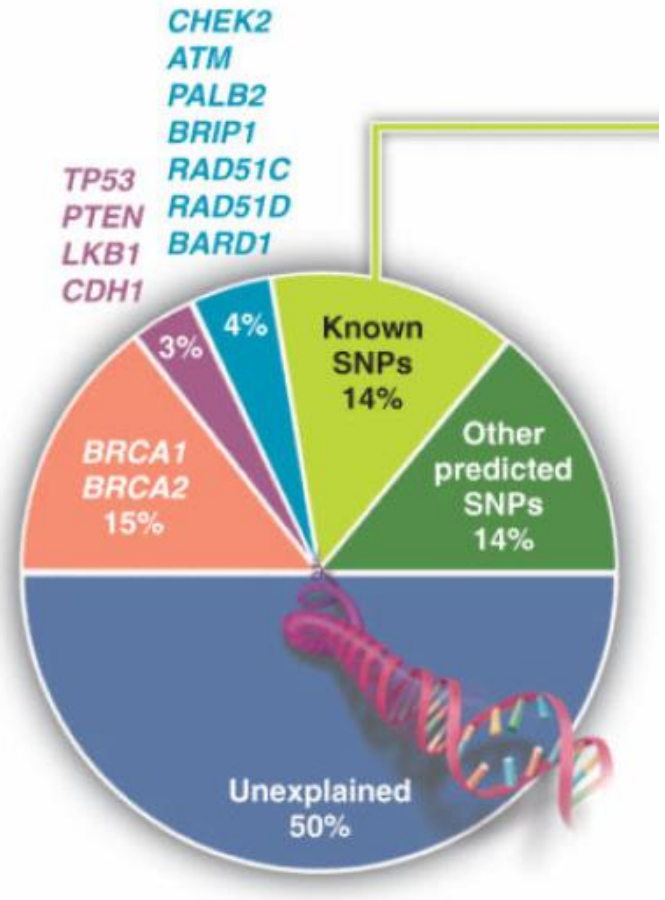
Meme Kanserinde Genomik Testler

Dr. Umut Demirci
Dr. A. Y. Ankara Onkoloji EAH
Tıbbi Onkoloji Kliniği

Meme Kanseri

- Kadınlarda kanser ölümlerinde 2. en sık neden
- Erken tarama ve tedavideki gelişmeler ile morbidite ve mortalite azaldı
- %10 olgu familyal



Couch et al Science 2014

İçerik

- Gen ekspresyon profili (GEP)
- *BRCA* mutasyonları ve klinik kullanımı

Genetik Test; Hasta bilgilendirme

- Potansiyel faydalar
- Riskler (klinik, psikolojik, sosyal)
- Testin sınırlılıkları

Gen Ekspresyon Profilleri

Adjuvan Tedavi Kararı?

Klasik

- Hastalık karakteristikleri (intrinsik moleküler alttip, grad, boyut, LN)
- Hasta karakteristikleri (yaş, menapozal durum, PS, komorbidite)

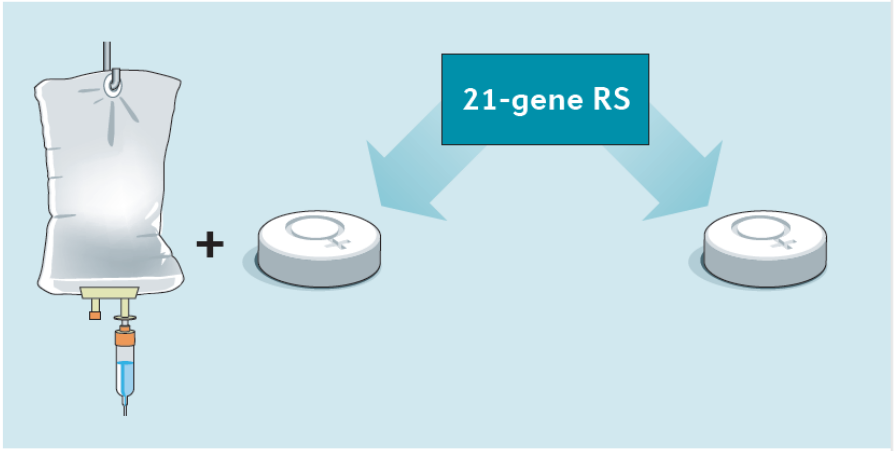
Yeni

- Genetik

(tm gen-ekspresyon profili)

Oncotype®- Dx

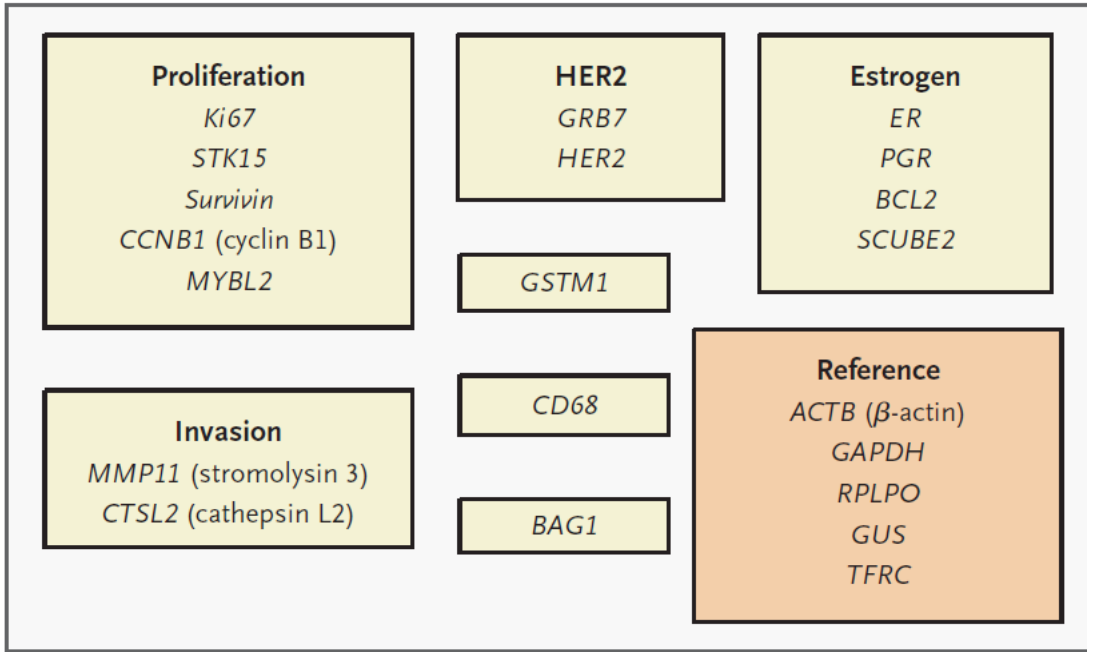
- ER+ LN- meme kanseri hastalarında
- uzak metastaz gelişim olasılığını
- tedaviden fayda oranını gösteren genetik test
- 2004 FDA onayı;
- 5cm ve altı
- LN – hastalar (2009 LN+)



Oncotype® Dx

- Prognostik ve Prediktif (Paik, 2004)
- Özellikle 21 gen RS <11 ise prognoz endokrin tedavi ile mükemmel (TailorX 2015)

- RS 0-100
  - 0-17 (Düşük risk)
  - 18-30 (Orta risk)
  - 31-100 (Yüksek risk



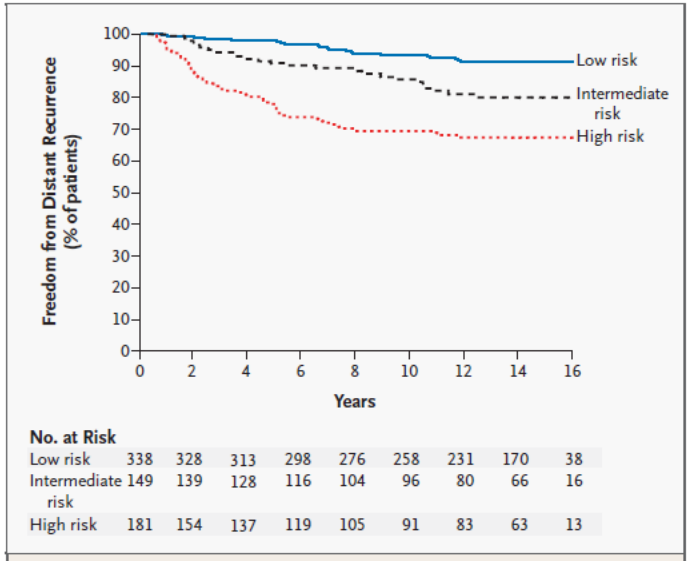
NSABP B-14

- LN- ve HR+ meme ca; tam vs adj yok
- 10 yıllık DFS düşük riskte %93.2, yüksek riskte %65.9,p <0.001

Table 1. Kaplan–Meier Estimates of the Rate of Distant Recurrence at 10 Years, According to Recurrence-Score Risk Categories.*

Risk Category	Percentage of Patients	Rate of Distant Recurrence at 10 Yr (95% CI)†
		percent
Low	51	6.8 (4.0–9.6)
Intermediate	22	14.3 (8.3–20.3)
High	27	30.5 (23.6–37.4)‡

* A low risk was defined as a recurrence score of less than 18, an intermediate risk as a score of 18 or higher but less than 31, and a high risk as a score of 31 or higher.
† CI denotes confidence interval.
‡ P<0.001 for the comparison with the low-risk category.

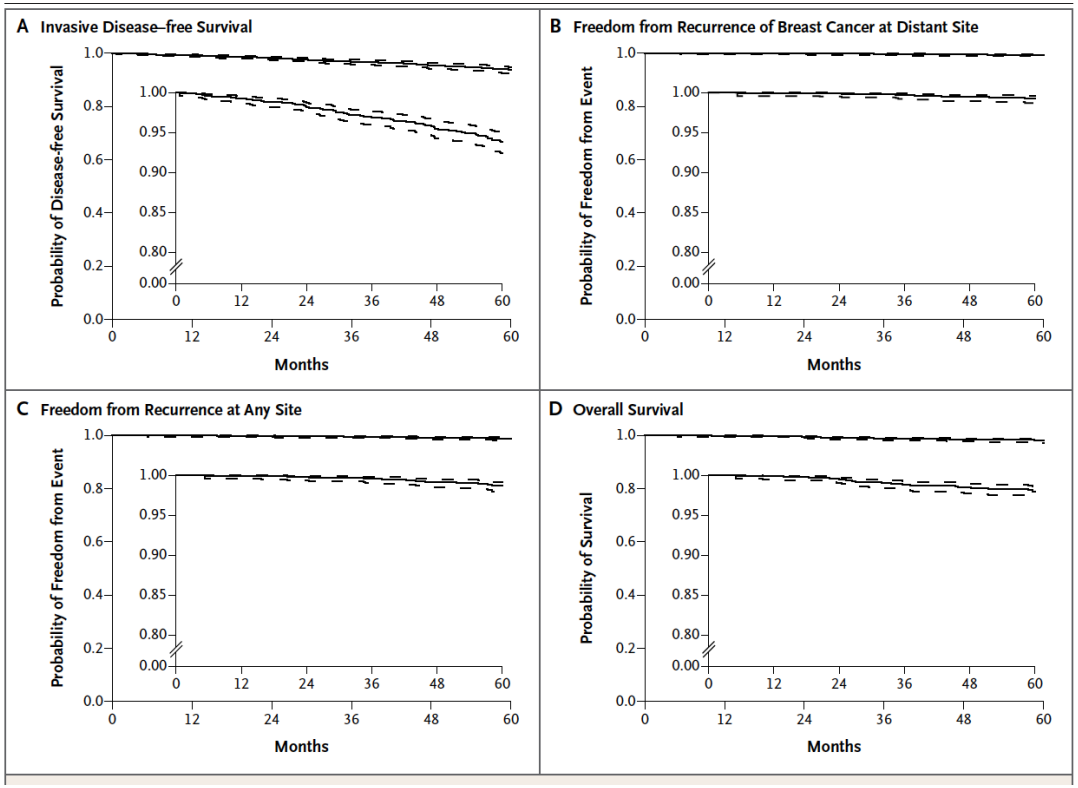


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 19, 2015 VOL. 373 NO. 21

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, E.A. Perez, J.A. Olson, Jr., J.A. Zujewski, T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.N. Atkins, J.L. Berenberg, and G.W. Sledge



Olgu-1

- 50y,K
  - ÖG: Sjogren,Hashımato
  - SG: Ca öyküsü yok
- Mayıs 2016 sol meme kitle eksizyonu
- Pat: IDK, gr2, tm 1.3cm, gr3 DCIS eşlik etmekte, CS+, ER %100,PR %80,HER2 ++,ki67 %40
- 24.6.16 Sol simple mastektomi+ SLNÖ
- Pat: Rezidü tm yok,1 adet reaktif LN,
- Her2 SISH (-)

Genomic Health® | oncotype DX® Breast Cancer Assay

Breast Cancer Report - Node Negative
Prediction of Chemotherapy Benefit

Genomic Health, Inc.
301 Penobscot Drive, Redwood City, CA 94063 USA
USA/Canada: +1.866.ONCOTYPE
International: www.oncotypedx.com/contact
www.oncotypedx.com
CLIA Number 05D1018272

Patient/ID: [redacted]
Gender: Female
Date of Birth: 08-Mar-1966

Report Number: OR000814018-01
Specimen Received: 15-Aug-2016
Date Reported: 24-Aug-2016

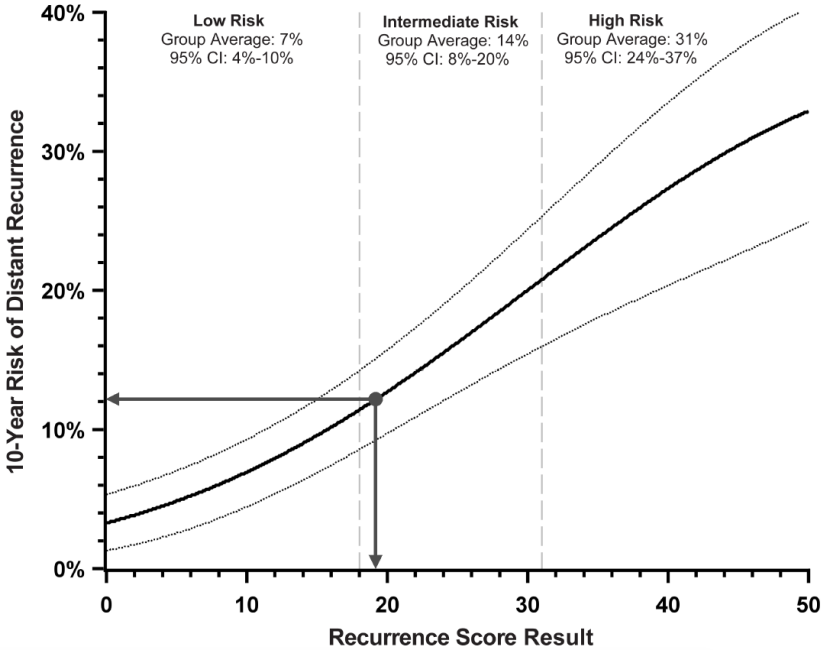
Recurrence Score® Result

19

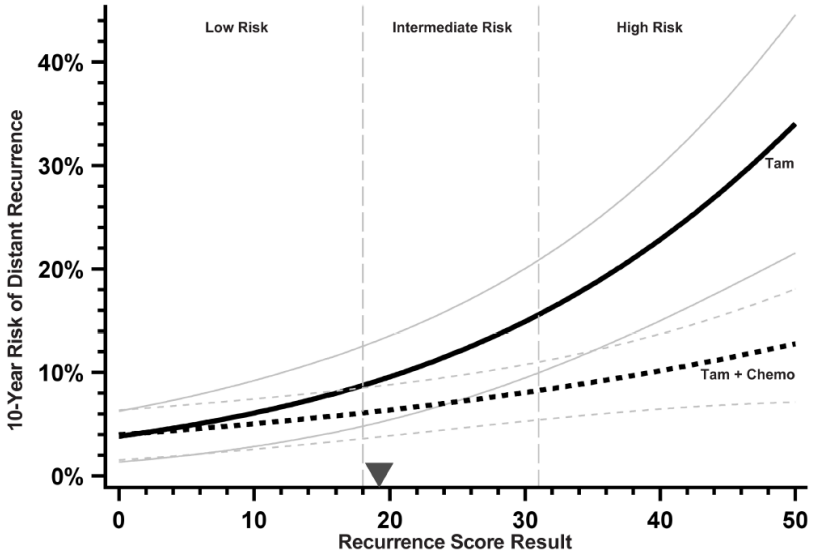
The findings are applicable to women who have stage I or II node negative (N–), estrogen receptor positive (ER+) breast cancer and will be treated with 5 years of tamoxifen (tam). It is unknown whether the findings apply to other patients outside these criteria.

Clinical Experience: The following results are from a clinical validation study that included 651 patients from the NSABP B-20 study. The study included female patients with stage I or II, N–, ER+ breast cancer. Patients were randomized to either tam alone or tam plus CMF or MF chemotherapy. For patients in the pre-specified group with Recurrence Score results ≥ 31, the group average 10-year risks (95% CI) of distant recurrence were 40% (25%, 54%) for tam alone and 12% (6%, 18%) for tam + CMF/MF.[1]

10yıl Uzak Rekürrens Riski (5yıl tam son)



KT Faydası



Olgu-1 Klinik

- Oncotype Dx RS 19 (intermediate grup)
- ki67%40 olması nedeni ile 4 kür Ac sonrası hormonoterapi planlandı

Open Access Original Article

DOI: 10.7759/cureus.522

Impact of Oncotype DX Recurrence Score on Treatment Decisions: Results of a Prospective Multicenter Study in Turkey

Vahit Ozmen [1], Ajlan Atasoy [2], Erhan Gokmen [3], Mustafa Ozdogan [4], Nilufer Guler [5], Cihan Uras [6], Engin Ok [7], Orhan Demircan [8], Abdurrahman Isikdogan [9], Pinar Saip [10]

Abstract

Introduction: Breast cancer is the most common malignancy among Turkish women and the rate of early stage disease is increasing. The Oncotype DX® 21-gene assay is predictive of distant recurrence in ER-positive, HER2-negative early breast cancer. We aimed to evaluate the impact of the Recurrence Score® (RS) on treatment decisions and physician perceptions in Turkey. We also studied correlations between RS and routine risk factors.

Patients and Methods: Ten academic centers across Turkey participated in this prospective trial. Consecutive breast cancer patients with pT1-3, pN0-N1mic, ER-positive, and HER2-negative tumors were identified at multidisciplinary tumor conferences. The initial treatment decision was recorded before tumor blocks were sent to the central laboratory. Each case was brought back to tumor conference after receiving the RS result. Both pre- and post-RS treatment decisions and physician perceptions were recorded on questionnaire forms. Correlations between RS and classical risk factors were evaluated using univariate and multivariate analyses.

Results: Ten centers enrolled a total of 165 patients. The median tumor size was 2 cm. Of 165 patients, 57% had low RS, 35% had intermediate RS, and 8% had high RS, respectively. The overall rate of change in treatment decision was 33%. Initially, chemotherapy followed by hormonal therapy (CT+HT) was recommended to 92 (56%) of all patients, which decreased to 61 (37%) patients post-RS assay ($p<0.001$). Multivariate analysis indicated that progesterone receptor (PR) and Ki-67 scores were significantly related to RS.

Conclusion: Oncotype DX testing may provide meaningful additional information in carefully selected patients.

Ozmen et al Cureus 2016

Diğer gen imza belirleyicileri

- MammaPrint: 70 gen imzası
- PAM50 intrinsik alt tip sınıflayıcısı
- Gen ekspresyon greyd İndex(GGI)...

Olgu-2

- 61 year old
- Screening
- Multifocal left breast cancer
- Right breast cancer
- End-stage renal failure new diagnosis
- New-onset peritoneal dialysis

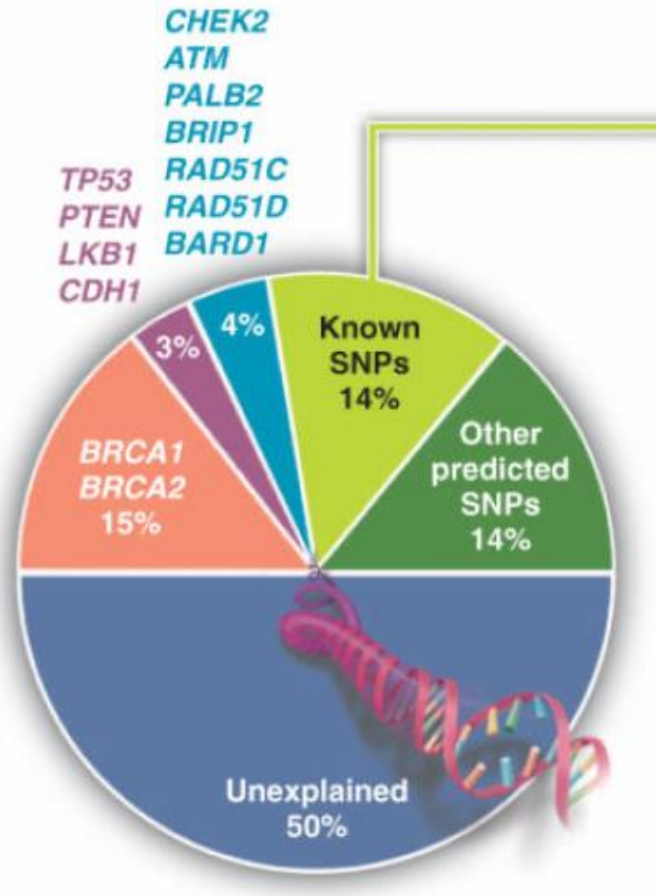
BRCA MUTASYON ANALIZI

Dr. Niyazi Karaman
Dr. A. Y. Ankara Onkoloji EAH
Genel Cerrahi Kliniği

Ailesel Meme Kanseri

- Tanım: ≥1 birinci ya da ikinci derecede akrabada meme kanseri hikayesi
- Birinci derece akrabaların sayısı arttıkça risk artıyor;
  - 1 →1.80
  - 2 → 2.93
  - 3 →3.90

1. **Yüksek penetranslı genler**: *TP53, CDH1, PTEN, STK11, RAD51C ve RAD51D*
2. **Düşük orta penetranslı genler**: *ATM, CHEK2, BRIP1, PALB2*
   - Li-Fraumeni sendromu → TP53
   - Cowden sendromu → PTEN
   - Peutz-Jeghers sendromu → STK11, LKB1



Couch et al Science 2014

Herediter meme ve over kanseri (HBOC)

Hastada

- ≤50 yaş meme ca;
  - Ort. 45 yaş,
    - BRCA1 → 40 yaş
    - BRCA2 → 43 yaş
- ≤60 yaş TN meme ca
- ≥2 primer meme ca
- Bilateral meme ca ↑
- İnv. over, tuba veya peritoneal ca
- Erkek meme kanseri
  - BRCA2 → erkek meme kanseri, prostat, pankreas, GIS, melanom
- Yüksek riskli etnik köken de HBOC ilişkili herhangi tm

Yakınlarında

- Bir veya daha fazla yakında ≤50 yaş meme kanseri
- Bir veya daha fazla yakında invaziv ovaryan, tubal veya peritoneal kanser
- İki veya daha fazla yakında meme, prostat ve/veya pankreas kanseri

BRCA-time line

Pre-vivor

Association of Risk-Reducing Surgery in *BRCA1* or *BRCA2* Mutation Carriers With Cancer Risk and Mortality

Susan M. Domchek, MD
Tara M. Friebel, MPH
Christian F. Singer, MD, MPH
D. Gareth Evans, MD
Henry T. Lynch, MD
Claudine Isaacs, MD
Judy E. Garber, MD, MPH
Susan L. Neuhausen, PhD
Ellen Matloff, MS
Rosalind Eeles, PhD
Gabriella Pichert, MD
Laura Van t'veer, PhD
Nadine Tung, MD
Jeffrey N. Weitzel, MD
Fergus J. Couch, PhD
Wendy S. Rubinstein, MD, PhD
Patricia A. Ganz, MD

Context Mastectomy and salpingo-oophorectomy are widely used by carriers of *BRCA1* or *BRCA2* mutations to reduce their risks of breast and ovarian cancer.

Objective To estimate risk and mortality reduction stratified by mutation and prior cancer status.

Design, Setting, and Participants Prospective, multicenter cohort study of 2482 women with *BRCA1* or *BRCA2* mutations ascertained between 1974 and 2008. The study was conducted at 22 clinical and research genetics centers in Europe and North America to assess the relationship of risk-reducing mastectomy or salpingo-oophorectomy with cancer outcomes. The women were followed up until the end of 2009.

Main Outcomes Measures Breast and ovarian cancer risk, cancer-specific mortality, and overall mortality.

Results No breast cancers were diagnosed in the 247 women with risk-reducing mastectomy compared with 98 women of 1372 diagnosed with breast cancer who did not have risk-reducing mastectomy. Compared with women who did not undergo risk-reducing salpingo-oophorectomy, women who underwent salpingo-oophorectomy had a lower risk of ovarian cancer, including those with prior breast cancer (6% vs 1%, respectively; hazard ratio [HR], 0.14; 95% confidence interval [CI], 0.04-0.59) and those without prior breast cancer (6% vs 2%; HR, 0.28 [95% CI, 0.12-0.69]), and a lower risk of first diagnosis of breast cancer in *BRCA1* mutation carriers (20% vs 14%; HR, 0.63 [95% CI, 0.41-0.96]) and *BRCA2* mutation carriers (23% vs 7%; HR, 0.36 [95% CI, 0.16-0.82]). Compared with women who did not undergo risk-reducing salpingo-oophorectomy, undergoing salpingo-oophorectomy was associated with lower

Photograph by Melodie McDaniel / Trunk Archive

''it was a cultural and medical earthquake''

Profilaktik uygulamaların sınırlılıkları

- RRM (%90↓)
- RRSO (%80-96↓, meme ≈%50↓) Genel mort.→ %60 ↓
- Kemoprevansiyon;
  - Tamoksifen (%40-50↓)
  - 2-4 yıl kullanım sonrası risk azalması → %75

BRCA 1&2 (Tanım ve sorunlar)

- Her ikisi de yüksek penetranslı tm süpresör gen ve temel olarak DNA hasarının saptanmasında, tamirinde rol oynuyorlar

- *BRCA1* (17q21) ve *BRCA2 (*13q12)
- Hem BRCA1 (24 exon, 1863 aa) hem de BRCA2 (27 exon, 3418 aa) oldukça kompleks genomik yapılar

- Kodlama bölgeleri ne kendilerinden önce tanımlanmış genlere ne de birbirlerine homoloji gösteriyor

- BRCA1 için >1800, BRCA2 için 2000 özgün mutasyon, polimorfizm ve variant raporlanmış

- VUS (Variants of unknown significance); Birçok lab. tarafından tanımlanamıyorlar

Herediter meme kanseri ve moleküler alt tipler

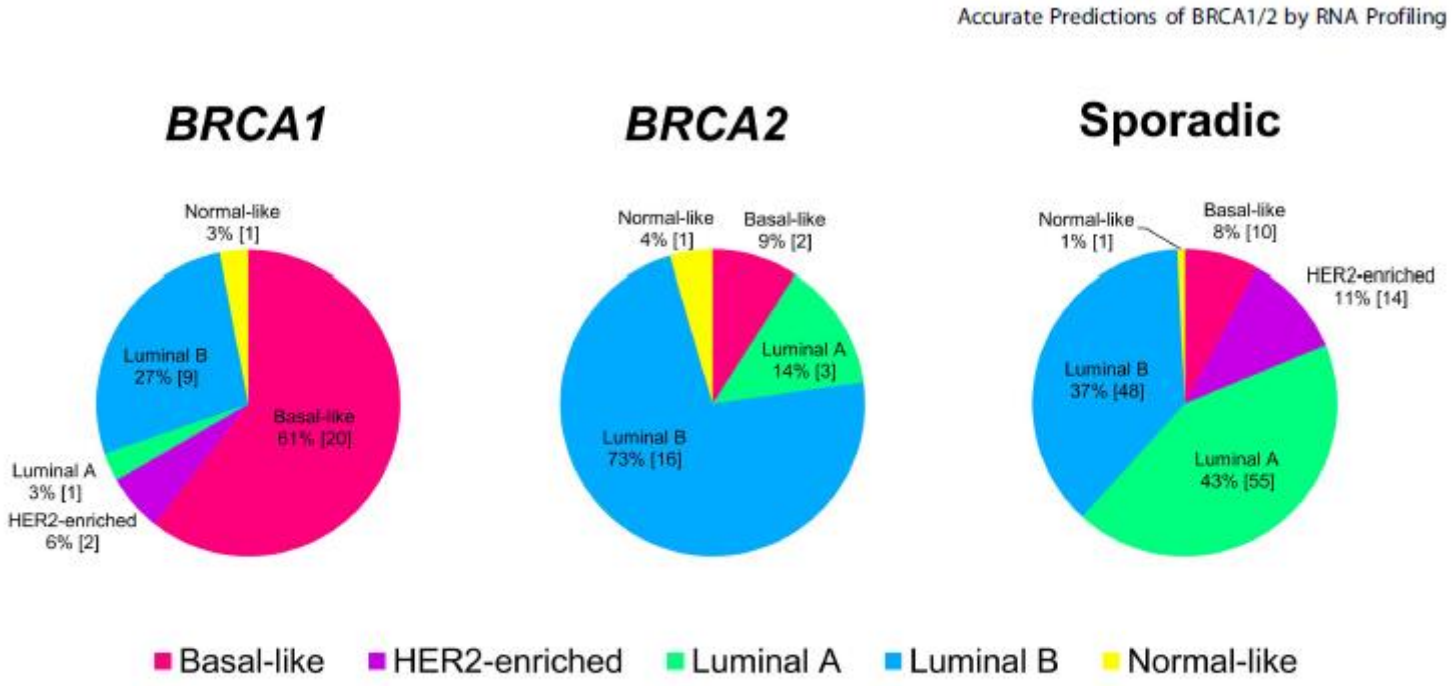


Figure 2. Association between hereditary breast cancers and molecular subtypes. Distribution of molecular subtypes among *BRCA1*, *BRCA2* and sporadic breast cancer samples. Tumors were classified into molecular subtypes using the PAM50 classifier. Numbers in brackets refer to number of samples in each group.
doi:10.1371/journal.pone.0064268.g002

BRCA için yüksek klinik risk

- BRCA1 ilişkili meme kanserleri %90 ER- ve eş zamanlı CK5/6 ve CK14 eksprese (normalde %50)
- BRCA2 (+) → İnv. Lobuler ve tübüler ca.↑, Çoğu G1/2
- ≤40 TN tümörlerde CK5/6 pozitifliği → BRCA1/2 mutasyon varlığına %10 hastada işaret eder
- Aile hikayesinden bağımsız olarak ≥%10 klinik risk

Ancak: Sitomorfolojik ve İHK bulguları ile BRCA1-2 mutasyon riskini öngörmek mümkün değil.

Riskin dağılımı

BRCA1(+)

<u>70 yaşında;</u>

Meme → %57

Over → %45-60

<u>80 yaşında;</u>

Meme → %81

Over → %63

BRCA2(+)

<u>70 yaşında;</u>

Meme → %49

Over → %11-35, %18

<u>80 yaşında;</u>

Meme → %83

BRCA mut. tarama

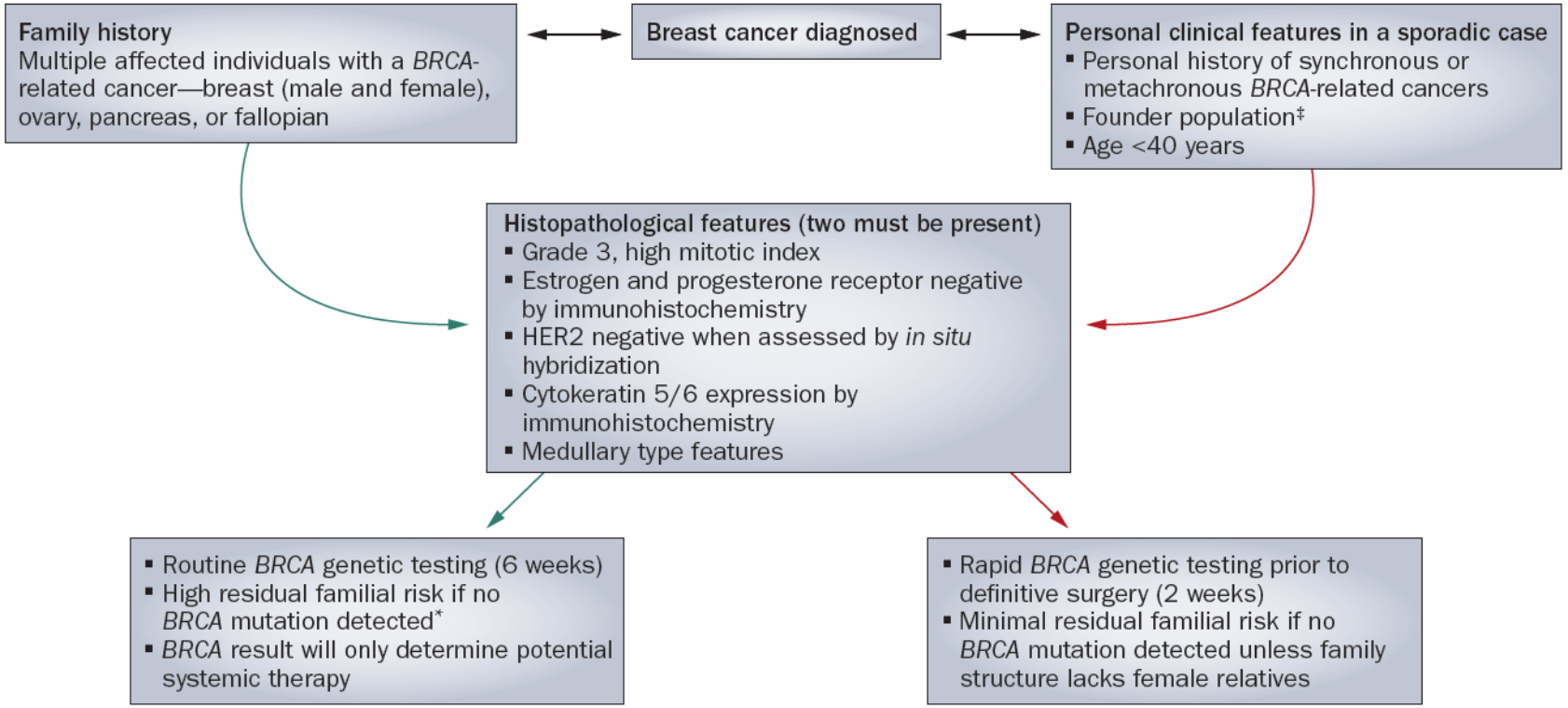
Nereden?

- Kan
- Tükürük
- Bukkal mukoza

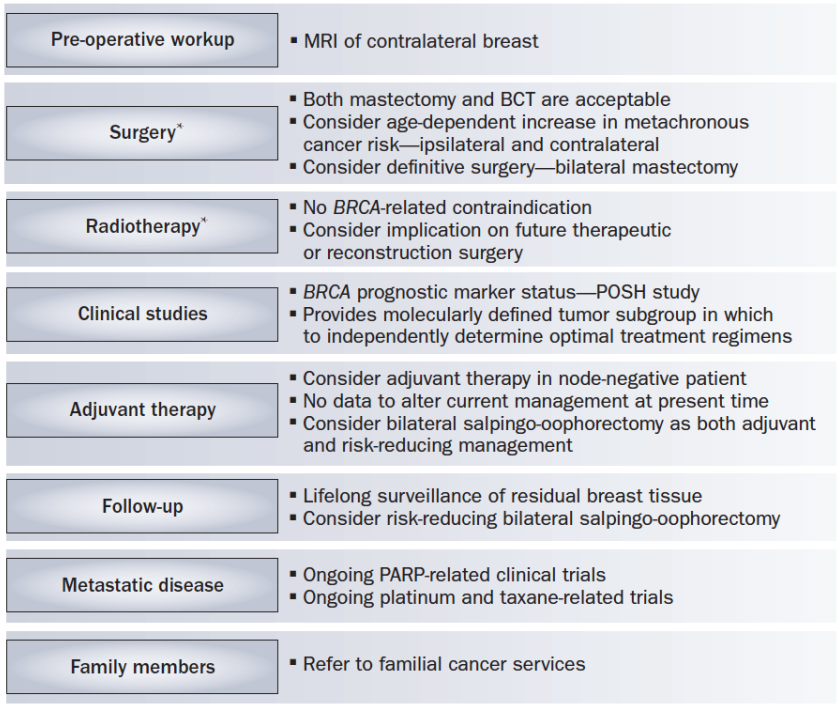
Yöntem?

- Next generation panel testing
- BRCA Analysis with Large genomic testing (BART)
- Tek mutasyon analizi

Genetik test endikasyonları



Yeni tanı meme kanserinde; BRCA



- Preop karşı meme MRI
- MKC: → "Makul bir seçenek olarak kabul edilebilir"

<u>MKC sonrası RT</u>;

- Güvenle uygulanabilir (lokal-bölgesel, uzak met açısından fark yok)
- Erken ve geç toksisite artışı yok

BRCA1 (+) → Sisplatin başarısı↑

PARP [poly(ADP-ribose)polymerase] inhibitörleri → Baz eksizyon onarım (BER)

Which *BRCA* genetic testing programs are ready for implementation in health care? A systematic review of economic evaluations

Elvira D'Andrea, MD[1], Carolina Marzuillo, BS[1], Corrado De Vito, MD[1], Marco Di Marco, MD[1], Erica Pitini, MD[1], Maria Rosaria Vacchio, BS[1] and Paolo Villari, MD, MPH[1]

Purpose: There is considerable evidence regarding the efficacy and effectiveness of *BRCA* genetic testing programs, but whether they represent good use of financial resources is not clear. Therefore, we aimed to identify the main health-care programs for *BRCA* testing and to evaluate their cost-effectiveness.

Methods: We performed a systematic review of full economic evaluations of health-care programs involving *BRCA* testing.

Results: Nine economic evaluations were included, and four main categories of *BRCA* testing programs were identified: (i) population-based genetic screening of individuals without cancer, either comprehensive or targeted based on ancestry; (ii) family history (FH)-based genetic screening, i.e., testing individuals without cancer but with FH suggestive of *BRCA* mutation; (iii) familial mutation (FM)-based genetic screening, i.e., testing individuals without cancer but with known familial *BRCA* mutation; and (iv) cancer-based genetic screening, i.e., testing individuals with *BRCA*-related cancers.

Conclusions: Currently *BRCA1/2* population-based screening represents good value for the money among Ashkenazi Jews only. FH-based screening is potentially very cost-effective, although further studies that include costs of identifying high-risk women are needed. There is no evidence of cost-effectiveness for *BRCA* screening of all newly diagnosed cases of breast/ovarian cancers followed by cascade testing of relatives, but programs that include tools for identifying affected women at higher risk for inherited forms are promising. Cost-effectiveness is highly sensitive to the cost of *BRCA1/2* testing.

Genet Med advance online publication 14 April 2016

Key Words: BRCA; breast cancer; cost-effectiveness; health-care programs; systematic review;

İzlem Önerileri

- Eğitim ve genetik danışmanlık → ≥18 yaş
- Kendi kendini muayene → ≥18 yaş
- Klinik meme muayenesi → ≥20 yaş, 6 ayda bir
- Mammografi → ≥25 yaş (MRI/BT değişimli olarak kullanılabilir)
- Over kanseri taraması → [TvUSG, CA125, muayene] → ≥30 yaş, yıllık
- Erkek taşıyıcılarda kendi kendine ve klinik muayene

Sonuç

- BRCA1 ≈ TN (basal-like) %61
- BRCA2 ≈ Luminal B (%73)

- BRCA 1 ve BRCA 2 mutasyon taşıyıcıları tamamen farklı biyolojik antiteleri temsil ediyorlar

- Germline mutasyonlarına ek olarak BRCA1/2'nin somatik ve epigenetik inaktivasyonu gibi diğer mekanizmalar da ortaya konmalı

Olgu 3

- 38 yaşında meme ca tanısı almış, şu anda 41 y.
- Kızkardeş: 40 yaşında meme ca tanısı almış, şu anda 52 y.
- Halası 55 yaşında meme ca tanısı almış, şu anda 70 y.

1. Önce ne yaparsınız?

A) Genetik test öneririm.
B) Etkilenmiş aile bireyine genetik test öneririm.
C) Genetik test önermem.
D) Meme kanser riskini değerlendirmek için Gail modeli uygularım.

(BRCA1 sequencing and 5-site rearrangement analysis & BRCA2 gene sequencing)

2. Mutasyon saptanmadı; Ne yaparsınız?

A) Daha fazla genetik test yaptırmam.

B) BART analizi (BRACAnalizi ® Rearrangement Testi) öneririm.

C) Meme ca olan diğer kız kardeşe test öneririm.

D) Risk azaltıcı BSO öneririm.

3. BART ® sonucu negatif; Risk azaltıcı yaklaşımız ne olur?

A) Risk azaltıcı BSO ?

B) Karşı memeye yönelik profilaktik mastektomi ve tarama önerilerini gözden geçiririm.

C)Test sonuçları negatif geldiği ve başka meme kanseri riski olmadığı için ek öneride bulunmam.

4. Hasta olmayan diğer kız kardeşler ve hastanın kızı için öneriniz nedir?

A) Genetik test öneririm.
B) Genel toplum meme kanser tarama programına alırım.
C) Yüksek risk meme kanseri tarama programı öneririm.
D) Yüksek risk meme ve over kanseri tarama programı öneririm.

5. Yüksek risk meme kanseri tarama programını nasıl uygularsınız?

A) 28 yaşından başlamak üzere 6 aylık dönüşümlü MG ve MRI.
B) 40 yaşından başlamak üzere 6 aylık dönüşümlü MG ve MRI.
C) 40 yaşından başlamak üzere yıllık MG.
D) 28 yaşından başlamak üzere yıllık MG.

6. Sonuç: VUS: “Önemi belirsiz varyant” Ne yaparsınız?

A) Bu ailede daha fazla teste gerek yok.

B) Tüm aile bireylerini VUS için tara.

C) Ailedeki diğer meme ya da over kanserli hastalardan kapsamlı BRCA1 ve 2 testi iste.

D) Ailede test için adayları saptamak üzere aileyi ücretsiz “Myriad varyant yeniden sınıflama programı”na dahil et.

7. Sonuç: VUS: “Önemi belirsiz varyant” Ne yapmazsınız?

A) Risk azaltıcı BSO öneririm.

B) Bilat. mastektomi seçeneğini tartışırım.

C) Ailedeki hasta olmayan kadınlara yüksek risk meme kanseri tarama programı öneririm.

D) Aileye VUS’un klinik önemini değerlendirmek üzere yıllık kontrol öneririm.