”Hurtigtest” – egnet for formålet?

Åpent møte 7 januar 2008

Gentesting ved bryst- og eggstokkreft

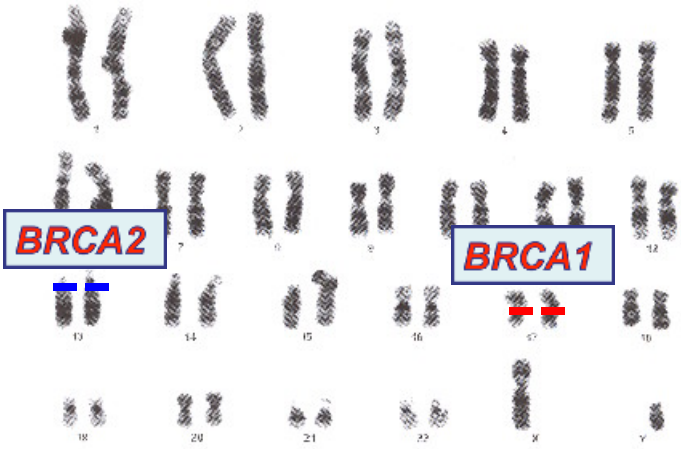
Overlege dr philos Torunn Fiskerstrand
Haukeland Universitetssykehus

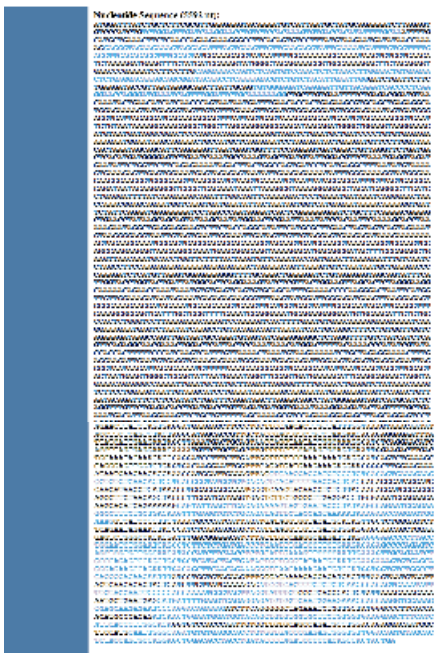
***BRCA1* mutasjoner**		
1675delA		
3[illegible]delAG		
1135insA		
816delGT		
3297G>T		
2[illegible]delT		
3203del11		
[illegible]86[illegible]delA		
c.1A>G		
T191delC		
185insA		
185delAG		
913delCT		
3171insTGAGA		
***BRCA2* mutasjoner**		
3036delACAA		
4075delGT		
[illegible]088delA		
5049delTGAinsC		
5[illegible]5delTTTAAGT		

“Hurtigtesten”

som utføres per i dag

23 par kromosomer i hver celle





- Fullt søk etter mutasjon
  - SEKVENSERING
  - MLPA-analyse
- Hurtigtest for hyppige mutasjoner i norsk befolkning
  - 2/3 av alle med mutasjon I BRCA-genene har en av 10 hyppige mutasjoner
    - *Møller P et al. Genetic epidemiology of BRCA mutations--family history detects less than 50% of the mutation carriers. Eur J Cancer. 2007 Jul;43(11):1713-7*

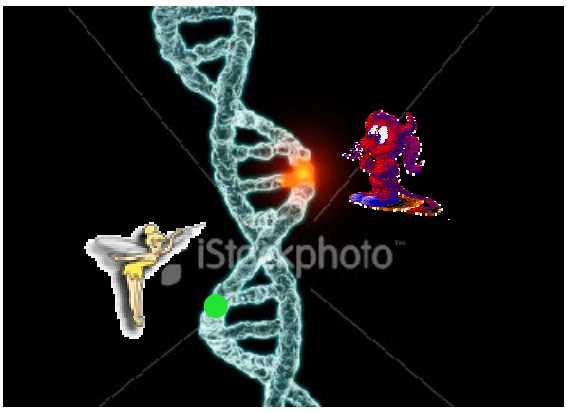
Hvorfor ikke tilby fullstendig søk etter mutasjon til alle?

- Dyre, arbeidskrevende tester
  - Teknisk gjennomføring
    - Innen få år er dette endret

Ny sekvenseringsteknologi

Personlig genom "vanlig" innen 5-10 år?

Når vi finner en variant i et gen, hvordan vet vi at den gir sykdom?

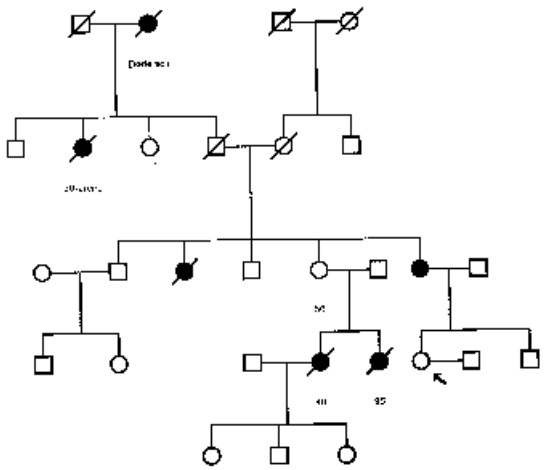


Hvorfor ikke tilby fullstendig søk etter mutasjon til alle?

- Dyre, arbeidskrevende tester
  - – Teknisk – selve analysen
    - Innen få år er dette endret
  - – Tolkning - vi finner sekvensvarianter som vi ikke vet hvordan vi skal tolke
    - *Familiehistorien* er viktig når vi skal tolke funn!

Funn av sekvensvariant i denne familien

– sannsynlig sammenheng med sykdomsrisiko



Foundermutasjoner- forekomst

Møller et al 2007

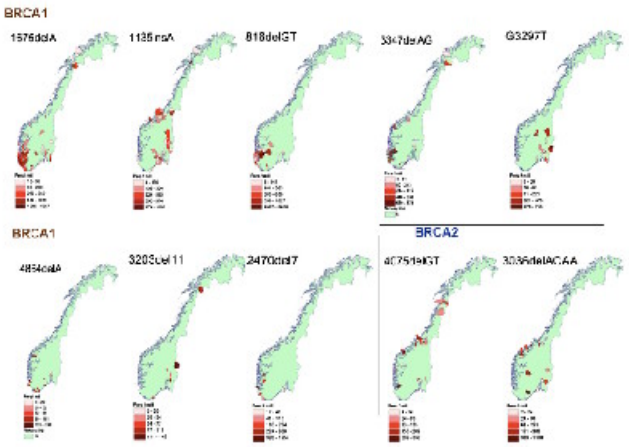
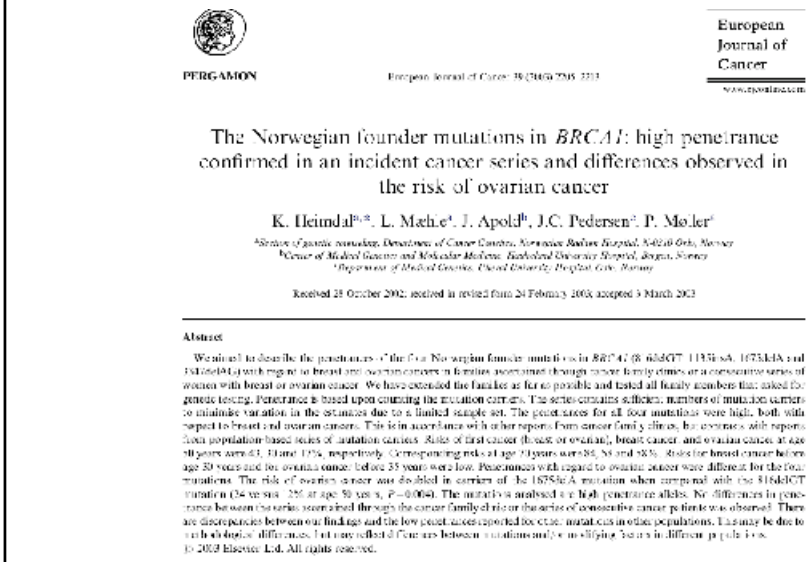


Fig. 1 – Incidence for each mutation tested for, according to municipality, as computed by linking our computerised medical files with the ArcView® digital map of Norway and population structure. Most of the Norwegian population is concentrated in some areas along the coast, and most of the inland, large areas of the coast have only limited numbers of inhabitants, if any. Together, the areas indicated as having high prevalences of one or more mutations indicate the areas where the majority of the population live.



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European Journal of Cancer

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The Norwegian founder mutations in *BRCA1*: high penetrance confirmed in an incident cancer series and differences observed in the risk of ovarian cancer

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Received 28 October 2002; received in revised form 24 February 2003; accepted 5 March 2003

Abstract

We aimed to describe the penetrance of the five Norwegian founder mutations in *BRCA1* (8.1bpdelGT, 1135insA, 1675delA and 1961delA) with regard to breast and ovarian cancers in families ascertained through cancer family clinics or a consecutive series of women with breast or ovarian cancer. We have extended the families as far as possible and tested all family members that asked for genetic testing. Penetrance is based upon counting the mutation carriers. The series contains sufficient numbers of mutation carriers to minimize variation in the estimates due to a limited sample set. The penetrances for all four mutations were high, both with respect to breast and ovarian cancers. This is in accordance with other reports from cancer family clinics, but overrates with reports from population based series of mutation carriers. Risks of first cancer (breast or ovarian), breast cancer and ovarian cancer at age 70 years were 63, 61and 13%, respectively. Corresponding risks at age 70 years were 38, 38 and 8%. Risks for breast cancer before age 50 years and for ovarian cancer before 35 years were low. Penetrances with regard to ovarian cancer were different for the four mutations. The risk of ovarian cancer was doubled in carriers of the 1675delA mutation when compared with the 816delGT mutation (24 vs. 11%, 25% at age 50 years, $P=0.004$). The mutations analysed are high penetrance alleles. No differences in penetrance between the series ascertained through the cancer family clinic or the series of consecutive cancer patients was observed. There are discrepancies between our findings and the low penetrances reported for other mutations in other populations. This may be due to methodological differences, but may reflect differences between mutations and/or modifying factors in different populations.

BRCA1 mutasjoner	IIIS	Radium
1675delA		
3347delAG		
1135insA		
816delGT		
3297G>T		
2270del7		
3203del11		
4986delA		
c.1A>G		
1191delC		
185insA		
185delAG		
913delCT		
3171insTGAGA		
***BRCA2* mutasjoner**		
3036delACAA		
4075delGT		
7088delA		
5029delTGAinsC		
5445delTTTAAGT		

"Hurtigtesten"

som utføres per i dag

Ca 3 % funn

familier med mistanke om arvelig bryst- eggstokkreft

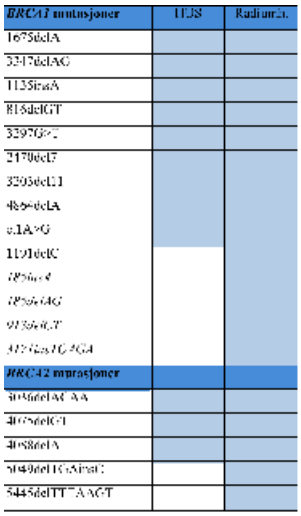
	Haukeland		Radiumhospitalet	
Mutasjon	**Totalt**	**% andel**	**Totalt**	**% andel**
Totalt	**1134**	**100,0**	**1396**	**100,0**
Ingen mutasjon	1093	96,6	1353	97,1
***BRCA1* mutasjoner**				
1675delA	11	1,0	12	0,9
3347delAG	10	0,9	1	0,1
1135insA	5	0,4	7	0,5
816delGT	5	0,4	2	0,1
5297G>T	3	0,3	5	0,4
2470del7	2	0,2	4	0,3
3203delTT	1	0,1	1	0,1
4864delA	1	0,1	Satt opp	
1191delC			1	0,1
***BRCA2* mutasjoner**				
5036delACAA	1	0,1	3	0,2
4075delGT	Satt opp		4	0,3
4088delA	Satt opp		1	0,1

Funnprosent ved fullt søk etter ukjent mutasjon

familier med mistanke om arvelig bryst- eggstokkreft

- *BRCA1* sekvensering
  - 1.5%
- *BRCA2* sekvensering
  - 3-6%
- *BRCA1* og *BRCA2* MLPA-analyse
  - 1.5%

Hvilke mutasjoner bør inngå i hurtigtesten?



BRCA1 mutasjoner	UUS	Radium…
1675delA		
3347delAG		
1135insA		
816delGT		
3297G>T		
2170delT		
3203del11		
486+6delA		
c.1A>G		
1191delC		
1854ins4		
1756delAG		
914delGT		
4374ins1GAGA		
***BRCA2* mutasjoner**		
3036delACAAA		
4075delGT		
4088delA		
9149delTGAinsC		
5445delTTCAAGT		

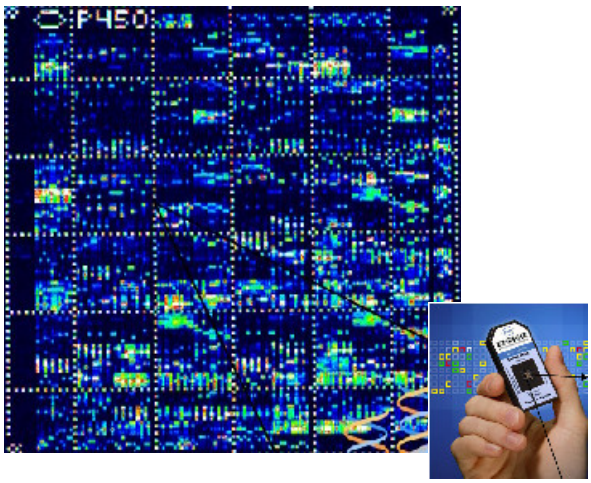
- Utvides?
- Teste for færre?

Mutasjoner i BRCA-genene i Norge

- Ca 100 antatt sykdomsgivende mutasjoner er sett *BRCA1* og *BRCA2* i Norge per i dag
- Er det mulig å teste for alle disse på en enkel måte?

Chip-teknologi -

Teste for alle BRCA-mutasjoner på en Chip?



Problemer med å "utvide" hurtigtesten?

- Kun de 4 hyppigste mutasjoner i Norge er *spesifikt* undersøkt med tanke på risiko for sykdom (penetrans)
  - OK å bruke de samme risikotall for mutasjoner som er sett i kun en familie?
- Spørsmål
  - *Er risiko for sykdom den samme i alle familier?*

Familier med høy mistanke om arvelig kreft

- Funn av sekvensvariant som med høy grad av sikkerhet antas å ødelegge BRCA-proteinet forklarer pasientens sykdom
  - Rammeskiftmutasjoner
  - Stoppmutasjoner
  - Spleisevarianter
  - Delesjon/duplikasjon av hele ekson(er)
- Friske familiemedlemmer veiledes om at de har høy risiko for brystkreft og eggstokkreft
  - For mutasjoner som er sett i mange familier er risikotallene noe sikrere
  - For mutasjoner som er spesifikke for en familie kan vi ikke gi sikre risikotall

Er kreftrisikoen lik for alle trunkerende mutasjoner?

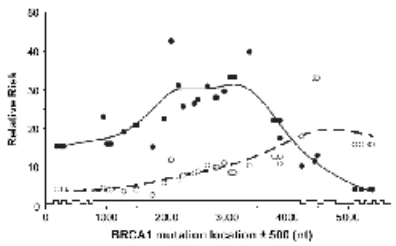


Fig. 1. Relative risks of ovarian and breast cancers in the general Ontario population for BRCA1 mutations within 500 nucleotides of the position plotted. Ovary = solid circles and solid line (smoothed); breast = open circles and dashed line (smoothed). The thin line at the bottom indicates locations of the 5′-untranslated region and exons 2, 3, and 5–24 according to positions in the cDNA. The long middle span in this line is exon 11.

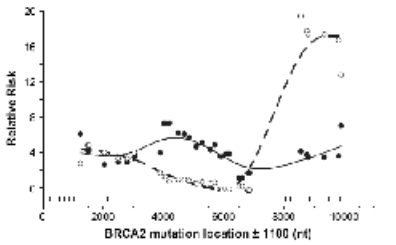
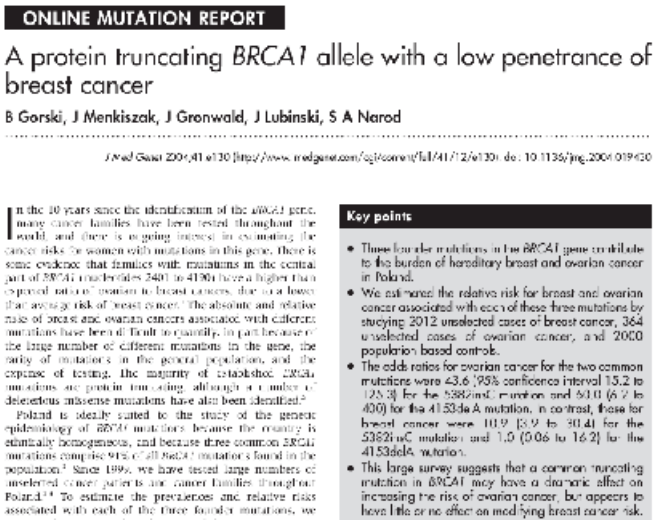


Fig. 2. Relative risks of ovarian and breast cancers in the general Ontario population for BRCA2 mutations within 1100 nucleotides of the position plotted. Ovary = solid circles and solid line (smoothed); breast = open circles and dashed line (smoothed). The thin line at the bottom indicates the locations of the 5′-untranslated region and exons 2–27 in the cDNA. The long middle span in this line is exon 11.



ONLINE MUTATION REPORT

A protein truncating *BRCA1* allele with a low penetrance of breast cancer

B Gorski, J Menkiszak, J Gronwald, J Lubinski, S A Narod

J Med Genet 2004;41:e130 (http://www.jmedgenet.com/cgi/content/full/41/12/e130) doi: 10.1136/jmg.2004.019430

In the 10 years since the identification of the *BRCA1* gene, many cancer families have been tested throughout the world, and there is ongoing interest in estimating the cancer risks for women with mutations in this gene. There is some evidence that families with mutations in the central part of *BRCA1* (nucleotides 2400 to 4190) have a higher than expected ratio of ovarian to breast cancers, due to a lower than average risk of breast cancer.[1] The absolute and relative risks of breast and ovarian cancers associated with different mutations have been difficult to quantify, in part because of the large number of different mutations in the gene, the rarity of mutations in the general population, and the expense of testing. The majority of established *BRCA1* mutations are protein truncating although a number of deleterious missense mutations have also been identified.[2]

Poland is ideally suited to the study of the genetic epidemiology of *BRCA1* mutations because the country is ethnically homogeneous, and because three common *BRCA1* mutations comprise 91% of all *BRCA1* mutations found in the population.[3] Since 1996, we have tested large numbers of unselected cancer patients and cancer families throughout Poland.[3 4] To estimate the prevalences and relative risks associated with each of the three founder mutations, we

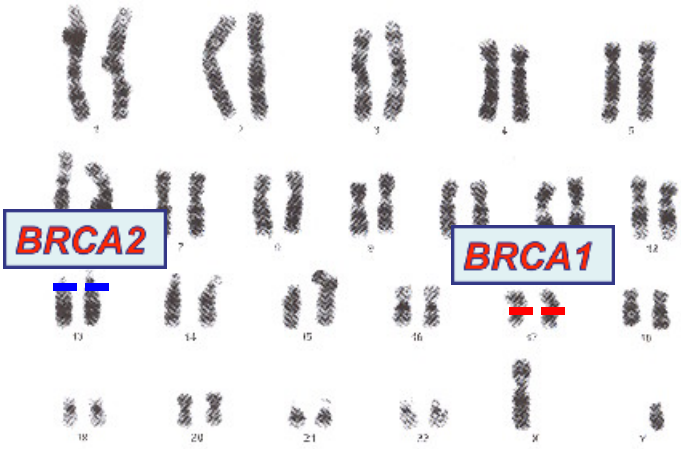
Key points

- Three founder mutations in the *BRCA1* gene contribute to the burden of hereditary breast and ovarian cancer in Poland.
- We estimated the relative risk for breast and ovarian cancer associated with each of these three mutations by studying 2012 unselected cases of breast cancer, 364 unselected cases of ovarian cancer, and 2000 population based controls.
- The odds ratios for ovarian cancer for the two common mutations were 43.6 (95% confidence interval 15.2 to 125.3) for the 5382insC mutation and 6.1.0 (6.2 to 400) for the 4153delA mutation, in contrast, those for breast cancer were 10.9 (3.9 to 30.4) for the 5382insC mutation and 1.0 (0.06 to 16.2) for the 4153delA mutation.
- This large survey suggests that a common truncating mutation in *BRCA1* may have a dramatic effect on increasing the risk of ovarian cancer, but appears to have little or no effect on modifying breast cancer risk.

Vesentlig spørsmål

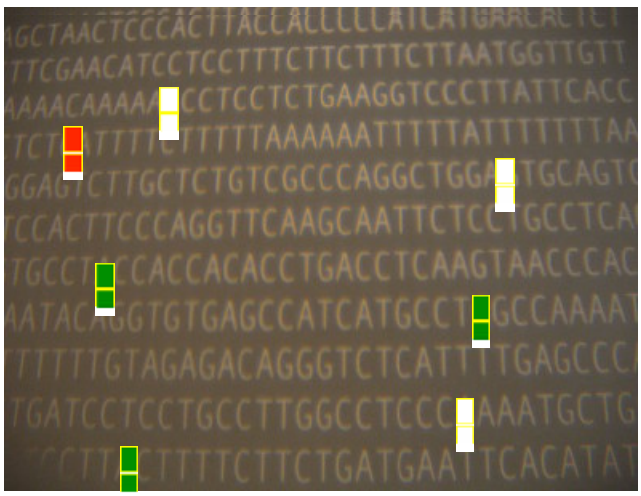
- Familier som får påvist kjent BRCA-mutasjon *som følge av* det nye tilbudet om gentesting
  - Ingen betydelig opphopning av kreft i familien
    - Har de lavere risiko enn de familiene de genetiske avdelingene til nå stort sett har arbeidet med?
      - Som rekrutteres pga mange med kreft i familien

25000 protein-kodende gener



Arvelig bryskreft – mutasjon i *BRCA1*

Gunstig multifaktoriell bakgrunn –lavere risiko (???)



CIMBA

(The Consortium of Investigators of Modifiers of BRCA1/2)

[Publications] [Contact Us]

Publications:

Gene et al. (2006) An investigation of the polymorphisms -309 T/G and Arg72Pro in p53 as breast cancer risk modifiers in *BRCA1* and *BRCA2* mutation carriers. *British Journal of Cancer* 95(8):974-7

Antoniou et al. (2006) Common breast cancer-predisposition alleles are associated with breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. *Am J Hum Genet* 79(6):1117-45

Robbook et al. (2006) No association of 76P>T L13P genotypes and breast cancer risk in *BRCA1* and *BRCA2* mutation carriers: a multi-center cohort study. *Breast Cancer Res Treat* Epub

Couch et al. (2007) ALDH3A1 SNP, Polymorphism and Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers: A Consortium of Investigators of Modifiers of *BRCA1/2* Study. *Cancer Epidemiol Biomarkers Prev* 2007 Jul;16(7):1410-21

Antoniou, et al (2007) RAD51 135G->C Modifies Breast Cancer Risk among *BRCA2* Mutation Carriers: Results from a Combined Analysis of 19 Studies. *Am J Hum Genet* 81(6):1186-200

Chenevix-Trench et al (2007) An international initiative to identify genetic modifiers of *BRCA1* and *BRCA2*: the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA). *Breast Cancer Research* 9(2):104

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Variation of Breast Cancer Risk Among *BRCA1/2* Carriers

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Åke Borg, PhD
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Patrick Concannon, PhD
Duncan C. Thomas, PhD
Bryan Langholz, PhD
Leslie Bernstein, PhD
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Janine L. Bernstein, PhD

Context The risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers has been examined in many studies, but relatively little attention has been paid to the degree to which the risk may vary among carriers.

Objectives To determine the extent to which risks for *BRCA1* and *BRCA2* carriers vary with respect to observable and unobservable characteristics.

Design, Setting, and Participants Probands were identified from a population-based, case-control study (Women's Environmental Cancer and Radiation Epidemiology [WECARE]) of asynchronous contralateral breast cancer conducted during the period of January 2000 to July 2004. Participants previously diagnosed with contralateral breast cancer or unilateral breast cancer were genotyped for mutations in *BRCA1* and *BRCA2*. All participants had their initial breast cancer diagnosed during the period of January 1966 to December 2000, before the age of 55 years.

Main Outcome Measure Incidence of breast cancer in first-degree female relatives of the probands was examined and compared on the basis of proband characteristics and on the basis of variation between families.

Results Among the 1399 participants with unilateral breast cancer, 73 (5.2%) were identified as carriers of deleterious mutations (42 with *BRCA1* and 31 with *BRCA2*). Among the 704 participants with contralateral breast cancer, 108 (15.3%) were identified as carriers of deleterious mutations (67 with *BRCA1* and 41 with *BRCA2*). Among relatives of carriers, risk was significantly associated with younger age at diagnosis in the proband ($P=.04$), and there was a trend toward higher risk for relatives of contralateral breast cancer vs unilateral breast cancer participants (odds ratio, 1.4 [95% confidence interval, 0.8-2.4]; $P=.28$). In addition, there were significant differences in risk between carrier families after adjusting for these observed characteristics.

Conclusion There exists broad variation in breast cancer risk among carriers of *BRCA1* and *BRCA2* mutations.

JAMA. 2006;295(2):184-201 www.jama.com

THE MAGNITUDE OF THE RISK OF breast cancer in carriers of mutations in *BRCA1* or *BRCA2* is critical for guiding decisions concerning cancer prevention options. Many previous studies have re-

Meta-analyse

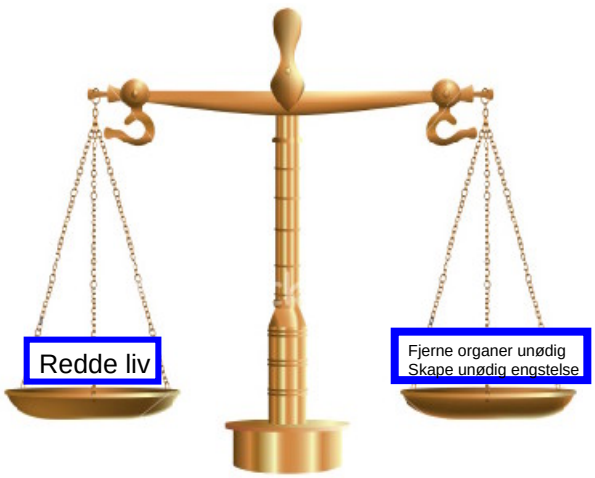
- Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with *BRCA1 or BRCA2 mutations detected in case series* unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet. 2003;72(5):1117*-1130
  - *Halvparten av stuidene: Cases selektert på basis av alder <50 år ved diagnose*

- Risiko for brystkreft ved 70 års alder
  - 65 % *BRCA1*
  - 45 % *BRCA2*

- *Risiko for eggstokkreft ved 70 års alder*
  - *39% BRCA1*
  - *11% BRCA2*

Risiko for sykdom er ikke 100%

Ved mutasjoner i BRCA1 og BRCA2



Er testen ”sikker nok”

- Kvantitative tester
  - Presisjon, reproduserbarhet, analytisk og klinisk validitet, sensitivitet, spesifisitet, positiv og negativ prediktiv verdi
- Forskjell på kvantitative og kvalitative tester
  - Genetiske tester er stort sett kvalitative
  - Høy presisjon og reproduserbarhet

Sammendrag

- Hurtigtest er egnet til formålet
  - Å tilby test for varianter i BRCA-genene som gir høy risiko for å utvikle kreft
    - Variantene i testen må være godt undersøkt i mange familier
  - Må vite at testen ikke påviser alle mutasjoner!
    - Familier med stor kreftopphopning bør henvises til genetisk avdeling
- For hver mutasjon i hurtigtesten skal det foreligge dokumentasjon om forekomst og risiko
  - Medisinsk genetiske avdelinger og lab’er må samarbeide om å fremskaffe dokumentasjonen
- Kan samme mutasjon i ulike familier gi forskjellig risiko, basert på ulik total genvariasjon?
  - Forskning på dette bør iverksettes sammen med tiltaket