HEREDITY & CANCER:
Breast cancer as a model

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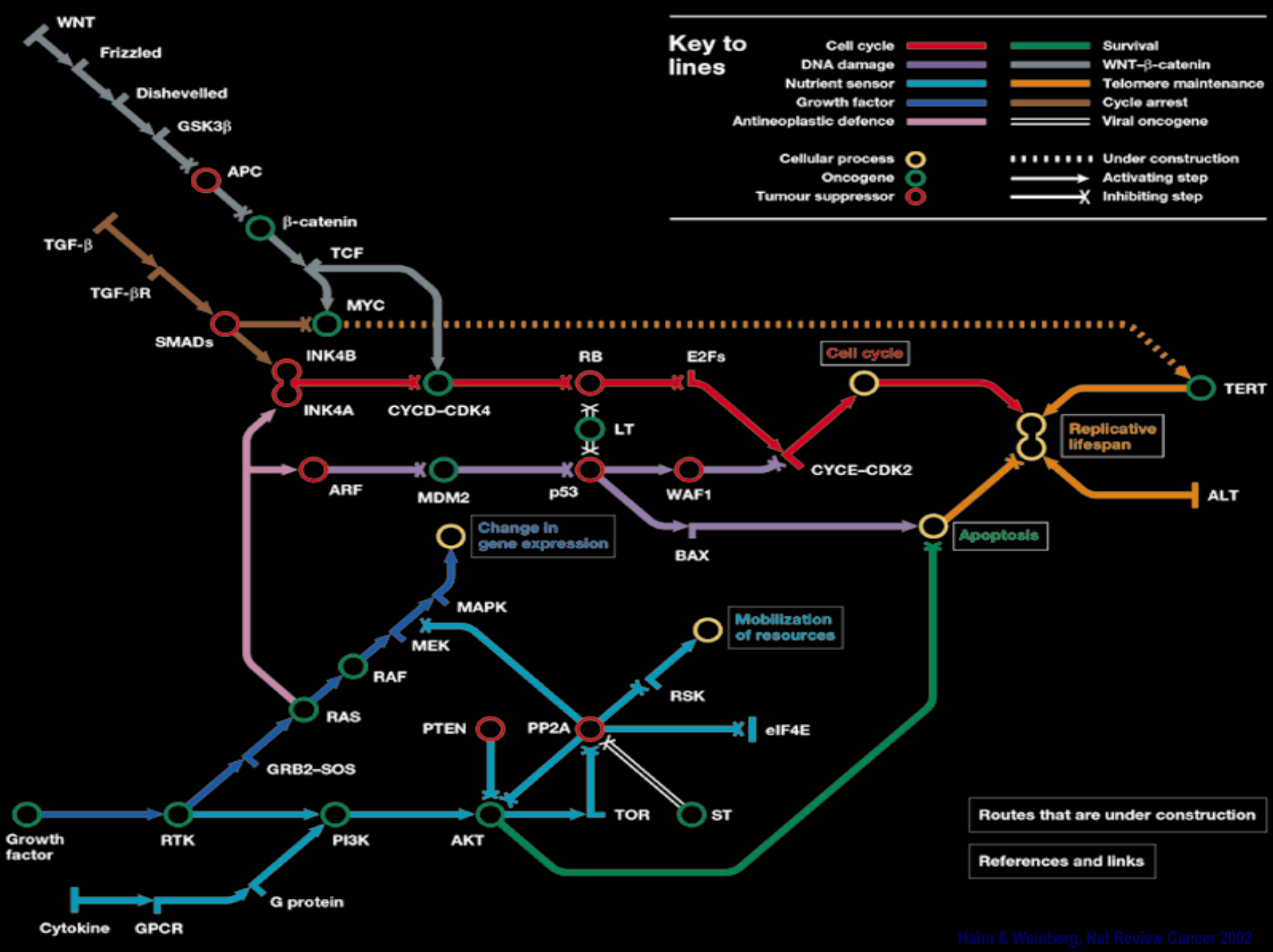
Genetics, Cancer and Heredity

- **Cancers** are **genetic diseases**

- **Predisposition** to some cancers is **hereditary**

  ⇨ ***"at risk" individuals***



Hahn & Weinberg, Nat Review Cancer 2002

“Hereditary” cancer: **Definition**

Cancer resulting from the inheritance, generally as an autosomal dominant trait, of a germline alteration in one gene, conferring a genetic susceptibility to the development of cancer.

“Hereditary” cancer:
RETINOBLASTOMA: a paradigm

- Childhood eye tumor
- Both hereditary and sporadic forms
- Sporadic forms always unilateral
- Hereditary forms usually bilateral

The two-hit hypothesis *[Knudson, 1978]*

- Each cell contains 2 copies of each autosomal gene
- In **HEREDITARY Rb**, one mutation of the *RB1* gene is passed to the child (sometimes *de novo*)
- Thus there is a single *RB1* mutation in all retinoblasts:
  - no advantage to the mutated cell
  - when a **second hit** occurs (to any retinoblast) there is no functioning Rb protein ⇨ **RETINOBLASTOMA**

The two-hit hypothesis *[Knudson, 1978]*

- Tumors often bilateral because each eye has 10^7 retinoblasts, so two hits in more than one cell is not so unlikely.

- In **SPORADIC**, non-hereditary Rb, BOTH hits have to occur post-natally in the retinoblasts: this is much less likely to happen, so sporadic Rb is late in onset *and* unilateral.

Hereditary predispositions to cancer

- 5-10% of all cancers
- Autosomal dominant transmission
  - ⇨ risk at each conception = **50%**
- Low prevalence, high penetrance

Familial Cancer Syndromes

Syndromes	*Genes*	Chromosomes
Hereditary breast cancer	***BRCA1***	***17q***
	BRCA2	***13q***
Hereditary nonpolyposis colorectal cancer (HNPCC; Lynch syndrome)	***MSH2***	2p
	MLH1	3p
	MSH6, PMS1, PMS2	2p, 2q, 7p
Familial adenomatous polyposis (FAP)	*APC*	5q
Li-Fraumeni	*TP53*	17p
Retinoblastoma	*RB1*	13q
Multiple endocrine neoplasia (MEN) 2	*RET*	10q
von Hippel-Lindau	*VHL*	3p
Familial melanoma	*CDKN2*	9p
	CDK4	12q
Familial gastric cancer	*CDH1*	16q
Cowden disease	*PTEN*	10q
Peutz-Jeghers	*STK11*	19p

Hereditary Cancer Syndromes:
Use of genetic testing

Molecular screening

dHPLC, SSCP, PTT, sequencing

Identification of pathogenic mutations

CARRIERS

Surveillance/prevention

NON CARRIERS

Reassurance

Genetic screening in oncology: **Who's concerned?**

Suggestive familial aggregation, if cancer:

- in $\geq$ 2 generations
- early age of onset
- identified in gender where usually uncommon
- associated with other types of cancer, congenital malformations or genetic syndromes
- in a defined ethnic background

Genetic screening in oncology: **Who's concerned?**

"Individual" susceptibility, if cancer:

- bilateral
- multicentric
- multiple
- at an unusual age, site or gender
- associated with congenital malformations or genetic syndromes
- in a defined ethnic background

Genetic screening in oncology: **Why?**

- Clarify risk evaluation
- Target screening/prevention efforts to the identified carriers of genetic predisposition to cancer
- Exclude the non-carriers of specific programs of screening/prevention
- No risk for the children of proven non-carriers
- Knowledge of the genetic status: *"need to know"*

Oncogenetic counseling process

Hôpitaux Universitaires de Genève

- Validation of diagnosis

1st Consultation

- Motivation, expectation
- Genetics, heredity and cancer
- Detailed personal and family history

Consensus consultation

- Risk evaluation
- Probability of genetic predisposition
- Screening and prevention measures
- Availability of genetic analysis

2nd consultation

- Limit and consequence of genetic analysis
- Types of result

Genetic testing

- Affected family member available?

3rd consultation

- Transmission of results

- Follow-up

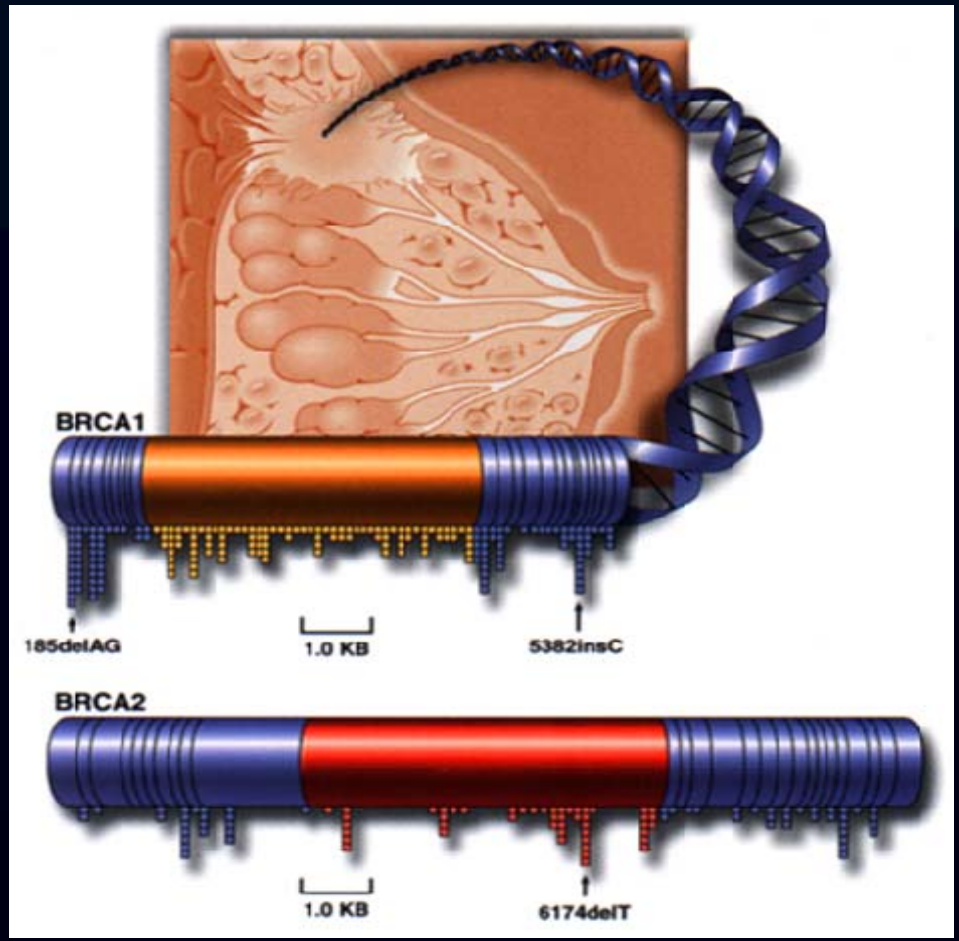
Genetic testing: **Types of result**

1. **Genetic alteration identified**
   - pathogenic mutation
   - variant (unknown biological significance)
   - polymorphism

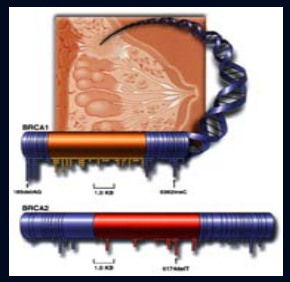
2. **No genetic alteration** ("*no mutation detected*")
   - does not exclude a genetic predisposition!
   - technical limits, other gene, phenocopy

3. **Genetic alteration excluded**
   - only when previously identified in the family

GENETIC PREDISPOSITION to BREAST CANCER



[Clin Breast Ca 2000]



BRCA1/BRCA2 germline mutations and breast cancer

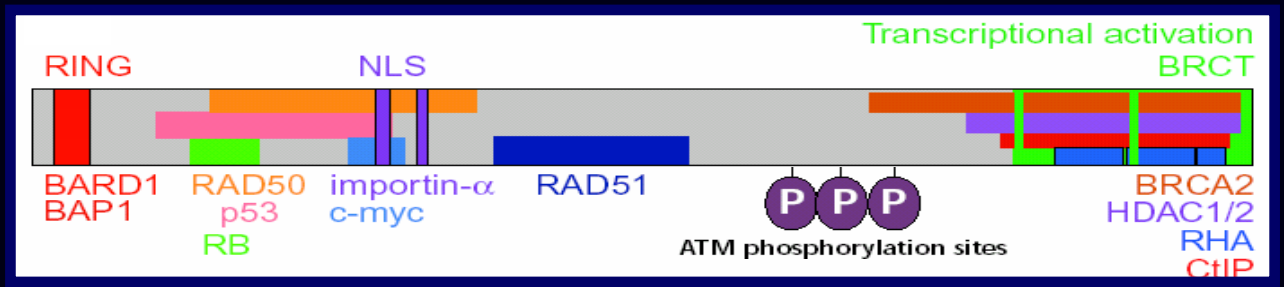
- **Major genetic predisposition to breast/ovarian cancer**
- Autosomal dominant transmission
- *BRCA1/2*-related breast cancers: histo-pathological characteristics usually associated with worse outcome
- Clinical outcomes incompletely defined
- Clinical management questions unanswered

Hereditary breast cancer:
Other predisposing genes

- ***TP53*** Li-Fraumeni syndrome
- ***ATM*** Ataxia telangiectasia
- ***STK11/LKB1*** Peutz-Jeghers syndrome
- ***PTEN*** Cowden syndrome
- *BRCA3* (?) locus on chromosome 13q21

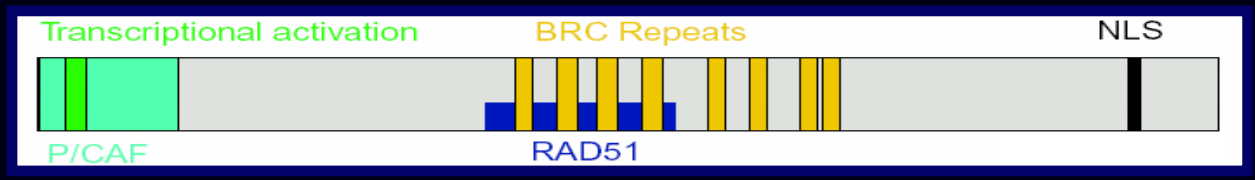
BRCA1 gene

- 17q21
- > 100 kb
- 24 exons
- > 500 different genetic alterations
- Nuclear phosphoprotein: 1863 aa / 220kDa
- Responsible for ~30% of site-specific hereditary breast cancer and ~50% of hereditary breast/ovarian cancer



BRCA2 gene

- 13q12
- > 70 kb
- 27 exons
- > 200 different genetic alterations
- Nuclear protein: 3418 aa / 384kDa
- Responsible for ~40% of site-specific hereditary breast cancer and ~15% of hereditary breast and ovarian cancer

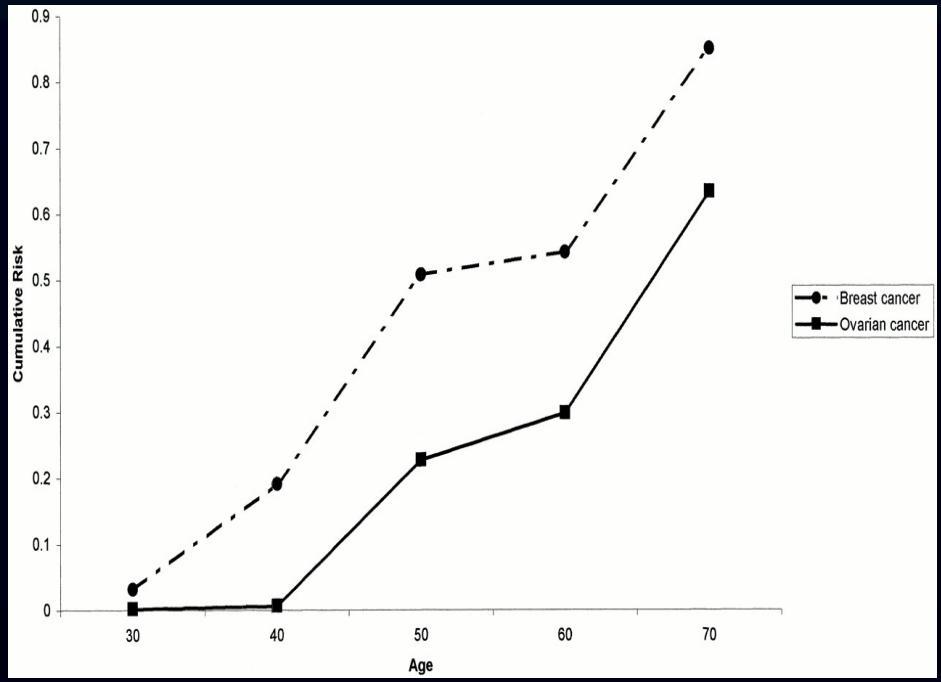


BRCA1 & BRCA2: Multifunctional proteins

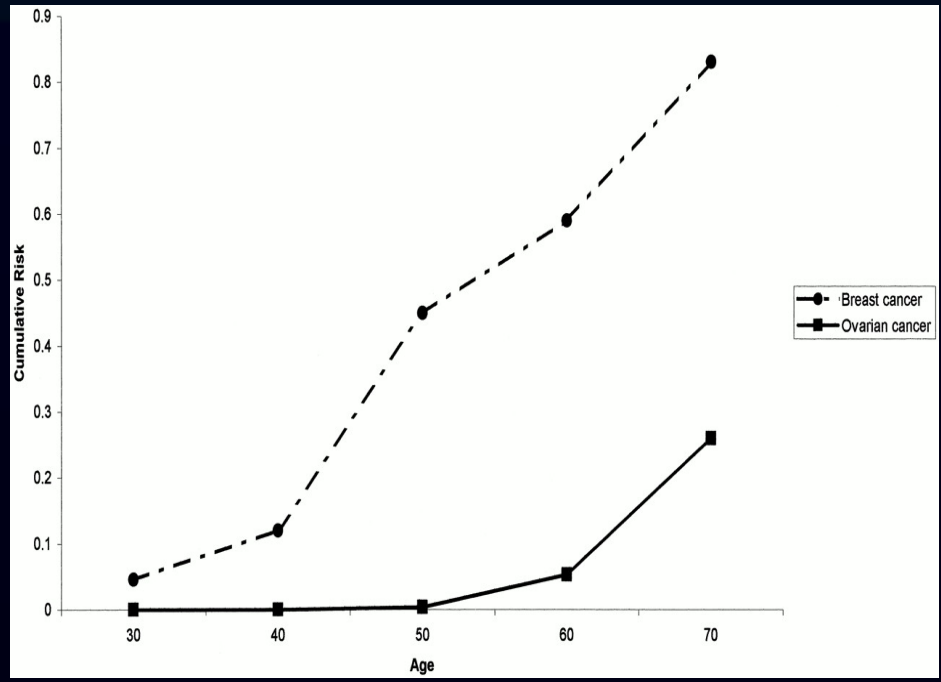
- Transcriptional regulation
- Cell cycle regulation (checkpoint control)
- Growth suppression
- **Response to DNA damage**
  - double strand-break repair
  - base excision repair (BRCA1)
- **Maintenance genome stability**
- Apoptosis induction

BRCA1/2 mutations: **Risk of breast/ovarian cancer**

BRCA1



BRCA2



[Eeles & Powles, J Clin Oncol 2000]

BRCA1/BRCA2 germline mutations: **Epidemiology**

	BRCA1	***BRCA2***
General population	1/830	?
Ashkenazi Jews	1/86 (185delAG, 5382insC)	1/74 (6174delT)

BREAST CANCER	*BRCA1 + BRCA2*
General population	**2 - 5%**
< 40 years	6 - 16%
Ashkenazi Jews	~12%
< 40 years	~40%

BRCA1-related breast cancer: **Clinicopathological features**

- Younger age of onset
- Invasive ductal — $P = 0.05$
- Medullary/atypical med. — $P < 0.0001$
- Histological grade 3 — $P < 0.0001$
- ER/PR negativity — $P < 0.0001$
- *TP53* mutation — $P = 0.0003$
- HER2 positivity (less) — $P < 0.0001$

[Sem Surg Oncol 2000; 18:287-95]

BRCA2-related breast cancer: **Clinicopathological features**

- Invasive ductal — $P = 0.06$
- Less tubule formation — $P < 0.0001$
- *TP53* mutations — $P = 0.03$

[Sem Surg Oncol 2000; 18:287-95]

“Hereditary” breast cancer: **Clinical presentation**

- Early age of onset (< 45 years)
- Several family members affected (≥ 3)
- More than one generation involved (autosomal dominant)
- Bilateral breast cancer
- Associated cancers:
  - #1: **ovarian cancer**, peritoneal and fallopian tube cancer
  - others: male breast, prostate, pancreas cancer (*BRCA2*)

High risk women for breast cancer: **OPTIONS**

- **SCREENING**
- **CHEMOPREVENTION**
- **PROPHYLACTIC SURGERY**
- Lifestyle modification?

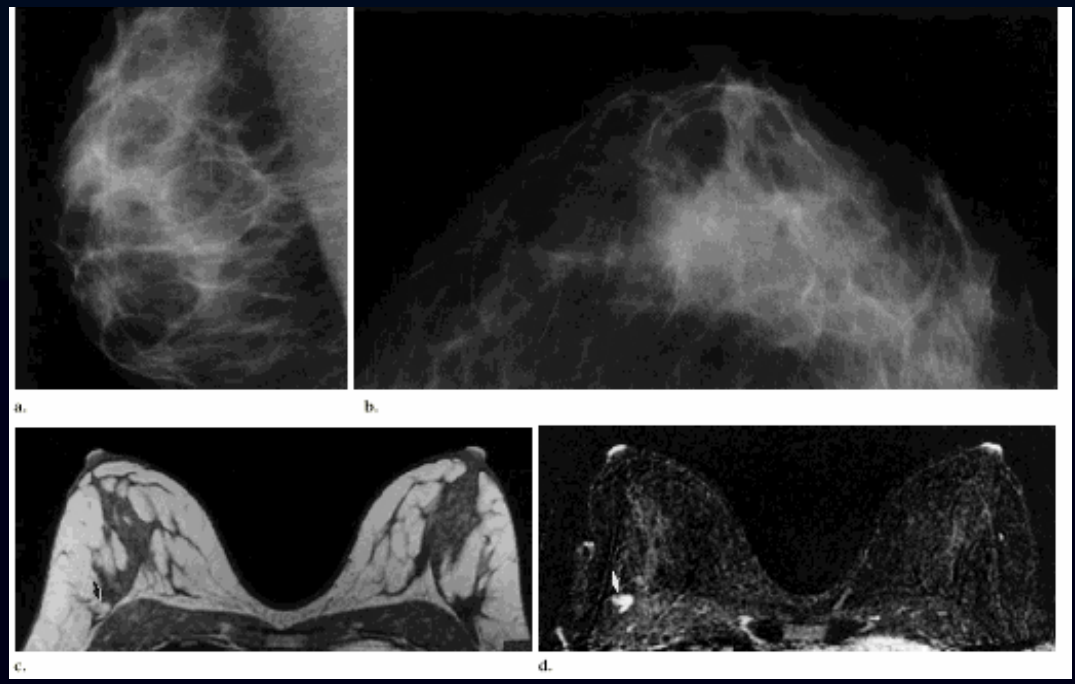
High risk women for breast cancer: **Screening recommendations**

Technique	Start	Frequency
Breast self examination	20 years	1x / month
Clinical breast examination	25 years	2-3x / year
Mammography ± US	25-30 years	1x / year
MRI (investigational)	25-30 years	1x / year

Surveillance in *BRCA1/2* mutation carriers: **Prospective studies**

	Brekelmans *et al.* *[J Clin Oncol 2001]*	**Meijers-Heijboer *et al.*** *[N Engl J Med 2001]*	**Scheuer *et al.*** *[J Clin Oncol 2002]*
***BRCA1/2* carriers**	128	63	165
Screening	BSE 1x/m, CBE 2x/y, mammo ± US 1x/y	BSE 1x/m, CBE 2x/y, mammo ± US 1x/y; MRI 1x/y (since 1995)	BSE 1x/m, CBE 2-4x/y, mammo ± US 1x/y
Mean follow-up	3 years	3 years	2 years
***In situ* carcinoma**	0	n/s	3
Invasive carcinoma	9	8	9
N+	5/9	4/8	3/9
Interval cancers	4/9	4/8	6/12
Sensitivity	**56%**	**50%**	**50%**

Mammography and MRI



- 5 studies in high risk women
- No randomization
- No data on mortality rates

High risk women for breast cancer: **Mammography** & **MRI 1x/year**

	Kuhl *et al.* *[Radiology 2000]*	**Tilanius-Linthorst *et al.*** *[Breast Ca Res Treat 2000]*	**Meijers-Heijboer *et al.*** *[N Engl J Med 2001]*	**Stoutjesdijk *et al.*** *[J Natl Cancer Inst 2001]*	**Warner *et al.*** *[J Clin Oncol 2001]*
Population studied	192 "high risk" 35 *BRCA1/2*	109 > 25% risk + > 50% dense tissue 12 *BRCA1/2*	63 *BRCA1/2*	179 "high risk" 47 *BRCA1/2*	196 high risk 96 *BRCA1/2*
Type of study	prospective	retrospective	prospective	historical cohort	prospective
Mean follow-up	2.5 years	n/s	3 years	n/s	1.5 years
***In situ*/invasive BC**	2/7	0/3	0/8	3/10	1/6
Mammography	3/9 (2/9: "fibroadenomas")	0/3	2/8	6/12	3/6
MRI	**9/9**	**3/3**	**6/6**	**13/13**	**6/7** (*in situ* not detected)
Positive predictive value	Mammo: 30% MRI: **64%**	Mammo: 0% MRI: **33%**	n/s	Mammo: 33% MRI: **43%**	Mammo: 66% MRI: **26%**

High risk women for breast cancer:
CHEMOPREVENTION

- **TAMOXIFEN**
- LHRH agonists
  aromatase inhibitors
  retinoids, …

High risk women for breast cancer:

PREVENTION by SURGICAL MEASURES

- **MASTECTOMY**
- **OOPHORECTOMY**

BRCA1/2 mutation carriers:

Breast cancer risk after prophylactic mastectomy

Study	n	Follow-up (years)	# breast cancer	Type of mastectomy
Hartmann *et al.* *[N Engl J Med 1999]*	Moderate risk: 425 High risk: 214	14	4 3	subcutaneous subcutaneous
Hartmann *et al.* *[J Natl Cancer Inst 2001]*	*BRCA1/2*: 26	16	**0**	total
Meijers-Heijboer *et al.* *[N Engl J Med 2001]*	*BRCA1/2*: 76	2.9	**0**	total
Scheuer *et al.* *[J Clin Oncol 2002]*	*BRCA1/2*: 29	2	**0**	n/s

BRCA1/2 mutation carriers:
Breast cancer risk after prophylactic mastectomy

Study	n	Follow-up (years)	# breast cancer	Type of mastectomy	Surveillance group
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Meijers-Heijboer *et al.* *[N Engl J Med 2001]*	*BRCA1/2*: 76	2.9	**0**	total	**8 breast cancers** in 63 carriers ($P = 0.003$)
Scheuer *et al.* *[J Clin Oncol 2002]*	*BRCA1/2*: 29	2	**0**	n/s	**12 breast cancers** in 165 carriers ($P = 0.13$)

Prophylactic oophorectomy and breast cancer risk

Study	Gene	n	Follow-up	RR
Rebbeck *et al*., *[J Natl Cancer Insr 1999]*	*BRCA1*	43	9.6 years	0.53 (0.33-0.84)
Eisen *et al*., *[J Clin Oncol 2000]*	*BRCA1/2*	n/s	n/s	*BRCA1:* 0.39 (0.2-0.75) *BRCA2:* 0.56 (0.16-1.95)

- Lower risk with > 10 year follow-up
- Reduction risk not lost by HRT
- **Risk reduction greatest when oophorectomy ≤ 40 years**

Prophylactic surgery and breast cancer risk: **Remaining issues**

- Early data look encouraging
- No evidence of long-term effectiveness mastectomy in *BRCA1/2* mutation carriers ascertained prospectively
- Psychological impact
- Prolongation of survival?

Genetic testing in oncology: **Conclusions**

- Highly specific, but low sensitivity
- Population concerned is limited
- Predicitive oncology = probabilistic medicine
- Standard of care
- Multidisciplinary approach
- Psycho-social and ethical implications

Genetic testing in oncology: **Unresolved issues**

- Validation of tests
- Pathogenicity of rare variants
- Geno/phenotypic correlations
- Modifier genes/environmental factors
- Psycho-social issues
- Surveillance and prevention

Genetic testing in oncology: **Perspectives**

- **Multigenic disorders**
- **Sporadic cancers:** *population screening*
- **Changes in social/medical behaviors:**

  "medicine for well-being individuals"
- **Innovative preventive strategies**