published online 2010 February 11. doi: 10.3410/B2-10.
PMCID: PMC2948351

PARP inhibitors in BRCA1/BRCA2 germline mutation carriers with ovarian and breast cancer

Christina M Annunziata and Susan E Bates

Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, 10 Center Drive - Room 12N226, Bethesda, MD 20892-1906, USA

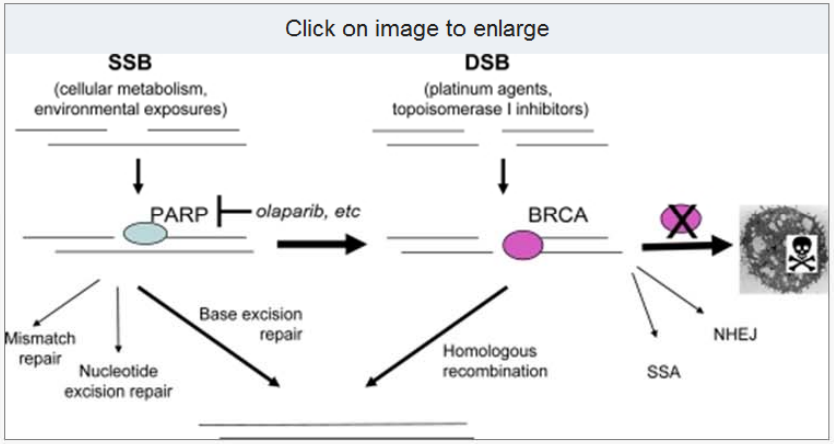


Figure 1.

Mechanism of sensitivity to PARP inhibition in BRCA-deficient cells

Cells acquire DNA damage through environmental exposures or chemotherapy agents. Repair of single-strand breaks relies on PARP; repair of double-strand breaks depends on BRCA. With PARP inhibition, single-strand breaks progress to double-strand breaks. In the absence of functional BRCA, the accumulation of double-strand breaks overwhelms DNA repair mechanisms. Irreparable DNA damage triggers cell death. DSB, double-strand break; NHEJ, non-homologous end joining; PARP, poly-ADP ribose polymerase; SSA, single-strand annealing; SSB, single-strand break.

BRCA1/2+ un PARP inhibitori

Early results of these phase II trials were presented at the American Society of Clinical Oncology (ASCO) 2009 Annual Meeting. The phase II trial of the PARP inhibitor olaparib in BRCA-deficient advanced breast cancer accrued two sequential cohorts of patients [9]. The first 27 patients received olaparib at 400 mg twice daily, and the second 27 patients received olaparib 100 mg twice daily since the pharmacodynamic results from the phase I trial showed maximal PARP inhibition in peripheral blood cells at the 100 mg dose. The therapy was well tolerated, and investigators reported a 41% overall response rate in the patients of the first cohort, with a median progression-free survival of 5.7 months. The second clinical trial tested the same two sequential dose cohorts in women with BRCA-deficient advanced ovarian cancer [10]. At the time of the preliminary report, 33 patients were treated at the 400 mg dose, with response in 57.6% of patients and a median progression-free survival of 5.8 months. Of 24 other patients treated at the 100 mg dose, 16.7% had achieved a response, with a progression-free survival of 1.9 months. Although not statistically powered to evaluate differences between the two dose cohorts, these preliminary results suggest that the pharmacodynamic saturation of PARP inhibition, as tested in peripheral blood cells of the patients in the phase I trial, may not have adequately reflected the level of activity of this compound in the tumors.

BRCA1/2+ un ķirurģija

Survival Analysis of Cancer Risk Reduction Strategies for *BRCA1/2* Mutation Carriers

Allison W. Kurian, Bronislava M. Sigal, and Sylvia K. Plevritis

See accompanying editorial on page 189

From the Departments of Medicine, Health Research and Policy, and Radiology, Stanford University School of Medicine, Stanford, CA.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2802-222/$20.00

DOI: 10.1200/JCO.2009.22.7991

A B S T R A C T

Purpose
Women with *BRCA1/2* mutations inherit high risks of breast and ovarian cancer; options to reduce cancer mortality include prophylactic surgery or breast screening, but their efficacy has never been empirically compared. We used decision analysis to simulate risk-reducing strategies in *BRCA1/2* mutation carriers and to compare resulting survival probability and causes of death.

Methods
We developed a Monte Carlo model of breast screening with annual mammography plus magnetic resonance imaging (MRI) from ages 25 to 69 years, prophylactic mastectomy (PM) at various ages, and/or prophylactic oophorectomy (PO) at ages 40 or 50 years in 25-year-old *BRCA1/2* mutation carriers.

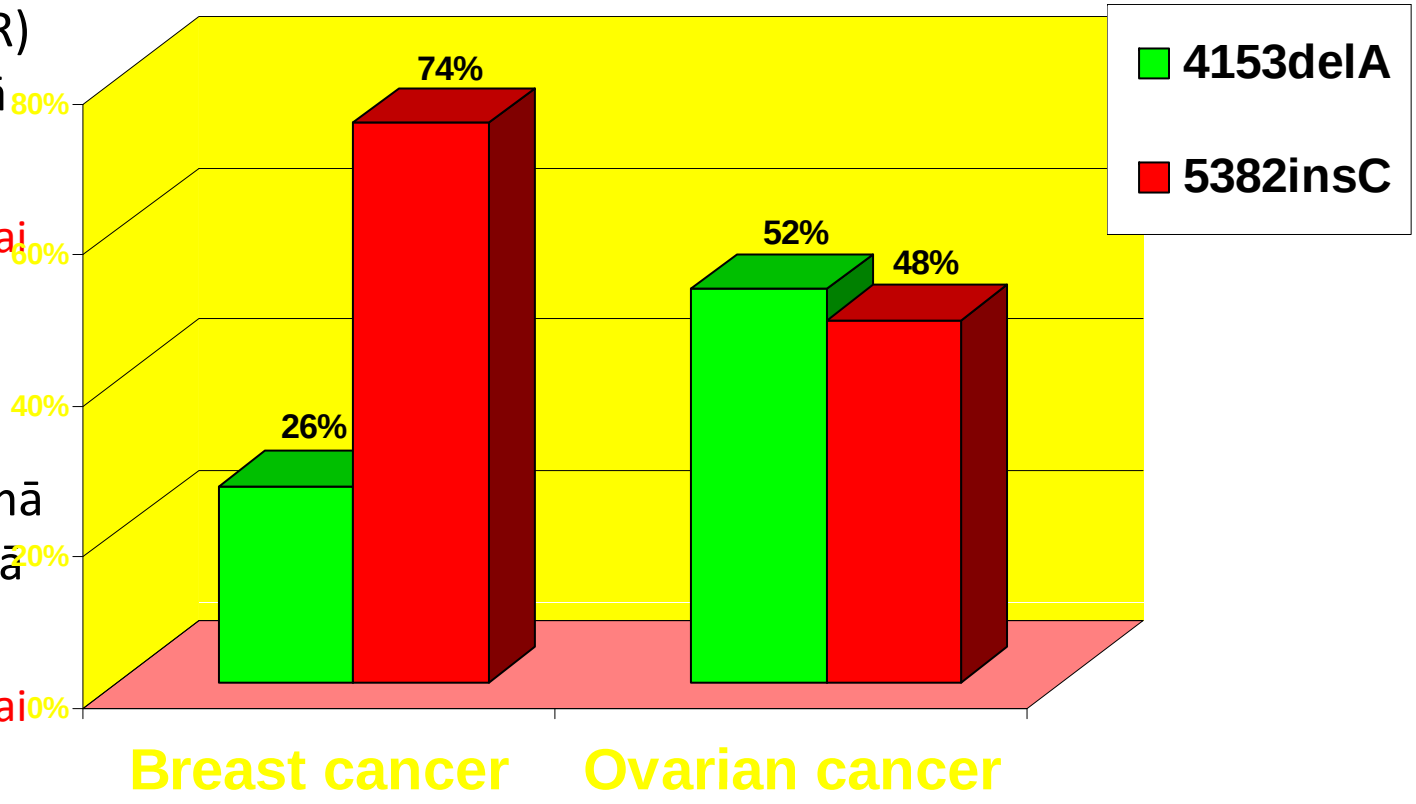
Results
With no intervention, survival probability by age 70 is 53% for *BRCA1* and 71% for *BRCA2* mutation carriers. The most effective single intervention for *BRCA1* mutation carriers is PO at age 40, yielding a 15% absolute survival gain; for *BRCA2* mutation carriers, the most effective single intervention is PM, yielding a 7% survival gain if performed at age 40 years. The combination of PM and PO at age 40 improves survival more than any single intervention, yielding 24% survival gain for *BRCA1* and 11% for *BRCA2* mutation carriers. PM at age 25 instead of age 40 offers minimal incremental benefit (1% to 2%); substituting screening for PM yields a similarly minimal decrement in survival (2% to 3%).

Conclusion
Although PM at age 25 plus PO at age 40 years maximizes survival probability, substituting mammography plus MRI screening for PM seems to offer comparable survival. These results may guide women with *BRCA1/2* mutations in their choices between prophylactic surgery and breast screening.

J Clin Oncol 28:222-231. © 2009 by American Society of Clinical Oncology

Genotipa - fenotipa korelāciju nozīme individualizētā terapijā

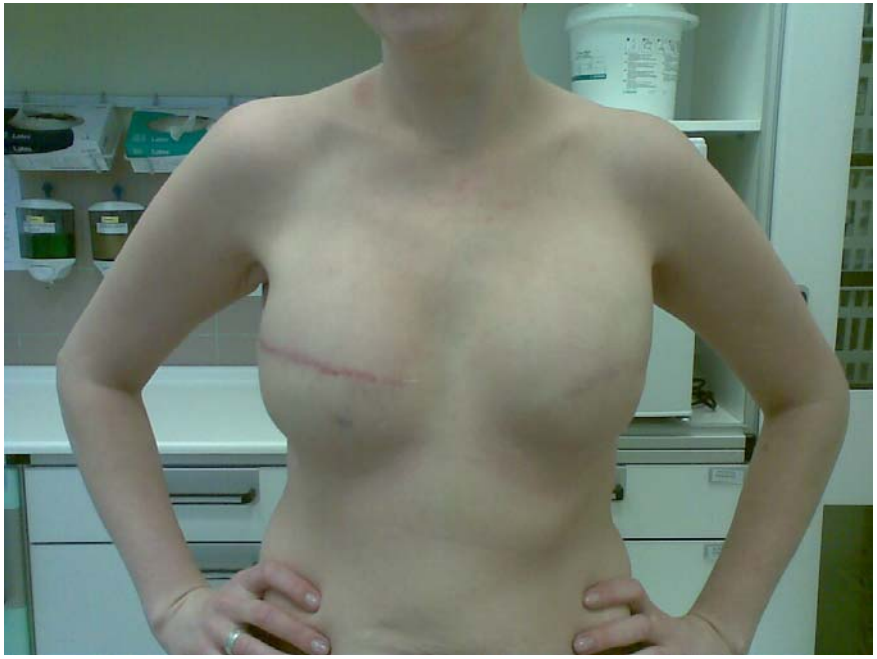
- BRCA1+ex20 (5382insC) gadījumā krūts vēža risks (OR) 2,8 reizes lielāks kā olnīcu vēža risks
  - Risku samazinošai mastektomijai lielāka loma
- BRCA1+ex11 (4153delA) gadījumā krūts un olnīcu vēžā risks līdzīgs
  - Risku samazinošai adnexektomijai lielāka loma



Klīniskais gadījums nr. 1, BRCA1+,ex20

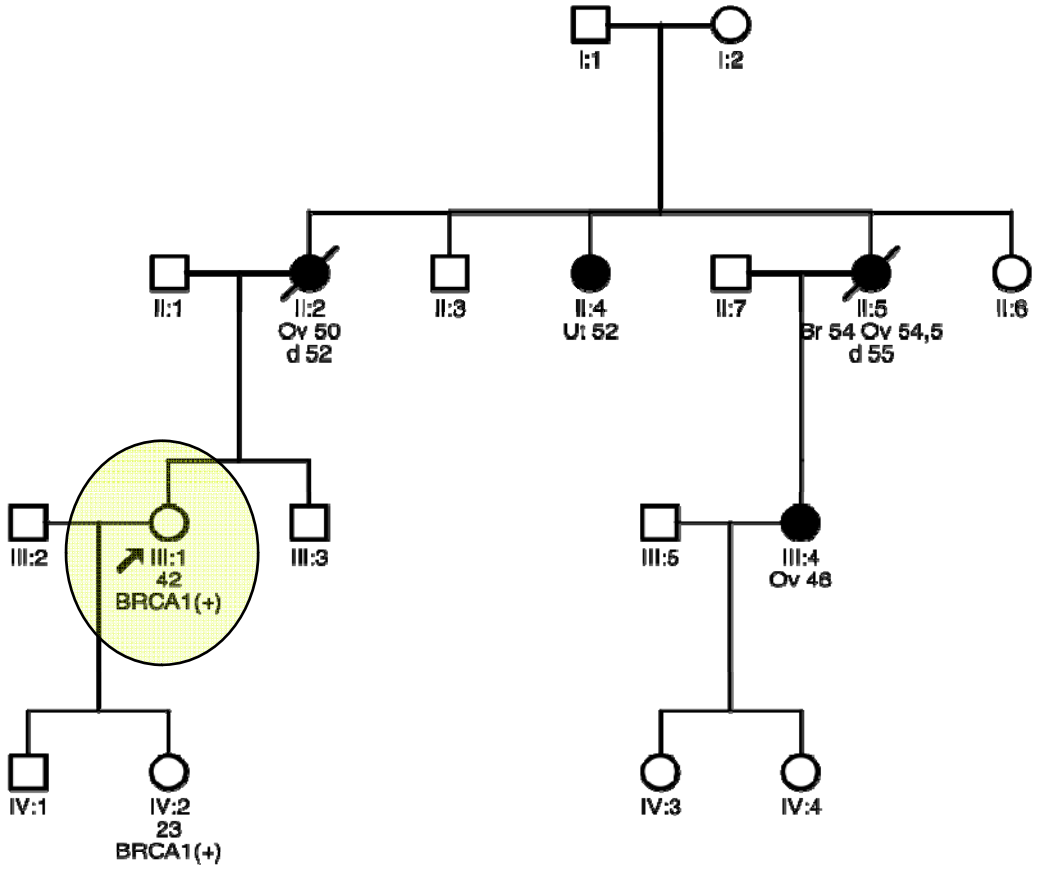
- Paciente V., 28 g.v.
- Lb. krūts vēzis pT1N0M0 2008
  - Lb. mastektomija 2008
  - Adjuvanta ķīmijterapija 2008
    - Cisplatīns + doxorubicin
  - Pretējās puses risku samazinoša mastektomija un tūlītēja abpusēja rekonstrukcija 2009 - 2010

4 mēn. pēc op



Klīniskais gadījums nr.2,BRCA1+, ex11

- Paciente S., 42 g.v., onkoloģiski vesela (2003)
- Profilaktiska adneksektomija (2003)
- Onkoloģiski vesela (2011)



Vēlamā klīniskā prakse krūts vēža gadījumā šodien

- Ja aizdomīgs veidojums krūtī, tad pirmās vizītes laikā
  - Core biopsija
  - Venozo asiņu paraugs BRCA1/2 testam
- Rezultāti 1 nedēļas laikā
- Ja konstatēts BRCA1/2+ krūts vēzis, tad pirmsārstēšanas konsīlijs lemj par
  - Ķirurģijas apjomu
  - Ķīmijterapijas shēma ar Cisplatīnu
    - Neoadjuvanti
    - Adjuvanti

Secinājumi I

- Informācija par BRCA1/2 statusu pielīdzināma Hormon receptoru (ER/PR) statusa nozīmei krūts vēža medikamentozajā un ķirurģiskajā ārstēšanā

BRCA1/2+ un aizkuņģa dziedzera vēzis

Cancer Biol Ther. 2011 Aug 1;12(3). [Epub ahead of print]

Complete remission, in BRCA2 mutation carrier with metastatic pancreatic adenocarcinoma, treated with cisplatin based therapy.

Sonnenblick A, Kadouri L, Appelbaum L, Peretz T, Sagi M, Goldberg Y, Hubert A.

Hadassah - Hebrew University Medical Center, Ein Kerem, Jerusalem, Israel.

Abstract

Carriers of a germline mutation in the BRCA genes, in particular BRCA2, have an increased risk of developing pancreatic adenocarcinoma when compared with the general population. While the addition of cisplatin to gemcitabine did not produce survival benefit compared to single-agent gemcitabine in prospective trials it is postulated that the addition of DNA cross-linking agent such as cisplatin to standard gemcitabine chemotherapy should be considered in known BRCA mutation carriers. We report a case of pancreatic adenocarcinoma arising in a 60-year-old carrier of a rare BRCA2 (1153insertionT) germline mutation. The patient received gemcitabine without any response and actually progression of the disease had occurred. Therefore cisplatin was added in combination with gemcitabine. A dramatic complete response to therapy was encountered with no evidence of disease in both CT scans and markers (CA19-9). In conclusion, in patients with known BRCA mutation associated pancreatic adenocarcinoma, the addition of a DNA cross-linking agent such as cisplatin should be considered. Physicians should consider BRCA mutation testing when the diagnosis of pancreatic cancer is established, especially when the patient belongs to an ethnic group where founder mutations exist, and/or there is strong personal or family history of cancer. This may be applied also to other metastatic tumors diagnosed in BRCA1/2 carriers.

Secinājums II

BRCA1/2 tests visiem vēža gadījumiem

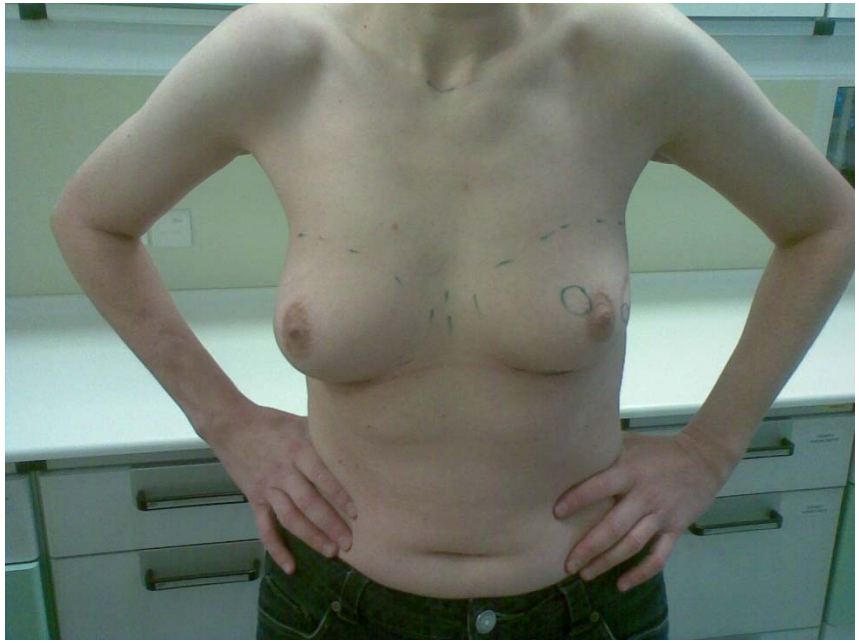
ja founder mutācijas populācijā

ja pozitīva ģimenes onkoloģiskā anamnēze

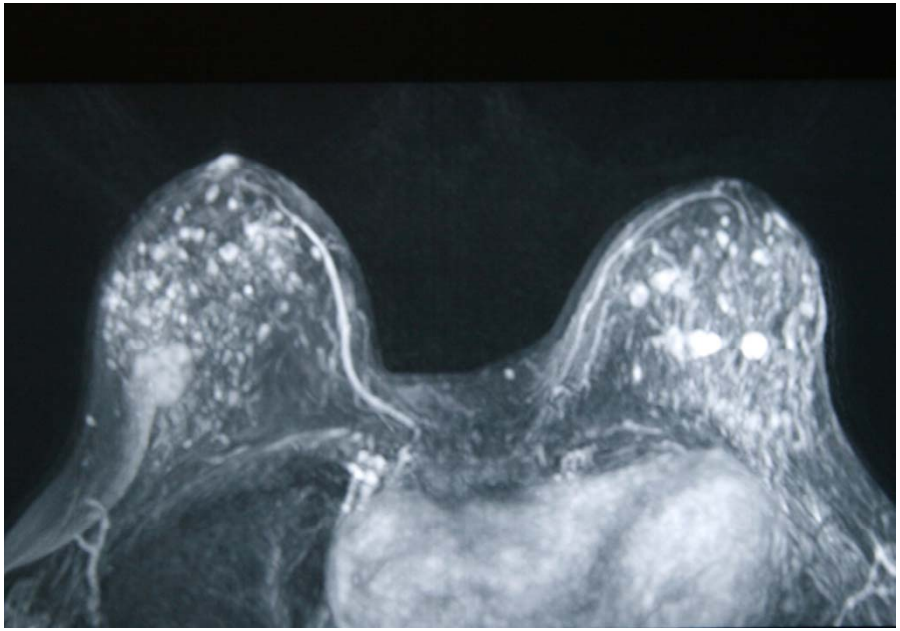
Cowden’s sindroms, PTEN+

Paciente Z., 35 g.v., krūts vēža risks dzīves laikā 50%

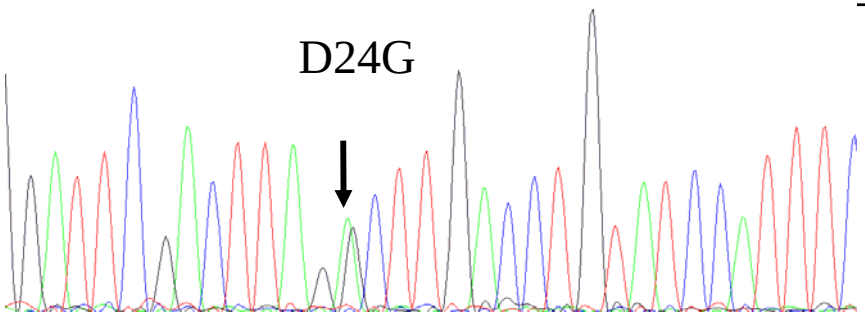
Pirmsop



Pirmsop KMR



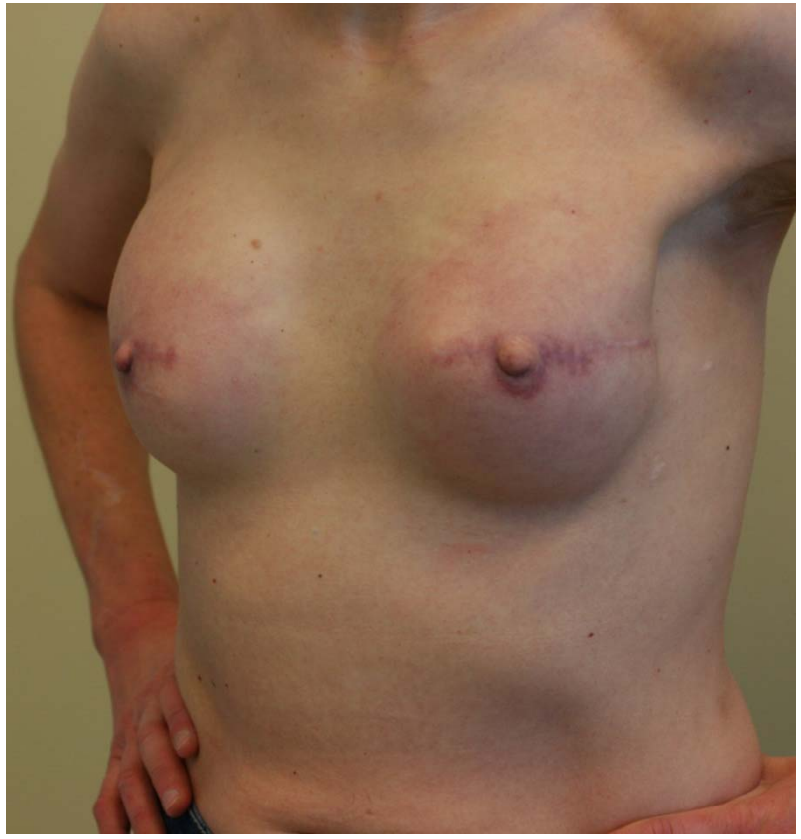
Paciente ar Cowden sindromu

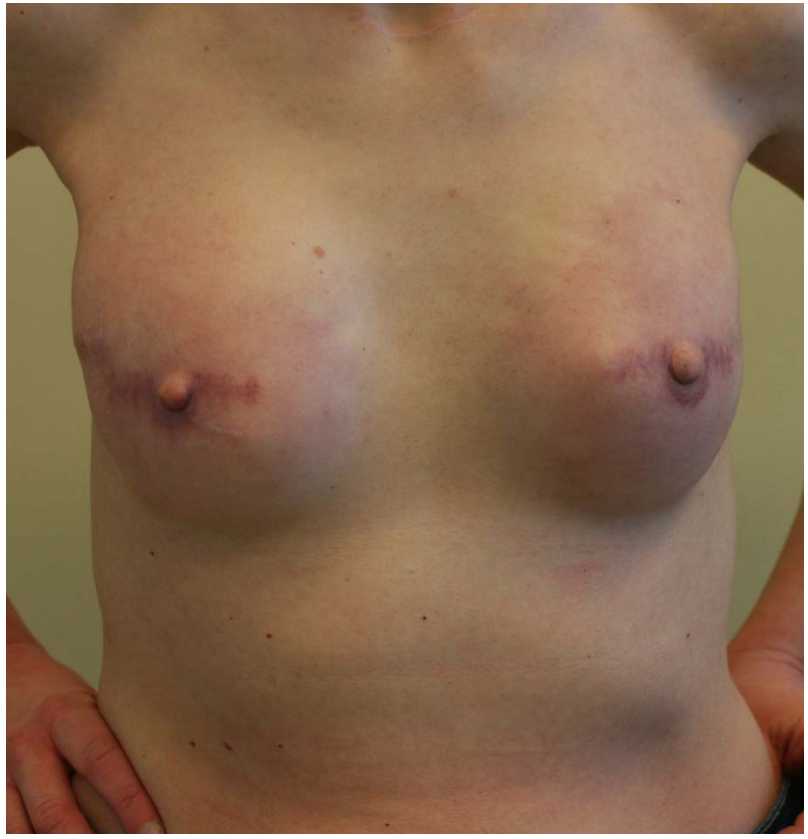


- Tireoīdektomija nodulārās strumas gadījumā
- Histerektomija ar abpusēju olvadu un olnīcu izņemšanu endometrija adenokarcinomas (IA stadija) dēļ 34 g. vecumā
- Palmoplantāra keratoze, lipomatoze
- Multiplas abpusējas krūts fibroadenomas, papilārās cistadenomas
- Abpusēja subkutāna mastektomija ar tūlītēju rekonstrukciju

Cowdens sindroms, PTEN+

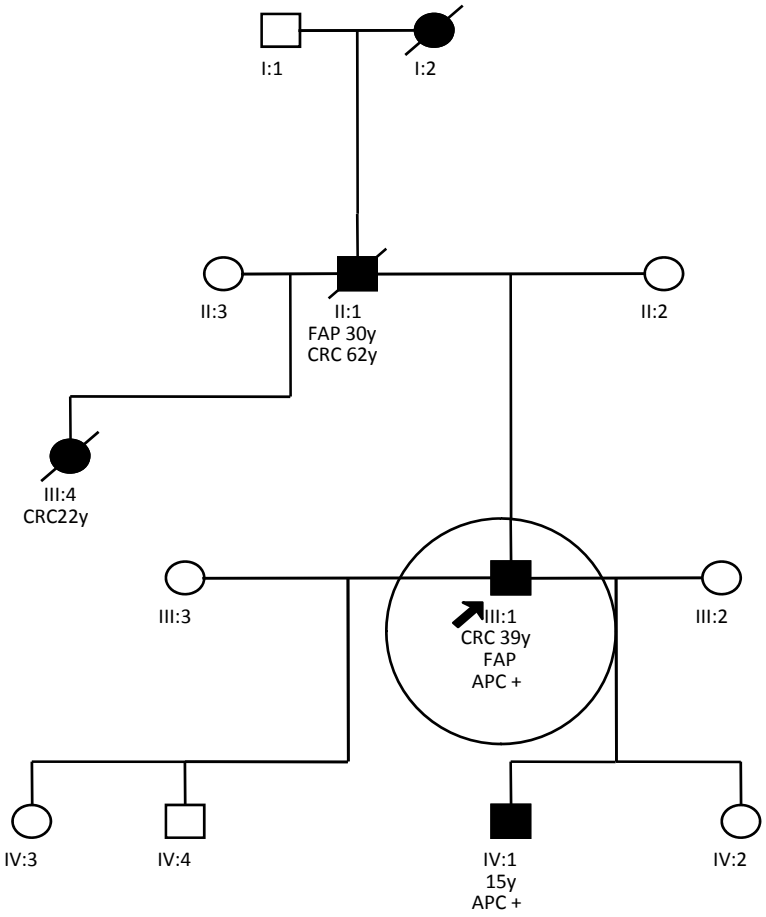
Pēcop (6 mēneši)

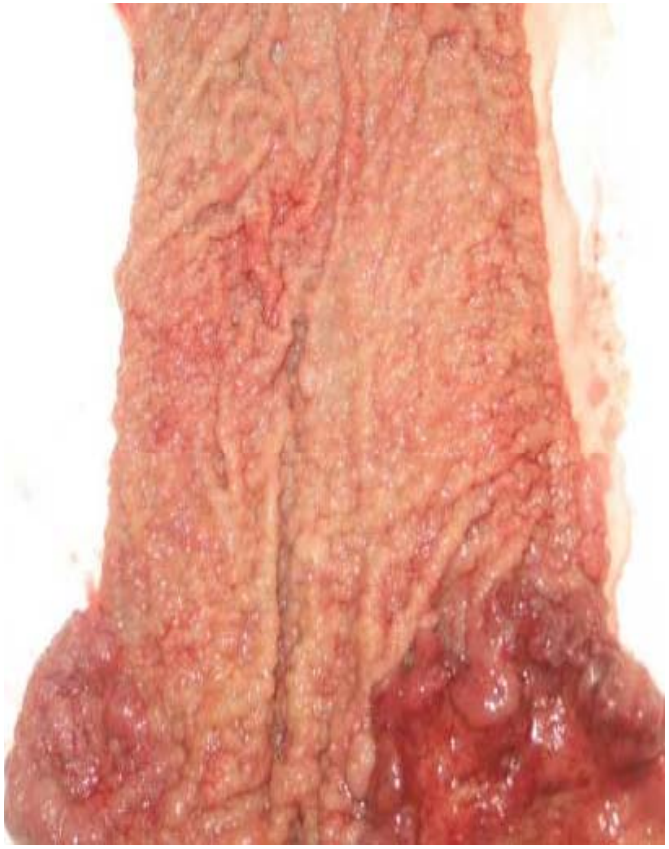




Klīniskais gadījums, APC+

Pacients B., tēvs, 39.g.v. (Kolorektālais vēzis un totāla proktokolektomija 2008)

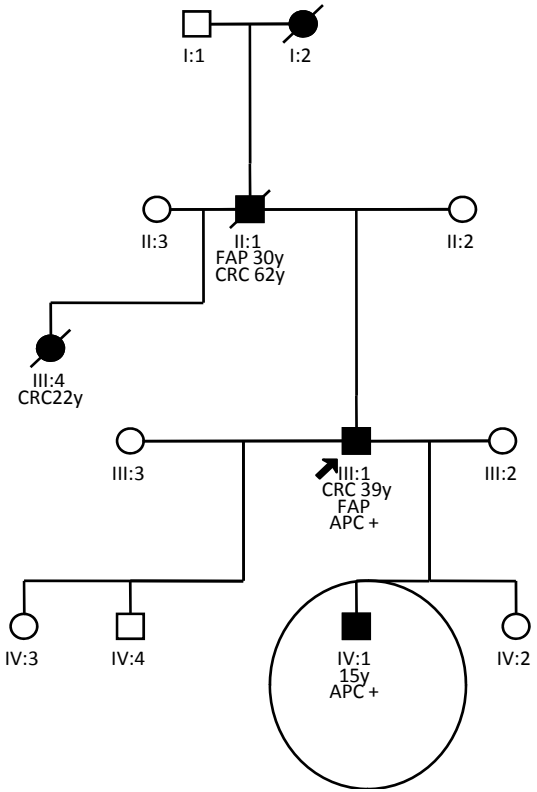


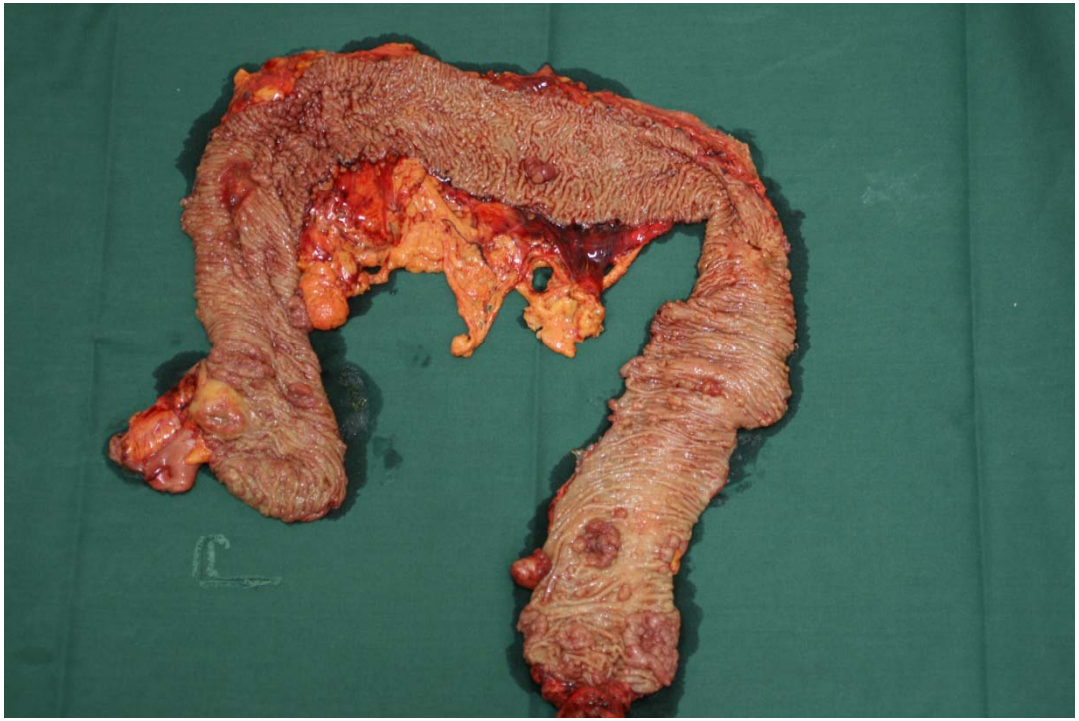


Ģimenes adenomatozā polipoze, APC+

Pacients B., dēls, 18.g.v, onkoloģiski vesels

Profilaktiska laparoskopiska proktokolektomija (2011)





Secinājumi

- Vēža etioloģija un patoģenēze ir ļoti heterogēna un sarežģīta
- Esošās vēža morfoloģiski - molekulārās klasifikācijas sniedz nepilnīgu priekšstatu par dažādām vēža apkšgrupām, un to efektīvāko ārstēšanu
- Molekulāri – ģenētiskajam statusam ļoti svarīga loma profilakses un terapijas izvēlē
- Iespēja optimizēt diagnostikas un ārstēšanas izmaksas

Nākotnes perspektīva

Zināmo vēzi predisponējošo gēnu mutāciju noteikšana visos vēža gadījumos, ja eksistē efektīva profilakse vai ārstēšana