GENETICA E CANCRO DELLA MAMMELLA

Marina Guenzi

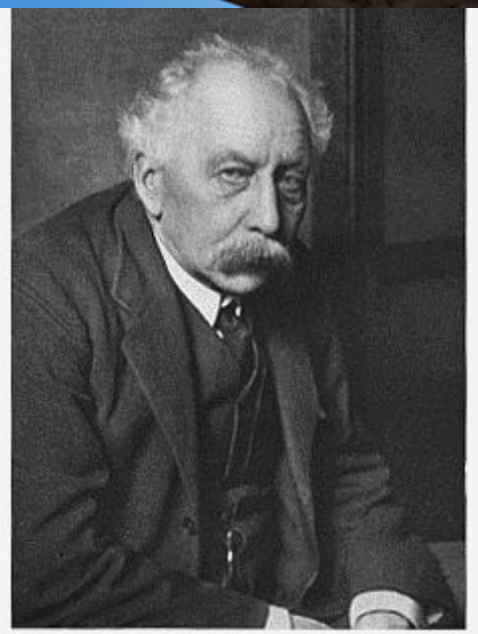
Genova

GENETICA E CANCRO DELLA MAMMELLA

QUALE RUOLO NELLA CLINICA

XXV CONGRESSO NAZIONALE
AIRO 2015
PALACONGRESSI - Rimini, 7-10 novembre

dal greco antico γενετικός, *ghenetikós*,
«relativo alla nascita»,
da γένεσις *ghénesis*, «genesi, origine»

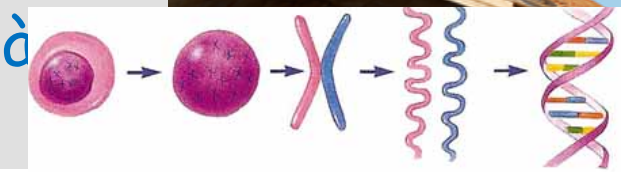


Whitby, 8 agosto 1861 – Londra, 8 febbraio 1926)

La **genetica**…

…. è la branca della biologia che studia i geni, l'ereditarietà e la variabilità genetica negli organismi viventi.

La genetica… …. è la branca della biologia che studia i geni, l'ereditarietà e la variabilità genetica

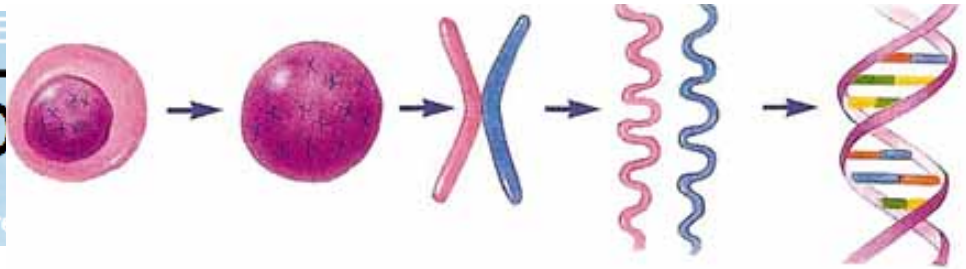


Genes are pieces of DNA inside each cell that tell the cell what to do and when to grow and divide.

Most genes are contained in chromosomes

A chromosome is a long strand of DNA wrapped around a special protein called histone.

Most chromosomes contain many different genes

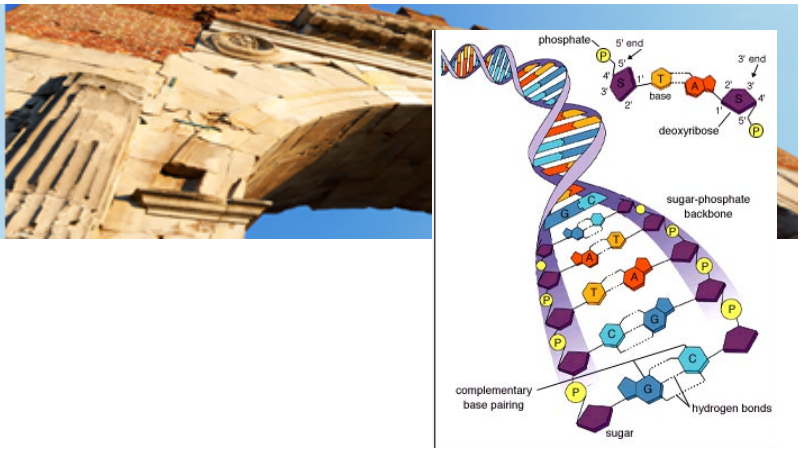


Each gene is made up of a specific DNA sequence that contains the code to make a certain protein, each of which has a specific function

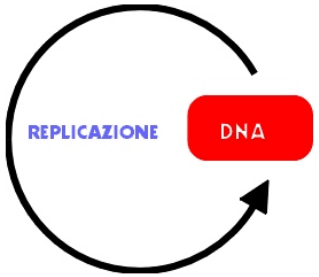
A cell uses its genes selectively; it can turn on (activat) the genes it needs at the right moment and turn off other genes that it doesn't need.

In this way cell becomes specialized

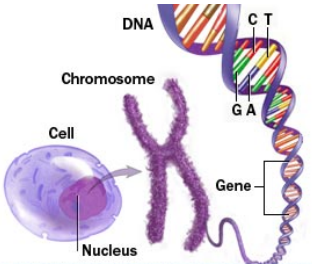
All the cells in the body (except egg and sperm) contain the same genes.

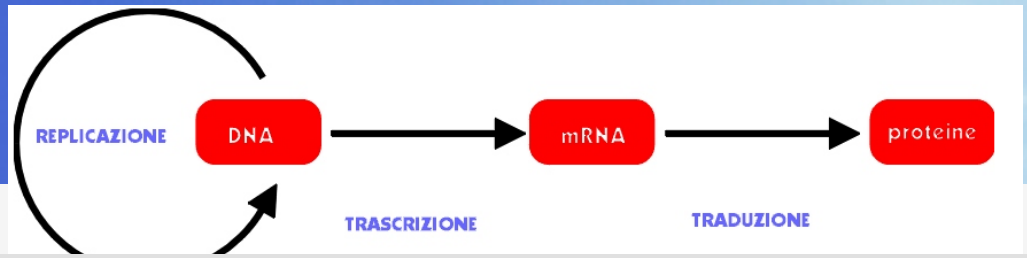


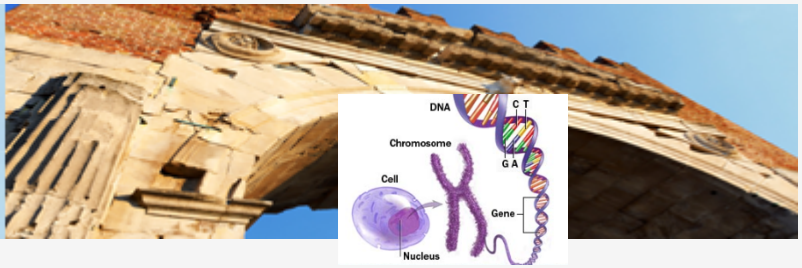
L'informazione genetica risiede essenzialmente nel DNA.



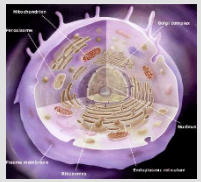
L'informazione genetica viene riprodotta prima che una cellula si divida mediante la *replicazione del DNA*



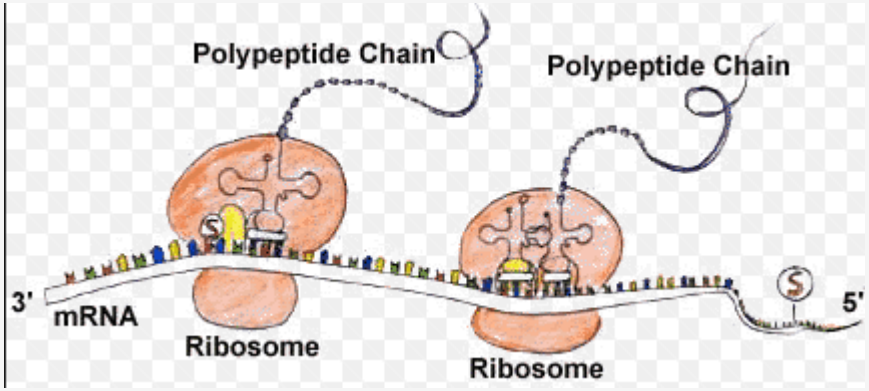




L'informazione di un frammento di Dna viene ricopiata in un filamento di RNA (trascrizione)

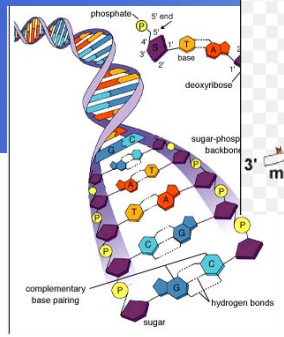


mRNA trasporta l'informazione dal Dna ai ribosomi→ produzione delle proteine in base alla sequenza di nucleotidi



un amminoacido → sequenza 3 nucleotidi (*tripletta*).

Il *codice genetico* è la regola di corrispondenza tra le triplette e gli amminoacidi



stop a protein
change the protein
more of the protein than usual

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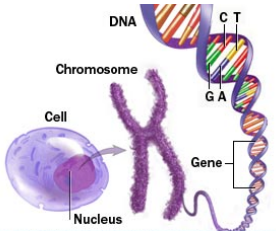
Molecular Biology and Genetics of Breast Cancer Development: A Clinical Perspective

Thomas A. Buchholz and David E. Wazer

Seminars in Radiation Oncology, Vol 12, No 4 (October), 2002: pp 285-295

Breast Cancer Is a Genetic Disease

Breast cancer results from a series of complex genetic and epigenetic events that result in a malignant transformation of a normal epithelial cell.



Le **mutazioni** possono verificarsi

spontaneamente

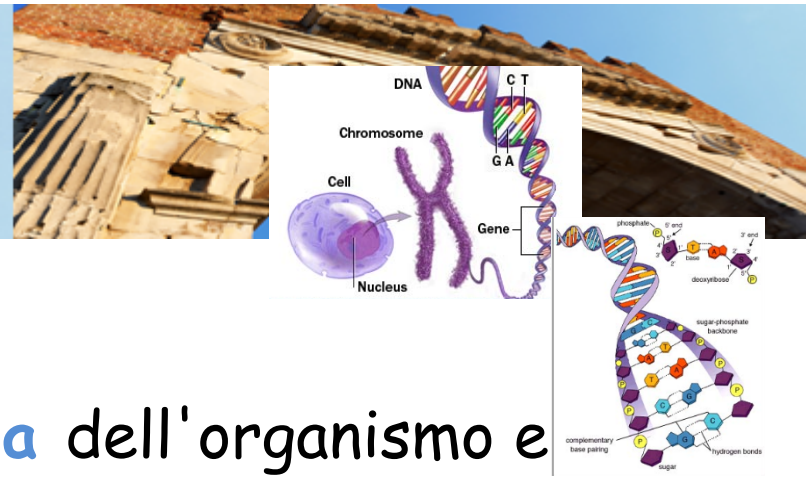
derivare da errori di replicazione

derivare da danni al DNA

fattori ambientali…

agenti fisici (ad esempio le radiazioni)

sostanze chimiche (ad esempio il fumo di sigaretta)



mutazioni somatiche,

insorte **in una singola cellula** dell'organismo e **trasmesse alla sua progenie** a costituire un **clone cellulare**.

non possono essere trasmesse ai discendenti

sono coinvolte nella **cancerogenesi**

mutazioni germinali,

trasmesse alla progenie attraverso i gameti

sono presenti **in tutte le cellule dell'individuo**

it takes **more than one mutation** in a cell for **cancer** to occur

Usually, the cell detects the change and repairs it.

If it can't be repaired, the cell will get a signal telling it to die in a process called apoptosis.

But if the cell doesn't die and the mutation is not repaired, it may lead to develope cancer.

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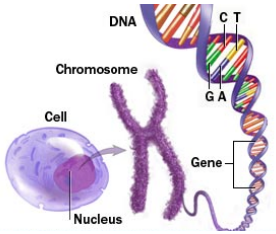
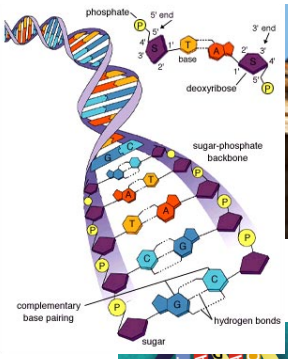
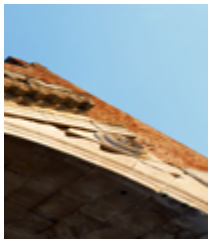
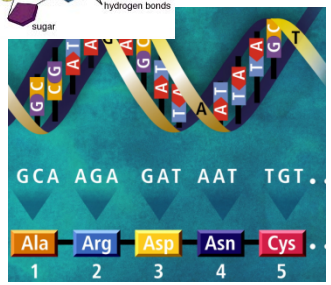




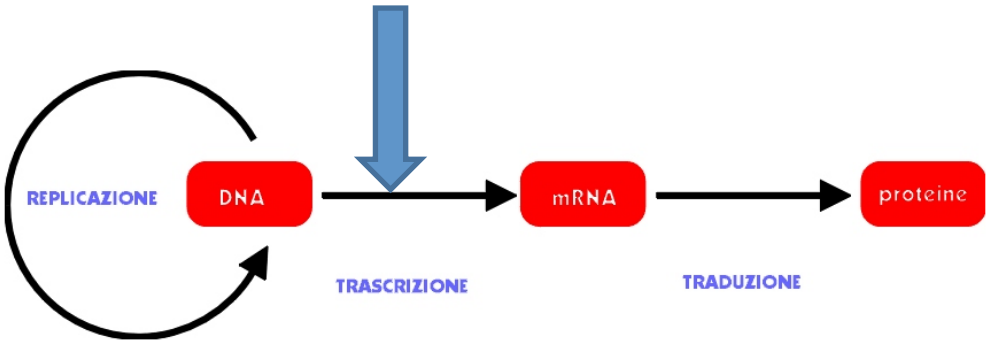


Epigenetic changes

Cells can also be **altered without a change** in their **intrinsic genetic code**, in what is known as an epigenetic phenomenon.

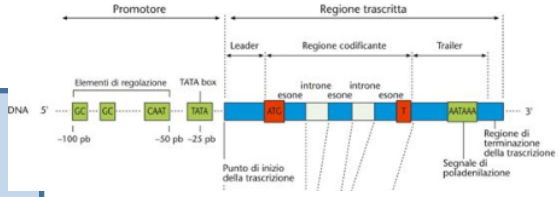


Epigenetic changes result in an **inhibition or a change in the transcription of a gene**,
<u>without an alteration in its normal base-pair sequence.</u>



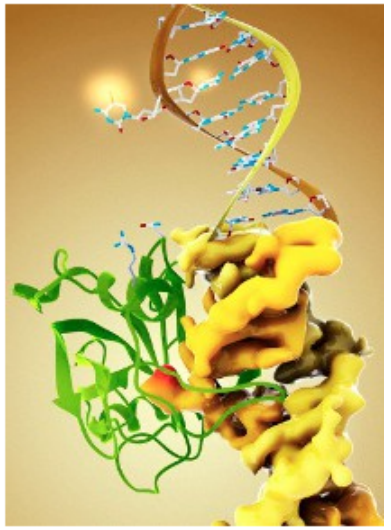
Epigenetic changes

in breast cancer formation is **hypermethylation** of the promoter region of the gene.



regione di DNA costituita da specifiche sequenze dette consenso, alla quale si lega la RNA polimerasi per iniziare la trascrizione di un gene,

methylation, which **inhibits RNA binding** to the promoter region and thereby **prevents transcription.**



L'adesione di un gruppo metile *(in alto a sinistra, alone giallo)* alla doppia elica del DNA in prossimità di un gene ne blocca la possibilità di essere trascritto. (© 3dciencia. Ramón Andrade/Science Photo Library/Corbis)

no protein product is produced and the gene function can be lost.

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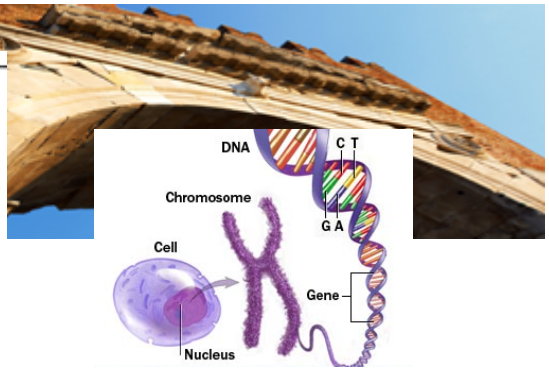

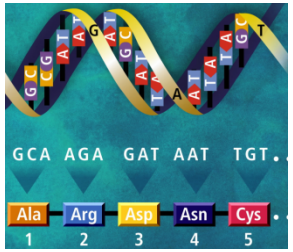

Genetic mutations can result in either

a loss of function

or

an aberrant gain of function.

FOR A BREAST CANCER TO DEVELOP

it must acquire the capacity

to invade,

to recruit a vascular supply,

to proliferate

activation of oncogenes

deactivation of tumor suppressor genes

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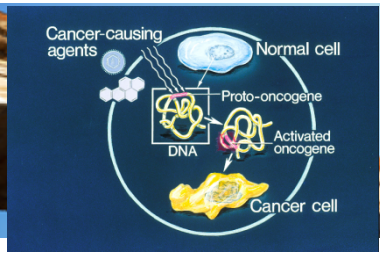
2015

PALACONGRESSI - Rimini, 7-10 novembre



FOR A BREAST CANCER TO DEVELOP

activation of oncogenes

result from mutations in **proto-oncogenes**

directly **promote** a **malignant phenotype**,

such as uncontrolled cell growth.

as it may encode proteins that facilitate
- invasiveness,
- cell-cycle progression,
- recruitment of a vascular supply for the T

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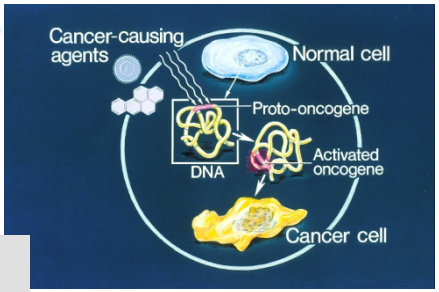
FOR A BREAST CANCER TO DEVELOP

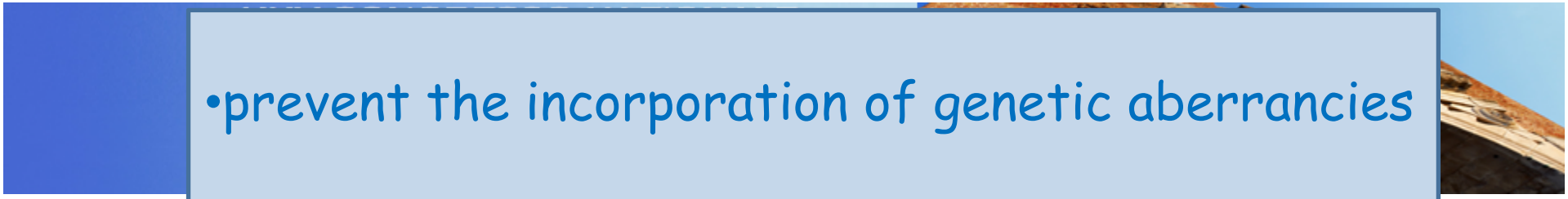
activation of oncogenes



Proto-oncogenes with relevance to breast cancer formation HER2/neu, EGFR, Ras, Myc

result in a **gain** of **function**

are exclusively the **consequence of somatic mutations**



- prevent the incorporation of genetic aberrancies
- repair injuries to the DNA
- activate apoptotic pathway

checkpoint

Deactivation (mutation) of **tumor suppressor genes**

inhibit many of these malignant traits and function to **maintain the genomic integrity of cells**

loss of function

deactivation→ **mutation**

germline mutations

somatic mutations

Over the past decades, there have been significant discoveries of **germline** conditions that **predispose individuals to breast cancer formation.**

Breast cancer formation was found to be associated with germline tumor suppressor gene mutations in **BRCA1, BRCA2, p53, and PTEN genes.**

All of these mutations are in **high-penetrance genes**, meaning that **if the mutation is inherited, breast cancer is likely**

La **genetica clinica** raccoglie numerose applicazioni della genetica alla medicina....

studio del patrimonio genetico di una donna

identificare mutazioni germinali

consulenza genetica

identificare donne predisposte geneticamente allo sviluppo di una neoplasia mammaria

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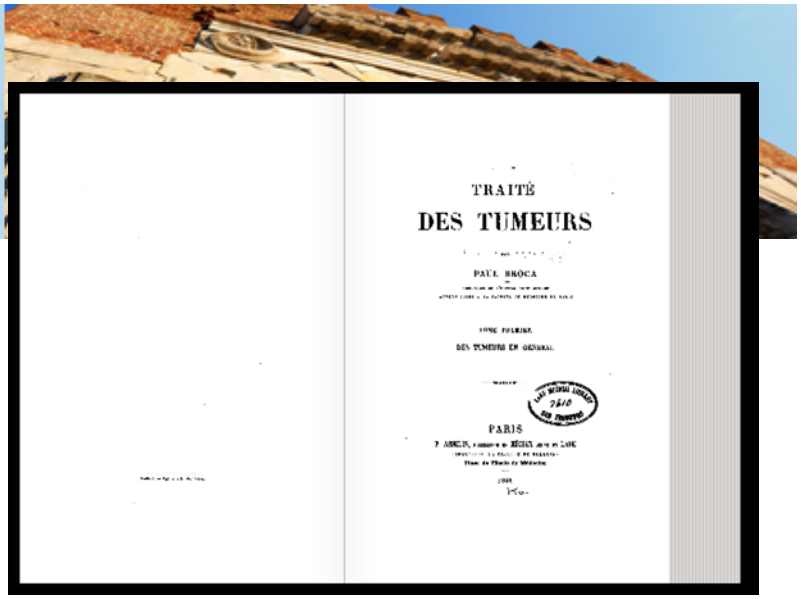

1-1-1979

Contributions of Pierre Paul Broca to Cancer Genetics

Anne J. Krush
Johns Hopkins University

In 1866, Paul Broca was the first to describe a family with a high prevalence of carcinoma of the breast.

His wife suffered from early onset of breast cancer and when he made a pedigree of her family, **four generations with breast cancer could be identified** .

The "Broca" report is the first of many that pointed out that breast cancer can be inherited, passing through from one generation to the other.

Cell Oncol. (2011) 34:71–88
DOI 10.1007/s13402-011-0010-3

ORIGINAL PAPER

Pathology of hereditary breast cancer

Petra van der Groep · Elsken van der Wall · Paul J. van Diest

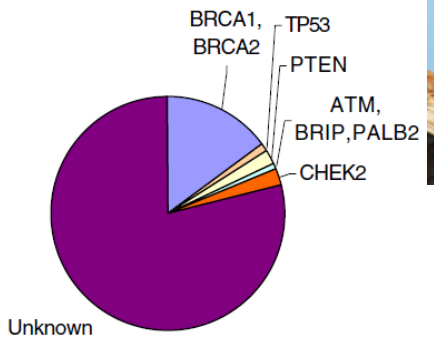

Fig. 2 Affected genes in hereditary breast cancer

In about **5%** of all the breast cancer cases, the disease is part of a **hereditary cancer** syndrome,

caused by mutations in high penetrance susceptibility genes.

About **16%** of hereditary breast cancers can be attributed to germline mutations in either of the **BRCA** (breast cancer 1 and 2) early onset genes.

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Both BRCA genes are involved in DNA repair.

The **levels of expression of BRCA1, BRCA2** increase in cells when they enter the **S phase**, indicating that they function during or after **DNA replication**.

This confims that **BRCA1 and BRCA2 function** in a common pathway that is **responsible for the integrity of the genome and the maintenance of chromosomal stability**

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Carriers of the BRCA1 and BRCA2 mutations do not only develop breast cancer and ovarian cancer but also bear an increased risk for developing Fallopian tube, colon, melanoma, prostate and pancreatic cancer

The median age of diagnosis was found be to be **40 years among BRCA1** and **43 years among BRCA2** mutation carriers

Mavvadat N, Cancer Epidemiol Biomarkers Prev.2012

Even though germline **mutations in *BRCA1* and *BRCA2*** confer **high risk of breast and ovarian cancers**, the **penetrance of these genes is incomplete.**

The **risk** in *BRCA1* and *BRCA2* mutation carriers of **develop breast cancer by the age of 70 is 45–87%.**

12%

For **ovarian cancer**, the risk is **45–60% among *BRCA1*** carriers and **11–35% among *BRCA2*** mutation carriers

1.3%

The WECARE Study Group calculated the breast cancer risk by the same age to even **exceed 90%** in case of the presence of a BRCA1/2 mutation
Begg, JAMA 2008

Pathological Characteristics of Hereditary Breast Cancer

BRCA1

The majority are invasive ductal carcinomas (74%-80%).
A higher frequency of **BRCA1** tumors are classified as medullary carcinomas compared to sporadic tumors (9% vs 2%)

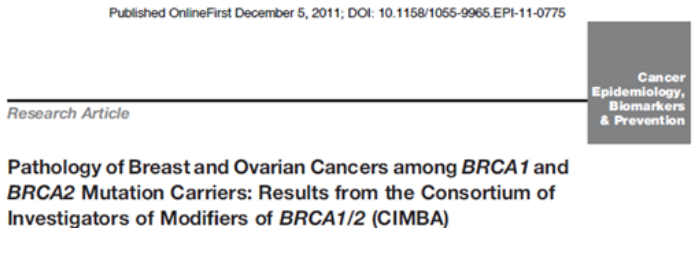
BRCA1 tumors are more frequently **high-grade** compared to sporadic tumors with a **higher number of mitosis**, and a high frequency of **necrotic areas**

Pathological Characteristics of Hereditary Breast Cancer

BRCA1

A study examining pathology data (4,325 BRCA1) reported that **78%** of tumors arising in **BRCA1** carriers were **ER-negative**

and PGR and/or Her2 negative, the so-called **triple-negative tumor (69%)**



The majority of BRCA1 tumors basal/ myoepithelial phenotype

All these features point toward **a more aggressive tumor**

Pathological Characteristics of Hereditary Breast Cancer

BRCA2

Most **BRCA2** tumors are **grade 2/3** with **high mitotic rates**.

Excess of invasive lobular and tubular carcinomas has been reported for BRCA2 relative to BRCA1 tumors

***BRCA2* tumors** seem to be **more similar to sporadic** tumors with relation to the expression of IHC markers.

Most BRCA2 breast tumors show a **luminal phenotype**

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Breast Cancer: Basic and Clinical Research

Hereditary Breast Cancer: Clinical, Pathological and Molecular Characteristics

Martin J. Larsen[1,2], Mads Thomassen[1,2], Anne-Marie Gerdes[3] and Torben A. Kruse[1,2]

[1]Department of Clinical Genetics, Odense University Hospital, Odense, Denmark. [2]Human Genetics, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark. [3]Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

Published OnlineFirst December 5, 2011; DOI: 10.1158/1055-9965.EPI-11-0775

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Pathology of Breast and Ovarian Cancers among *BRCA1* and *BRCA2* Mutation Carriers: Results from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA)

Pathological Characteristics of Hereditary Breast Cancer

BRCA2

pathology data about **2,568 BRCA2** mutation carriers reported only **23% of tumors ER-negative**.

HER2-overexpression was observed in approximate **10%** of the tumors from mutation carriers.

Only 16% of the BRCA2 tumors were **TN**

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BRCA1 related breast cancer

Prognosis

In **BRCA1** associated tumors, a lower rate of bone metastases and a **higher frequency of lung and brain metastases** have been described.

Investigating **overall survival** in BRCA1 associated breast cancer versus age matched sporadic breast cancer patients have yielded **contradictive results** with some studies describing a worse survival and others a similar survival rate

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BRCA2 related breast cancer

In women with BRCA2 associated breast cancer, **bone and soft tissue metastases** are observed more frequently likely associated with their more frequent ER positivity.

As is the case in BRCA1 patients, for **BRCA2** patients **conflicting data with regard to survival** have been presented

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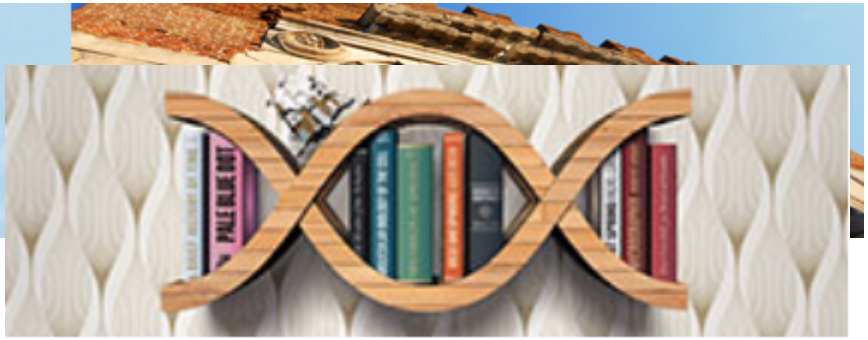

Quale risvolto clinico hanno le cognizioni sul ruolo della genetica nell'insorgenza di un tumore mammario ?

studio del patrimonio genetico di una donna→ consulenza genetica

In chi?

NIH NATIONAL CANCER INSTITUTE

- Breast cancer diagnosed before age 50 years
- Cancer in both breasts in the same woman
- Both breast and ovarian cancers in either the same woman or the same family
- Multiple breast cancers
- Two or more primary types of *BRCA1*- or *BRCA2*-related cancers in a single family member
- Cases of male breast cancer
- Ashkenazi Jewish ethnicity

There is no single definition of 'familial' breast cancer, but generally accepted criteria include:

(i) at least three breast and/or ovarian cancer cases in a family;

(ii) two breast cancer cases in close relatives, with at least case diagnosed before age 50;

(iii) two breast cancer cases in a family diagnosed before 40 years

(iv) any male breast cancer with a family history of ovarian cancer or early onset female breast cancer;

(v) Ashkenazi Jewish ancestry with breast cancer, particularly triple-negative breast cancer diagnosed before age 60;

(vi) breast and ovarian cancer in the same patient

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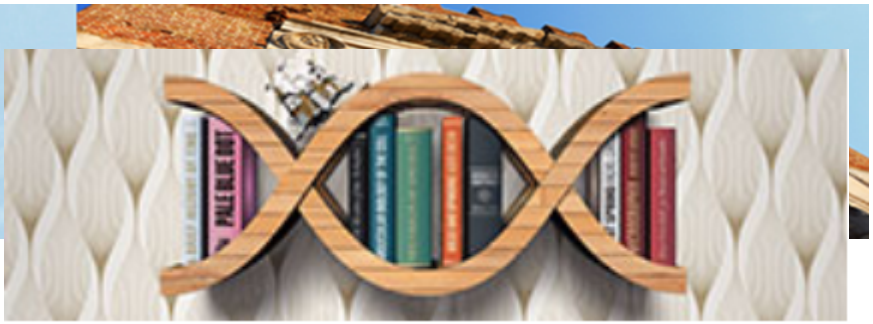
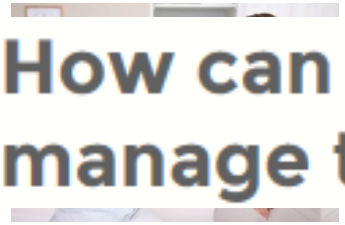


Due scenari

donna con una storia familiare che decide di eseguire il test→ positivo



How can a person who has a positive test result manage their risk of cancer?

How can a person who has a positive test result manage their risk of cancer?

Enhanced screening

Prophylactic (risk-reducing) surgery

Chemoprevention

XXV CONGRESSO NAZIONALE

AIRO 2015

Genetics of breast cancer: a topic in evolution

S. Shiovitz[1,2*] & L. A. Korde[1,2,3]

[1]Divison of Medical Oncology, University of Washington, Seattle; Divisions of [2]Clinical Research; [3]Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, USA

Annals of Oncology 26: 1291–1299, 2015

Tamoxifen has **not been well studied** in women with a known or suspected familial cancer syndrome.

Limited clinical data suggest that **tamoxifen may reduce risk of breast cancer** in women with a **BRCA1 or BRCA2** mutation who have **not undergone prophylactic oophorectomy** before menopause

Gail MH, J Natl Cancer Inst 1999

Gronwald J, Int J Cancer 2006

King MC, (NSABP-P1) Breast Cancer Prevention Trial. JAMA 2001

Future Oncol. (2014) 10(4), 499–502

EDITORIAL

Breast cancer prevention for *BRCA1* and *BRCA2* mutation carriers: is there a role for tamoxifen?

Phillips KA, Lindeman GJ

ORIGINAL CONTRIBUTION

Tamoxifen and Breast Cancer Incidence Among Women With Inherited Mutations in *BRCA1* and *BRCA2*

National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial

Mary-Claire King,

JAMA, November 14, 2001–

NSABP-P1 breast cancer prevention trial

13.388 pz ad aumentato rischio random tam vs placebo

the risk ratio for breast cancer with tam
1.67 for BRCA1 / 0.38 for BRCA2 mutation carrier

8 BRCA1, 11 BRCA2 /288 breast cancer

XXV CONGRESSO NAZIONALE

2015

Rimini, 7-10 novembre

ORIGINAL CONTRIBUTION

Tamoxifen and Breast Cancer Incidence Among Women With Inherited Mutations in *BRCA1* and *BRCA2*

National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial

Mary-Claire King,

JAMA, November 14, 2001–

Conclusion Tamoxifen reduced breast cancer incidence among healthy *BRCA2* carriers by 62%, similar to the reduction in incidence of ER-positive breast cancer among all women in the Breast Cancer Prevention Trial. In contrast, tamoxifen use beginning at age 35 years or older did not reduce breast cancer incidence among healthy women with inherited *BRCA1* mutations. Whether tamoxifen use at a younger age would reduce breast cancer incidence among healthy women with *BRCA1* mutations remains unknown.

XXV CONGRESSO NAZIONALE

AIRO 2015

Genetics of breast cancer: a topic in evolution

S. Shiovitz[1,2*] & L. A. Korde[1,2,3]

[1]Divison of Medical Oncology, University of Washington, Seattle; Divisions of [2]Clinical Research; [3]Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, USA

Annals of Oncology 26: 1291–1299, 2015

2464 BRCA breast cancer pts mutation carriers (observational study)

837 → tam following unilateral therapeutic mastectomy,

non significant trend toward a lower risk of contralateral breast cancer

the effect of tamoxifen did not vary by the estrogen status of the original breast cancer.

Phillips KA, JCO 2013

"...for those who **decline bilateral mastectomy**, or choose to delay it until they are older, **tamoxifen should be considered and should be discussed** along with the evidence of **benefits and potential side effects**, thereby enabling an **informed choice for women** who wish to consider prevention therapy."

Phillips KA, Lindeman GJ

Prophylactic (risk-reducing) surgery

chemoprevention

Adjuvant tamoxifen reduces the risk of contralateral breast cancer in affected *BRCA* mutation carriers [III, B], while benefit of tamoxifen for primary prevention of breast cancer in *BRCA* carriers has not been demonstrated [Ib,A].

BRCA in breast cancer: ESMO Clinical Practice Guidelines

How can a person who has a positive test result manage their risk of cancer?

Enhanced screening

Prophylactic (risk-reducing) surgery

Chemoprevention

clinical practice guidelines

Annals of Oncology 22 (Supplement 6): vi31–vi34, 2011
doi:10.1093/annonc/mdr373

BRCA in breast cancer: ESMO Clinical Practice Guidelines

J. Balmaña[1], O. Díez[2,3], I. T. Rubio[4] & F. Cardoso[5,6]
On behalf of the ESMO Guidelines Working Group*

Surveillance of breast cancer in BRCA carriers includes

monthly self-examinations starting at age 18,

from age 25

clinical breast examinations twice a year
yearly mammograms
magnetic resonance imaging (MRI) of breasts

There are as yet **no data** available to determine whether alternating mammogram and MRI every 6 months or having both once yearly is more effective at **young ages**, considering **the high rate of interval cancers in BRCA1 carriers.**

Breast Cancer Res Treat (2014) 145:663–672
DOI 10.1007/s10549-014-2931-9

CLINICAL TRIAL

MRI breast screening in high-risk women: cancer detection and survival analysis

Evans D. Gareth · Kesavan Nisha · Lim Yit · Gadde Soujanye · Hurley Emma · Nathalie J. Massat · Anthony J. Maxwell · Ingham Sarah · Eeles Rosalind · Martin O. Leach · MARIBS Group · Howell Anthony · Duffy Stephen

Sensitivity of MRI+ mammography →93 % (63 % specificity)

Fewer cancers detected on MRI were N+ (vs mammography/no additional screening).

Survival was significantly higher in the MRI-screened group (95.3 %) no intensive screening (73.7 %; p = 0.002).

Breast Cancer Res Treat (2014) 145:663–672
DOI 10.1007/s10549-014-2931-9

CLINICAL TRIAL

MRI breast screening in high-risk women: cancer detection and survival analysis

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Extended follow-up of larger numbers of high-risk women is required to assess long-term **survival.**

Breast Cancer Res Treat (2014) 147:685–687
DOI 10.1007/s10549-014-3097-1

LETTER TO THE EDITOR

MRI screening of women with hereditary predisposition to breast cancer: diagnostic performance and survival analysis

Filippo Santoro · Franca Podo · Francesco Sardanelli

The **capability of MRI to detect invasive breast cancers at early stages**

American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography

CA Cancer J Clin 2007;57:75–89

Debbie Saslow, PhD; Carla Boetes, MD, PhD; Wylie Burke, MD, PhD; Steven Harms, MD; Martin O. Leach, PhD; Constance D. Lehman, MD, PhD; Elizabeth Morris, MD; Etta Pisano, MD; Mitchell Schnall, MD, PhD; Stephen Sener, MD; Robert A. Smith, PhD; Ellen Warner, MD; Martin Yaffe, PhD; Kimberly S. Andrews; Christy A. Russell, MD (for the American Cancer Society Breast Cancer Advisory Group)

ABSTRACT New evidence on breast Magnetic Resonance Imaging (MRI) screening has become available since the American Cancer Society (ACS) last issued guidelines for the early detection of breast cancer in 2003. A guideline panel has reviewed this evidence and developed new recommendations for women at different defined levels of risk. Screening MRI is recommended for women with an approximately 20–25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease. There are several risk subgroups for which the available data are insufficient to recommend for or against screening, including women with a personal history of breast cancer, carcinoma in situ, atypical hyperplasia, and extremely dense breasts on mammography. Diagnostic uses of MRI were not considered to be within the scope of this review. *(CA Cancer J Clin 2007;57:75–89.)*

Courtesy Massimo Calabrese

VOLUME 33 · NUMBER 10 · APRIL 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Triple-Modality Screening Trial for Familial Breast Cancer Underlines the Importance of Magnetic Resonance Imaging and Questions the Role of Mammography and Ultrasound Regardless of Patient Mutation Status, Age, and Breast Density

Christopher C. Riedl, Nikolaus Luft, Clemens Bernhart, Michael Weber, Maria Bernathova, Muy-Kheng M. Tea, Margaretha Rudas, Christian F. Singer, and Thomas H. Helbich

In a single-center, prospective, nonrandomized **comparison** study, *BRCA* mutation carriers and women with a high familial risk (20% lifetime risk) for breast cancer were offered screening with mammography, ultrasound, and MRI every 12 months.

The **sensitivity of MRI (90.0%)** was significantly higher (P .001) than that of mammography (37.5%) and ultrasound (37.5%).

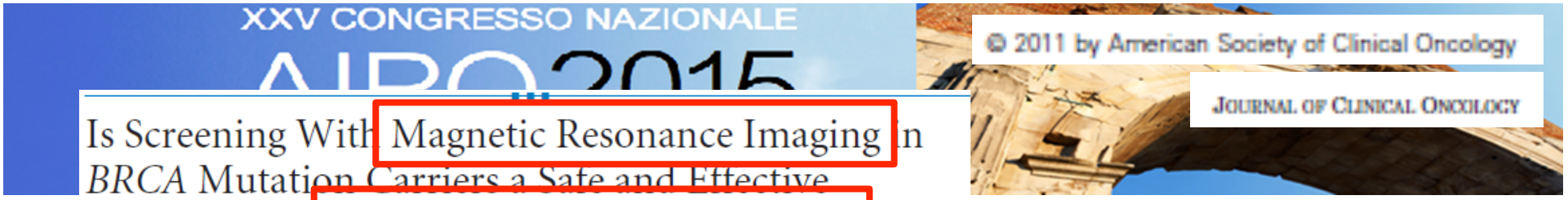
Of 40 cancers, 18 (45.0%) were detected by MRI alone.

Age, mutation status, and breast density had no influence on the sensitivity of MRI

Conclusion

MRI allows early detection of familial breast cancer

The added value of mammography is limited, and there is no added value of ultrasound in women undergoing MRI for screening



Screening with **MRI and mammography** **beginning at 25 years of age results in a** **similar survival benefit** **to** **prophylactic mastectomy** and MRI screening is generally accepted to be cost effective in *BRCA* mutation carriers

Warner, 2004
Hagen AI, 2007
Sardanelli F, 2007
Kurian AW, 2010
Plevritis SK, 2006

Is Screening With Magnetic Resonance Imaging in *BRCA* Mutation Carriers a Safe and Effective Alternative to Prophylactic Mastectomy?

Monika L. Burness, *University of Chicago, Chicago, IL*
Olufunmilayo I. Olopade, *Center for Clinical Cancer Genetics and Global Health, University of Chicago, Chicago, IL*

MRI screening as a **reasonable alternative to prophylactic mastectomy.**

The American Cancer Society supports a combination of mammography and MRI
Saslow D, 2007

Additional studies are needed to determine the optimal screening frequency and improve specificity to avoid unnecessary biopsies.

.

How can a person who has a positive test result manage their risk of cancer?

Enhaced screening

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Chemoprevention

clinical practice guidelines

Annals of Oncology 22 (Supplement 6): vi31–vi34, 2011
doi:10.1093/annonc/mdr373

BRCA in breast cancer: ESMO Clinical Practice Guidelines

J. Balmaña[1], O. Díez[2,3], I. T. Rubio[4] & F. Cardoso[5,6]
On behalf of the ESMO Guidelines Working Group*

Prophylactic (risk-reducing) surgery

The objective is to reduce cancer risk and mortality.

Risk reduction options include
- prophylactic bilateral mastectomy,
- prophylactic bilateral salpingooophorectomy
- both

There are no randomized controlled trials
but recent prospective cohort studies have shown a consistent reduced risk in this population.

ORIGINAL CONTRIBUTION

Susan M. Domchek, JAMA, September 1, 2010—Vol 304, No. 9

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

PROSE: **Prevention and Observation of Surgical Endpoints consortium**

Prospective, multicenter cohort study of **2482 women with BRCA1 or BRCA2 mutations**

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**.

Women who **declined** risk reducing salpingo-oophorectomy or mastectomy were offered **increased surveillance**

ORIGINAL CONTRIBUTION

Susan M. Domchek, JAMA, September 1, 2010—Vol 304, No. 9

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

Table 1. Risk-Reducing Mastectomy and Risk of First Occurrence of Breast Cancer[a]

Mastectomia profilattica/tumore mammella

con ovariectomia

Mastectomia→ no tumori mammari

Non mastectomia → diagnosi tumori mammario 8%

senza ovariectomia

Mastectomia→ no tumori mammari

Non mastectomia → diagnosi tumori mammario 5.8%

Età media : 36.7-42 anni

FU: 2.5-3 anni

ORIGINAL CONTRIBUTION

Susan M. Domchek, JAMA, September 1, 2010—Vol 304, No. 9

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

Table 2. Risk-Reducing Salpingo-oophorectomy and Ovarian Cancer Risk[a]

Salpingo-ovariectomia profilattica/tumore ovaio

No precedente neoplasia mammaria

Salpingo-ovariec. Profil.→ tumori primitivi peritoneali: 1.3%
NO Salpingo-ovariec. profil→ diagnosi tumori ovarico: 5.8%

precedente neoplasia mammaria

Salpingo-ovariec. profil→ tumori primitivi peritoneali: 1.%
NO Salpingo-ovariec. Profil. → diagnosi tumori ovarico: 6%

Età media : 49.1-42.1 anni
FU: 6.2 - 3.3 anni

ORIGINAL CONTRIBUTION

Susan M. Domchek, JAMA, September 1, 2010—Vol 304, No. 9

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

Table 3. Risk-Reducing Salpingo-oophorectomy and Breast Cancer Risk[a]

Salpingo-ovariectomia profilattica/tumore mammella

Salpingo-ovariec. profilattica→ tumori mammari: 11.6%
NO Salpingo-ovariec. profilattica → tumori mammario 21.6%

Età media : 49.1-42.7 anni
FU: 4.0 – 4.8 anni

Table 5. Risk-Reducing Salpingo-oophorectomy and Breast Cancer–Specific Mortality[a]

Salpingo-ovariectomia profilattica/mortalità tumore mammella correlata

salpingo-ovariec. profilattica→

morte x tumore mammario: 2.1%

no precedente neop. Mammaria: 0.5%

precedente neop. Mammaria: 3.6%

NO Salpingo-ovariec. profilattica →

morte per tumore mammario: 5.7%

no precedente neop. Mammaria: 2.3%

precedente neop. Mammaria: 11.5%

Età media : 49.1-42.0 anni

FU: 8.6 – 2.9 anni

ORIGINAL CONTRIBUTION

Susan M. Domchek, JAMA, September 1, 2010—Vol 304, No. 9

Table 6. Risk-Reducing Salpingo-oophorectomy and Ovarian Cancer–Specific Mortality[a]

Salpingo-ovariectomia /mortalità tumore ovarico correlata

salpingo-ovariec. profilattica→

morte x tumore ovarico: 0.4%

no precedente neop. Mammaria: 0.7%

precedente neop. Mammaria: 0.2%

NO Salpingo-ovariec. profilattica →

morte per tumore ovarico: 2.5%

no precedente neop. Mammaria: 2.5%

precedente neop. Mammaria: 2.2%

Età media : 48.9-42.0 anni

FU: 9.1 – 6.6anni

XXV CONGRESSO NAZIONALE

AIRO 2015

-10 novembre

ORIGINAL CONTRIBUTION

Susan M. Domchek, JAMA, September 1, 2010—Vol 304, No. 9

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

Overall mortality was **improved** in women undergoing riskreducing **salpingo-oophorectomy**.

In **women** who underwent risk-reducing **salpingo-oophorectomy**
1.1% were subsequently diagnosed with **ovarian cancer**,
11.4% were subsequently diagnosed with **breast cancer**,
3.1% subsequently **died of any cause**

In women who did **not** undergo risk-reducing **salpingo-oophorectomy**
5.8% were subsequently diagnosed with **ovarian cancer**,
19.2% with **breast cancer**,
9.8% subsequently **died from any cause**.

XXV CONGRESSO NAZIONALE

015

novembre

ORIGINAL CONTRIBUTION

Susan M. Domchek, JAMA, September 1, 2010—Vol 304, No. 9

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

Conclusions

Among a cohort of women with *BRCA1* and *BRCA2* mutations,

•risk-reducing **mastectomy** →lower risk of breast cancer;

• risk-reducing **salpingo-oophorectomy** →lower risk of
ovarian cancer,
first diagnosis of breast cancer,
all-cause mortality,
breast cancer–specific mortality,
ovarian cancer–specific mortality

Genetics of breast cancer: a topic in evolution

S. Shiovitz[1,2*] & L. A. Korde[1,2,3]

[1]Divison of Medical Oncology, University of Washington, Seattle; Divisions of [2]Clinical Research; [3]Public Health Sciences,

Annals of Oncology 26: 1291–1299, 2015

Risk-reducing salpingo-oophorectomy is recommended by age 35–40, or earlier if either child bearing is complete or there is indication based on the family history

Rebbeck TR, 2002

For women who have not yet undergone RRSO, **screening** with pelvic ultrasound and serum CA-125 levels can be considered starting at age 30, though this **has not clearly been shown to be beneficial**

Evans DG, J Med Genet 2009

Woodward ER, BJOG 2007

XXV CONGRESSO NAZIONALE

AIRO 2015

Genetics of breast cancer: a topic in evolution

S. Shiovitz[1,2*] & L. A. Korde[1,2,3]

[1]Divison of Medical Oncology, University of Washington, Seattle; Divisions of [2]Clinical Research; [3]Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, USA

Annals of Oncology 26: 1291–1299, 2015

Prophylactic mastectomy may also be considered due to the high lifetime cancer risk and increased risk of secondary breast cancers, with discussion of a nipple-sparing approach

Balmana J, Ann Oncol 2011
Rebbeck TR, J Clin Oncol 2004 (PROSE)
Reynolds C, Ann Surg Oncol 2011

clinical practice guidelines

Annals of Oncology 22 (Supplement 6): vi31–vi34, 2011
doi:10.1093/annonc/mdr373

BRCA in breast cancer: ESMO Clinical Practice Guidelines

J. Balmaña[1], O. Díez[2,3], I. T. Rubio[4] & F. Cardoso[5,6]
On behalf of the ESMO Guidelines Working Group*

prophylactic bilateral mastectomy

This is the most effective strategy available for risk reduction of breast cancer in mutation carriers [III, B]. (risk reduction of at least 90%)

However, survival benefits have not been demonstrated with risk reduction breast surgery.

There have been no randomized trials comparing the effectiveness of different surgical techniques.

Int. J. Cancer: **122,** 2017–2022 (2008)

International variation in rates of uptake of preventive options in *BRCA1* and *BRCA2* mutation carriers

Kelly A. Metcalfe[1,2], Daphna Birenbaum-Carmeli[3], Jan Lubinski[4], Jacek Gronwald[4], Henry Lynch[5], Pal Moller[6], Parviz Ghadirian[7], William D. Foulkes[8,9,10], Jan Klijn[11], Eitan Friedman[12,13], Charmaine Kim-Sing[14], Peter Ainsworth[15], Barry Rosen[16], Susan Domchek[17,18], Teresa Wagner[19], Nadine Tung[20], Siranoush Manoukian[21], Fergus Couch[22], Ping Sun[2], Steven A. Narod[2]* and the Hereditary Breast Cancer Clinical Study Group

[1]*Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, ON, Canada*
[2]*Women's College Research Institute, Women's College Hospital, University of Toronto, ON, Canada*
[3]*Department of Nursing, University of Haifa, Haifa, Israel*
[4]*Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland*
[5]*Department of Preventive Medicine and Public Health, Creighton University School of Medicine, Omaha, NE*
[6]*Section for Inherited Cancer, Department of Medical Genetics, Rikshospitalet-Radiumhospitalet Medical Centre, Oslo, Norway*
[7]*Epidemiology Research Unit, Research Centre, Centre Hospitalier de l'Universitaire Montréal, CHUM Hôtel Dieu, Département de Nutrition, Faculte du Medicine, QC, Canada*
[8]*Department of Medicine, McGill University, Montréal, QC, Canada*
[9]*Department of Human Genetics, McGill University, Montréal, QC, Canada*
[10]*Department of Oncology, McGill University, Montréal, QC, Canada*
[11]*Department of Medical Oncology, Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*
[12]*The Suzanne Levy Gertner Oncogenetics Unit, The Chaim Sheba Medical Center, Tel-Hashomer, Israel*
[13]*The Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel*
[14]*British Columbia Cancer Agency Vancouver, BC, Canada*
[15]*London Regional Program, London Health Sciences Centre, London, ON, Canada*
[16]*Department of Gynecologic Oncology, Princess Margaret Hospital, Toronto, Canada*
[17]*Department of Hematology, University of Pennsylvania, Philadelphia, PA*
[18]*Department of Oncology, University of Pennsylvania, Philadelphia, PA*
[19]*Division of Senology, Department of Gynecology, Medical University of Vienna and Private Trust for Breast Health, Austria*
[20]*Beth Israel Deaconess Medical Centre, Boston, MA*
[21]*Medical Genetics Service, Department of Experimental Oncology and Laboratories, Istituto Nazionale Tumori, Milan, Italy*
[22]*Mayo Clinic, Rochester, MN*

Courtesy Massimo Calabrese

Variables	Italy, $N^1 = 46$, $N^2 = 20$, $N^3 = 18$
Prophylactic oophorectomy[1] ($n = 2,667$)	23 (50.0%)
Prophylactic mastectomy[2] ($n = 1,382$)	2 (10.0%)
Mammography[3] ($n = 1,133$)	18 (100%)
MRI[5] ($n = 1,134$)	13 (72.2%)
Tamoxifen/raloxifene[5] ($n = 1,134$)	0 (0%)

TABLE V – UPTAKE OF OPTIONS BY COUNTRY

Variables	Austria, $N^1 = 48$, $N^2 = 25$, $N^3 = 20$	Canada, $N^1 = 766$, $N^2 = 393$, $N^3 = 305$	France, $N^1 = 31$, $N^2 = 4$, $N^3 = 3$	Israel, $N^1 = 165$, $N^2 = 95$, $N^3 = 91$	Italy, $N^1 = 46$, $N^2 = 20$, $N^3 = 18$	Holland, $N^1 = 81$, $N^2 = 55$, $N^3 = 37$	Norway, $N^1 = 177$, $N^2 = 135$, $N^3 = 128$	Poland, $N^1 = 660$, $N^2 = 339$, $N^3 = 330$	USA, $N^1 = 703$, $N^2 = 317$, $N^3 = 202$	p Value[4]
Prophylactic oophorectomy[1] ($n = 2,667$)	25 (52.1%)	439 (57.3%)	22 (71.0%)	110 (66.7%)	23 (50.0%)	52 (64.2%)	130 (73.5%)	230 (34.9%)	500 (71.1%)	$<10^{-4}$
Prophylactic mastectomy[2] ($n = 1,382$)	5 (20.0%)	88 (22.4%)	1 (25.0%)	4 (4.2%)	2 (10.0%)	18 (32.7%)	6 (4.5%)	9 (2.7%)	115 (36.3%)	$<10^{-4}$
Mammography[3] ($n = 1,133$)	20 (100%)	294 (96.7%)	3 (100%)	87 (95.5%)	18 (100%)	37 (100%)	119 (93.0%)	216 (65.5%)	197 (97.5%)	$<10^{-4}$
MRI[5] ($n = 1,134$)	13 (65.0%)	146 (47.8%)	2 (66.7%)	2 (2.2%)	13 (72.2%)	35 (94.6%)	18 (14.1%)	22 (6.7%)	49 (24.4%)	$<10^{-4}$
Tamoxifen/raloxifene[5] ($n = 1,134$)	1 (5.0%)	30 (9.8%)	0 (0%)	10 (11.0%)	0 (0%)	0 (0%)	0 (0%)	21 (6.4%)	25 (12.4%)	0.001

[1]All subjects.–[2]Subjects without breast cancer; one subject with missing data on mastectomy excluded.–[3]Subjects without breast cancer and without prophylactic mastectomy; one subject with missing data on mammography excluded.–[4]chi-square test for the differences in frequency distributions of the 9 countries.–[5]Subjects without breast cancer and without prophylactic mastectomy.

Variables	France, N^1 = 31, N^2 = 4, N^3 = 3	Italy, N^1 = 46, N^2 = 20, N^3 = 18	Norway, N^1 = 177, N^2 = 135, N^3 = 128	USA, N^1= 703, N^2 = 317, N^3 = 202
Prophylactic oophorectomy[1] (n = 2,667)				
Prophylactic mastectomy[2] (n = 1,382)				
Mammography[3] (n = 1,133)				
MRI[5] (n = 1,134)				
Tamoxifen/ raloxifene[5] (n = 1,134)				

XXV CONGRESSO NAZIONALE AIR PALACONGRE

Enhaced screening

starting at age 25-30
clinical breast examinations twice a year
yearly mammograms +/- MRI

Prophylactic surgery

Bilateral salpingo-oophorectomy after age 35

↓ Ca ovarico
↓ Ca mammario
↓ mortalità

Bilateral mastectomy

↓ Ca mammario
↓ Mortalità????

Chemoprevention ???

Quali proposte di trattamento locale

Chirurgia Conservativa +RT
Mastectomia

Controllo di malattia??

Rischio di neoplasia controlaterale ???

Sopravvivenza?

Tossicità dei tessuti sani ??

XXV CONGRESSO NAZIONALE

AIRO 2015

PALACONGRESSI - Rimini, 7-10 novembre

The Breast 24 (2015) 100–106

Contents lists available at ScienceDirect

The Breast

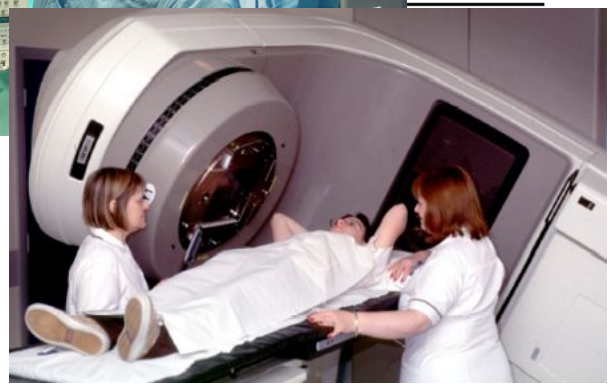
journal homepage: www.elsevier.com/brst

Review

Clinical relevance of normal and tumour cell radiosensitivity in BRCA1/BRCA2 mutation carriers: A review

Jacques Bernier [a, *], Philip Poortmans [b]

[a] Genolier Swiss Medical Network, Department of Radio-Oncology, Breast Unit, Genolier, Geneva, Switzerland
[b] Department of Radiation Oncology, Radboud University Medical Centre, Nijmegen, The Netherlands



Chirurgia Conservativa +RT

Radiation-induced DNA damage essentially consists of base damage, single-strand breaks, and double-strand breaks

BRCA1/2 gene functions are known to play a role in **DNA repair**, cell cycle control, programmed cell death, and maintenance of genomic stability

In normal tissues and tumours **laboratory experiments** have demonstrated that DNA damage significantly enhances response to radiation.

In a recent past, studies showed **higher radiosensitivity levels in mutation carriers.**
Beroukas, 2010,
Buchholz 2002,
Kote-Jarai 2006,
Barwell 2007

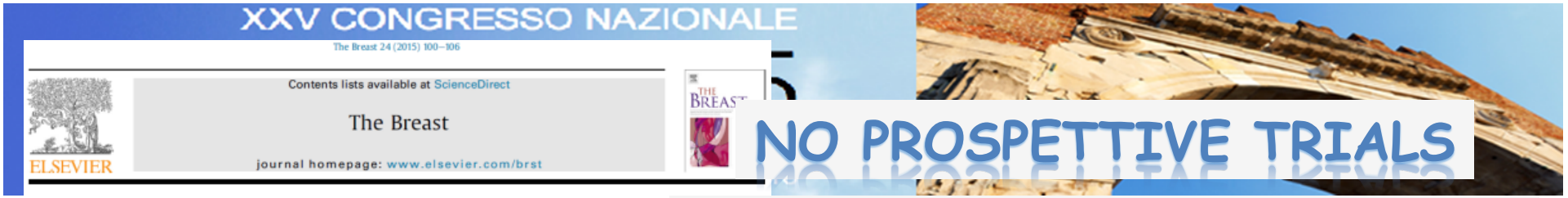
Other investigators were **unable to elicit a relationship between BRCA1/2 mutations and radiosensitivity .**
Nieuwenhuis 2002
Baeyens 2004

To our knowledge, **no distinction** can be made between the radiosensitivity of BRCA1 and BRCA2 mutation carriers,

In the hypothesis that the cells associated to BRCA1 and BRCA2 mutations are more radiosensitive,.....

Whilst malignancies in this patient population could respond better to radiation than those in sporadic controls

there is concern about the deleterious impact radiotherapy could have on normal tissues in BRCA1/2 mutation carriers, in terms of toxicity including radiation-induced malignancies



NO PROSPETTIVE TRIALS

CAUTION IN ANALYZING THE RESULTS

Tumour cell response to radiation and clinical disease control

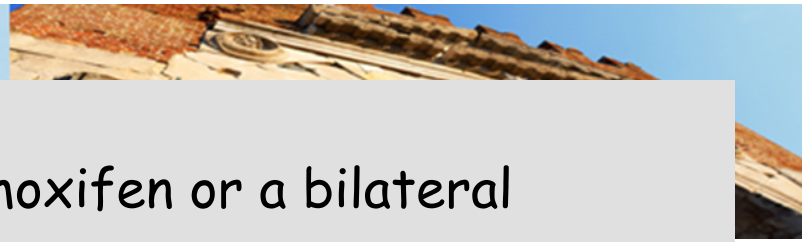
Biases:

for breast cancer →significant differences

pts age, tumour stage,
tumour biology, OT
prophylactic interventions

for radiotherapy→

different treatment schedules
timing



Haffty, 2002

- none of the pts in the study received tamoxifen or a bilateral oophorectomy
- by design this study included only pts diagnosed at age 42 or younger
- rates of new cancer or recurrence across the two groups diverged essentially **after the 6th year**
- **9 out of 11** in breast events **outside the index quadrant** or **different histotype→ second primary tumours**

(MSKCC, New-York)					
Seynaeve [60]	26/174[c]	21.8	12.2	0.05	6

Seynaeve, 2004

- In the hereditary pts more recurrences occurred **elsewhere** in the breast (**21%** versus **9.5%**), **new primaries??**
- Overall, the actuarial IBTR rate was similar at 2 years, but **higher** in hereditary as compared to sporadic patients at **5 years** (14% versus 7%) and at **10 years** (30% versus 16%) (P=0.05).

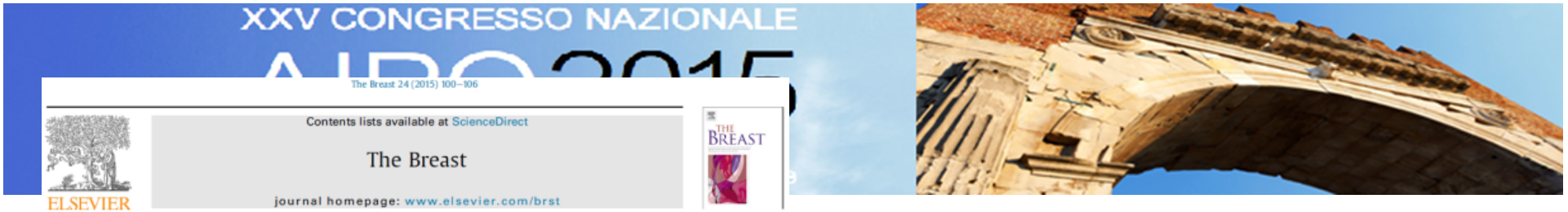
Table 1
Rates of local regional failures (LRF) following breast conserving surgery and PORT in BRCA1 – BRCA2 carriers compared with controls.

First author	Nb patients BRCA ½ versus controls	LRF (%) Genetic	LRF (%) Sporadic	P value	Median follow-up (years)
Verhoog [28] (Rotterdam)	18/196[c]	14	16	0.84	5
Pierce [41] (Collaborative, USA)	160/445	9 17	12 24[b]	0.19	7.9
Brekelmans [51] (Rotterdam)	109/410[c]	50	55	0.32	4.3
Garcia Etienne [42] (Milan)	54/162	27	4	0.03	4
Kirova [43] (Paris)	29/58[c]	36	33	0.42	13.4

Pierce 2006

- mutation was an independent predictor of IBTR **only** when mutation carriers who underwent **oophorectomy** were removed from the analysis (HR: 1.99; p 0.04)

- Most events appeared to be **second primary cancers** rather than failure to control the primary tumour.



The Breast 24 (2015) 100–106

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Clinical relevance of normal and tumour cell radiosensitivity in BRCA1/BRCA2 mutation carriers: A review

Jacques Bernier [a, *], Philip Poortmans [b]

[a] Genolier Swiss Medical Network, Department of Radio-Oncology, Breast Unit, Genolier, Geneva, Switzerland
[b] Department of Radiation Oncology, Radboud University Medical Centre, Nijmegen, The Netherlands

"In view of the limitations mentioned above, we can conclude that the **recent literature**

does not show that BRCA1/2 status is an independent predictor of ipsilateral breast new cancer or recurrence after BCT

provided risk-reducing strategies based on adequate systemic treatment are associated to the local treatment"

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Clinical relevance of normal and tumour cell radiosensitivity

Published in final edited form as:
Breast Cancer Res Treat. 2010 June ; 121(2): 389–398. doi:10.1007/s10549-010-0894-z.

Local Therapy in BRCA1 and BRCA2 Mutation Carriers with Operable Breast Cancer: Comparison of Breast Conservation and Mastectomy

655 breast cancer pts
with BRCA1/2 mutations

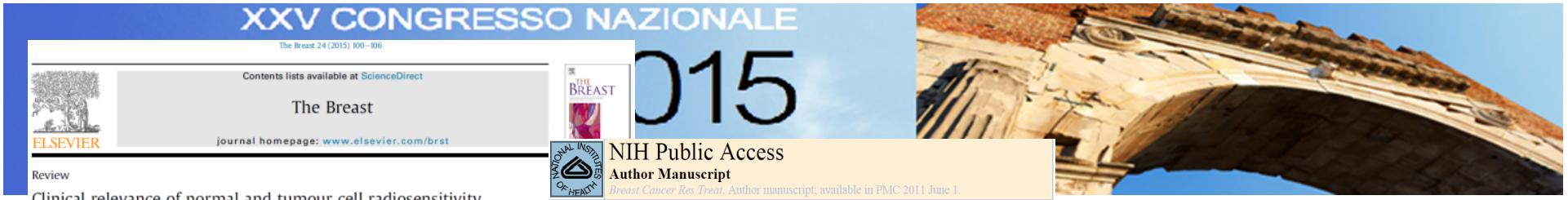
BCT →n=302
M →n=353

median FU 8.2 years BCT
8.9 years M

Local failure as first failure:
BCT (23.5%)
M (5%) at 15 years (p<0.0001);

15-year estimates in carriers treated with **BCT and chemotherapy was 11.9%** (p=0.08 when compared to M).

Increased chemo sensitivity in BRCA Fourquet, 2009



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Local relapses after BCT

30% same quadrant and same histology→true recurrence

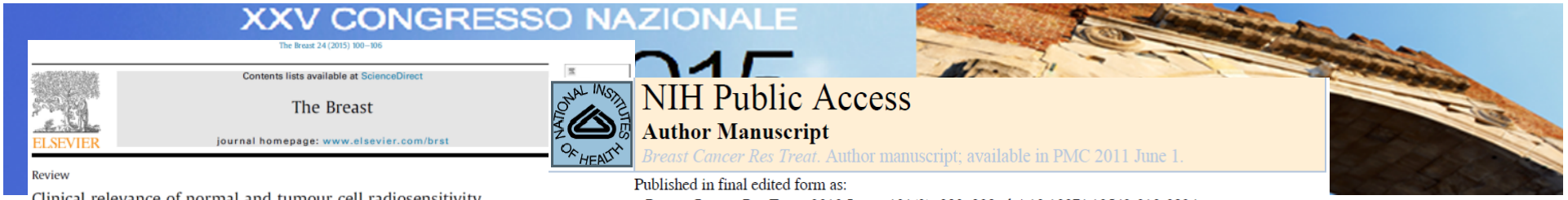
70% different quadrant - different histology or both→new primary

Local relapses after Mastectomy

18% different histology

82% similar histologies at diagnosis and recurrence.

The incidence estimates of **regional failures** as component of first failure **did not vary significantly by local treatment group**



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Local Therapy in BRCA1 and BRCA2 Mutation Carriers with Operable Breast Cancer: Comparison of Breast Conservation and Mastectomy

No significant difference in breast-cancer specific or **overall survival** was observed by local treatment type.

Breast cancer-specific survivals

BCT → 93.6% and 91.7% at 10 and 15 years
M→. 93.5% and 92.8% with M (p=0.85).

Tumour cell response to radiation and clinical disease control

Ipsilateral breast new cancer or recurrence

solo AA aumento di IBTR
soprattutto se no OT/ovariectomia/CT → **Secondi tumori**
altro quadrante/ diversa istologia/ lungo IL
No significant difference **overall survival**

Pierce 2010

Contralateral breast cancer (CBC)

Survival indices

Tumour cell response to radiation and clinical disease control

Ipsilateral breast new cancer or recurrence

Contralateral breast cancer (CBC)

Survival indices

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Review

Clinical relevance of normal and tumour cell radiosensitivity in BRCA1/BRCA2 mutation carriers: A review

Jacques Be

[a] Genolier Swiss
[b] Department of

It has been repeatedly substantiated that **the risk of CBC in BRCA1/2 germline carriers is high**, with bilateral breast cancer observed in up to 65% of these women

Table 2
Rates of contralateral breast cancers (CBC) following breast conserving surgery and PORT in BRCA1 – BRCA2 carriers compared with controls.

First author	Nb patients BRCA1-2 versus controls	CBC (%) Genetic	CBC (%) Sporadic	P value	Median follow-up (years)	Year of publication
Seynaeve [60] (Rotterdam)	26/174[a]	14	6	0.06	6	2004
Robson [44] (MSKCC, New-York)	28/277	27	9	0.002	10.3	1999
Pierce [37] (Collaborative, USA)	71/213[a]	20	2	<0.0001	5	2000
Haffty [40] (Yale, New-York)	22/105	42	9	0.001	12.7	2002
Brekelmans [51] (Rotterdam)	109/410[a]	20	5	<0.001	4.3	2007
Kirova [61] (Paris)	27/261[a]	37	7	0.0003	9	2005
Pierce [40] (Yale, New-York)	160/445	39	7	<0.0001	8	2006
Garcia Etienne [42] (Milan)	54/162[a]	25	1	0.03	4	2009
Kirova [43] (Paris)	29/58[a]	41	11	0.001	13.4	2010

[a] BRCA1/2 carriers age-matched to controls.

Published in final edited form as:
Breast Cancer Res Treat. 2010 June ; 121(2): 389–398. doi:10.1007/s10549-010-0894-z.

Lori J. Pierce

Local Therapy in BRCA1 and BRCA2 Mutation Carriers with Operable Breast Cancer: Comparison of Breast Conservation and Mastectomy

The cumulative incidence for CBC by the use of RT

No significant difference with RT

⇓

no increase in CBC from scatter RT.

Analysis by local treatment (BCT, M without RT, M with RT)

⇓

No significant differences.

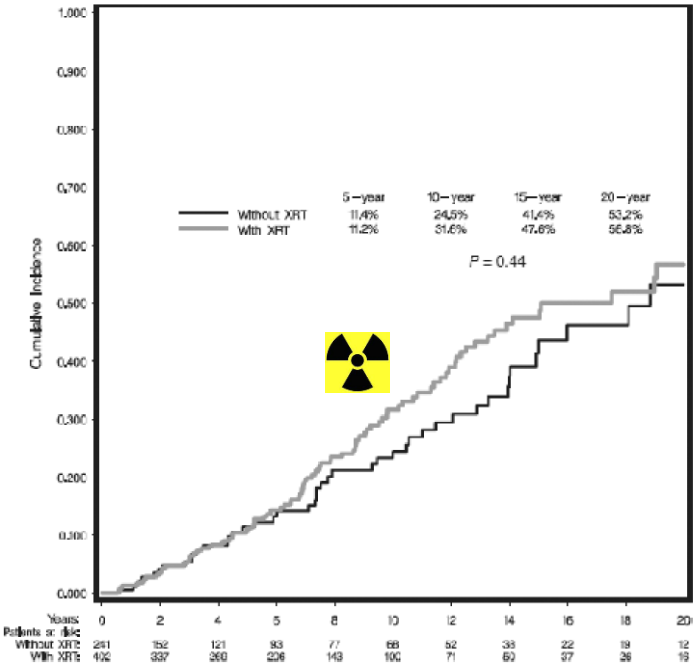


Figure 3.
Cumulative incidence estimates of contralateral breast cancer by use of adjuvant radiotherapy.

Tumour cell response to radiation and clinical disease control

Ipsilateral breast new cancer or recurrence → **Secondi tumori**

solo AA aumento di IBTR
soprattutto se no OT/ovariectomia
altro quadrante/ diversa istologia/ lungo IL

Contralateral breast cancer → **Aumentato rischio**

Survival indices

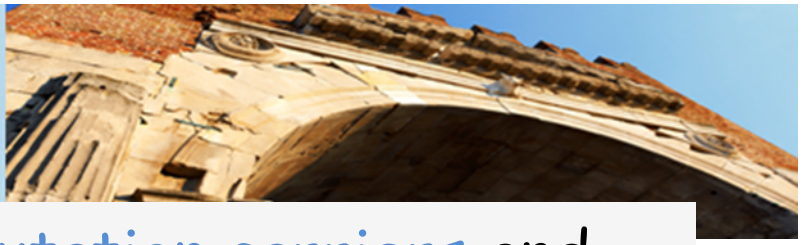
Tumour cell response to radiation and clinical disease control

Ipsilateral breast new cancer or recurrence → **Secondi tumori**

solo AA aumento di IBTR
soprattutto se no OT/ovariectomia
altro quadrante/ diversa istologia/ lungo IL

Contralateral breast cancer → **Aumentato rischio**

Survival indices



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Review

Clinical relevance of normal
in BRCA1/BRCA2 mutation

Jacques Bernier [a, *], Philip Poortmar
[a] Genolier Swiss Medical Network, Department of Radio-Onc
[b] Department of Radiation Oncology, Radboud University Me

comparing outcomes for mutation carriers and sporadic controls treated with BCT + RT →
no significant difference in survival

First author	Overall survival (%) Genetic	Overall Sporadi	Cause-specific survival (%) Genetic	Cause-specific survival (%) Sporadic	Median follow-up
Verhoog [28] (Rotterdam)	NS	NS	NS	NS	5
Robson [44] (MSKCC, New-York)	66	81 (P:0.05	72	87 (P:0.02)	10.3
Pierce [37] (Collaborative, USA)	86	91 (P:0.7)	92	91 (p:0.5)	5
Haffty [40] (Yale, New-York)	NS	NS	NS	NS	12.7
Brekelmans [51] (Rotterdam)	50	55 (P:0.32	62	59 (p:0.17)	4.3
Kirova [43] (Paris)	NS	NS	–	–	13.4

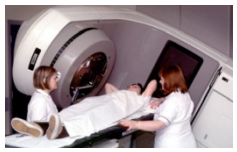
90 BRCA pts (93 tumours)
induction anthracycline-CT
and/or RT

sulle cellule neoplastiche →
con maggiore risposta?
Fourquet, 2009

complete clinical response
15/39 (**46%**) **BRCA-mutated**
7/54 (**17%**) **non-mutated**
(p =0.008).

RT maggiore "efficacia"
in BRCA carriers per impossibilità
a riparare il danno (lab)

sulle cellule sane ?????



normal tissue response to radiation

the presence of a **BRCA1/2** mutation does **not** appear to **enhance**, in the **clinical setting**, **normal cell sensitivity to radiotherapy**.

BRCA1/2 mutation carriers are **not more** susceptible than non-carriers **to radiation carcinogenic effects**

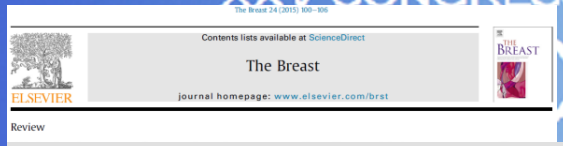
CAUTELA
FU….(HD)

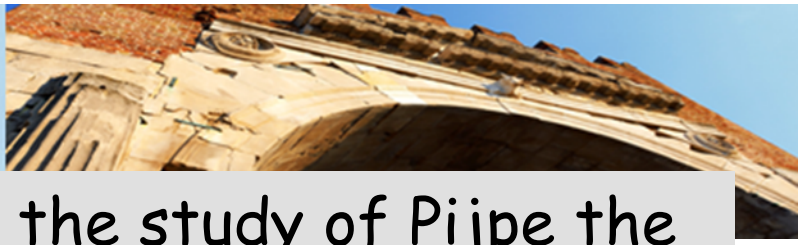
CANCEROGENESI

Risk of breast cancer in BRCA1/2 mutation carriers as a result of diagnostic imaging

ideal study → prospective cohort study→ not ethical

retrospective study





Taking into account the results of the study of Pijpe the Dutch guidelines
annual breast MRI screening at age 25,
mammography as of the age of 30 years

The United Kingdom National Institute for Health and Care Excellence (NICE) guidelines,
annual breast MRI screening at age 30,
annual mammography from age 40 years

The United States National Comprehensive Cancer Network (NCCN) guidelines
annual mammogram and breast MRI at age 25 years

Enhanced screening

Prophylactic surgery

Chemoprevention

Mastectomia

chirurgia conservativa +RT

La **genetica clinica** raccoglie numerose applicazioni della genetica alla medicina....

studio del patrimonio genetico di una donna

identificare mutazioni germinali

consulenza genet

identificare donne predisposte geneticame
sviluppo di una neoplasia mammaria

studio del patrimonio genetico del tumore

gene expression profile

intrinsic molecular classification of breast cancer
microarray-based prognostic markers

Breast Cancer 2

Lancet 2011; 378: 1812–23

Gene expression profiling in breast cancer: classification, prognostication, and prediction

Jorge S Reis-Filho, Lajos Pusztai

The advent of high-throughput platforms for analysis of gene expression, such as **microarrays**, has led to studies that have challenged the view of breast cancer

Perou CM, Nature 2000
Sorlie T, 2001

Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning*†, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein*

Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[g], Hilde Johnsen[b], Trevor Hastie[e], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[j], Thor Thorsen[k], Hanne Quist[l], John C. Matese[c], Patrick O. Brown[m], David Botstein[c], Per Eystein Lønning[g], and Anne-Lise Børresen-Dale[b,n]

2001

Breast Cancer 2

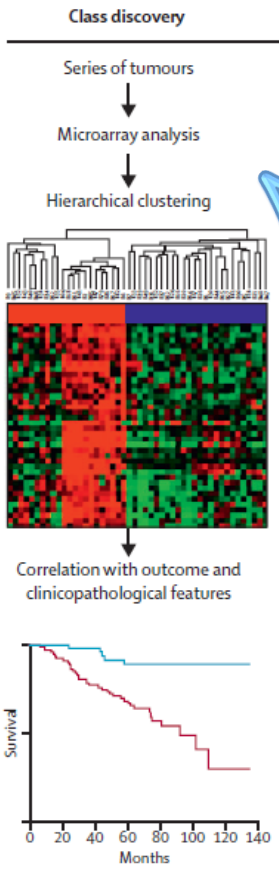
Lancet 2011; 378: 1812–23

Gene expression profiling in breast cancer: classification, prognostication, and prediction

Jorge S Reis-Filho, Lajos P...

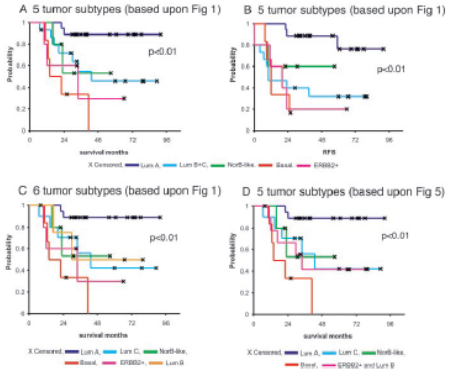
PAST

breast cancer is a single disease with variations in clinical behaviour and histopathological features



NOWADAYS

a collection of different diseases affect the same organ site from the same anatomical structure (terminal duct lobular unit)



Different

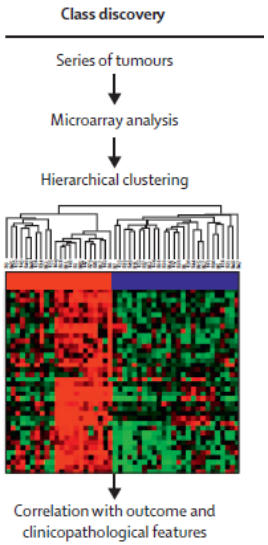
risk factors,
histopathological features,
prognosys
response to systemic therapies.

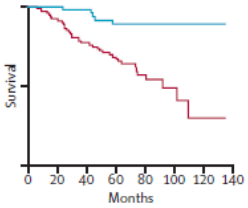
Breast Cancer 2

Lancet 2011; 378: 1812–23

Gene expression profiling in breast cancer: classification, prognostication, and prediction

Jorge S Reis-Filho, Lajos Pusztai





These studies also showed that **response to treatment** is not determined by anatomical prognostic factors (ie, tumour size or nodal status), but rather by **intrinsic molecular characteristics of the tumours that can be probed with molecular methods**

Reis-Filho JS, 2010
Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. 2009
Weigelt B, Baehner FL, Reis-Filho JS. The contribution of gene expression profi ling to breast cancer classifi cation, prognostication and prediction: a retrospective of the last decade. 2010;
Iwamoto T, Pusztai L. Predicting prognosis of breast cancer with gene signatures: are we lost in a sea of data? *Genome Med* 2010

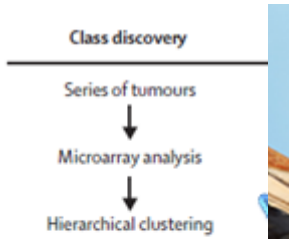
XXV CONGRESSO NAZIONALE

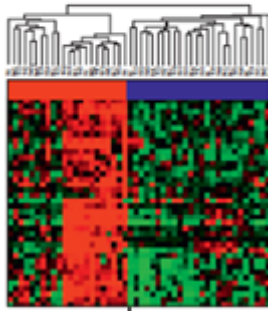
Gene expression profiling in breast cancer

C. Sotiriou & C. Desmedt

Institut Jules Bordet, Medical Oncology Clinic, Brussels, Belgium

Annals of Oncology, 2006



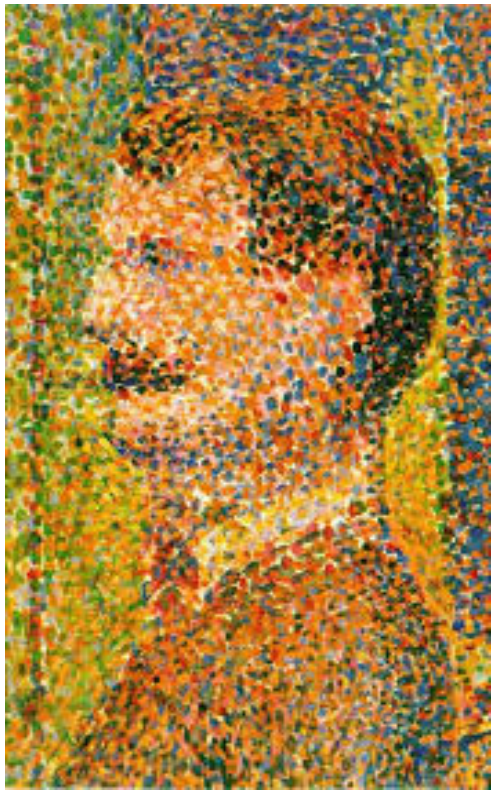


molecular classification of breast cancer

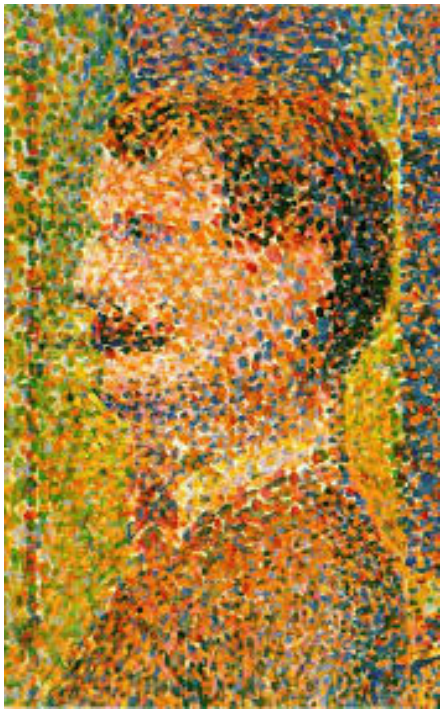
By detailing the expression levels of thousands of genes simultaneously from tumour cells and their surrounding microenvironment,

gene expression profiles have provided molecular 'portraits' of breast cancer

distinguished by extensive differences of gene expression in breast cancer samples



Intrinsic molecular classification



At the RNA level, the identification of these subtypes was shown to be mainly driven by the

expression of **ER and ER-related genes**, **proliferation-related genes**,

and to a lesser extent,

HER2 and genes mapping to the region of the HER2 amplicon on chromosome 17.

Invited review

Lessons learned from the intrinsic subtypes of breast cancer in the quest for precision therapy

J. H. Norum[1,3], K. Andersen[2] and T. Sørlie[1,3]

2014

Table 1 Characteristics, surrogate immunohistochemical definition and treatment recommendations for the intrinsic molecular subtypes of breast cancer GENE EXPRESSION

Intrinsic subtype	Characteristics	Immunohistochemical definition	Recommended treatment
Luminal A	ER+, highly express luminal epithelial genes, *PIK3CA* mutations, diploid, low grade, cyclin D1 overexpression, whole chromosome arm aberrations	ER+ and/or PR+ HER2− Ki-67 low	Hormone therapy
Luminal B	ER+ (low), proliferative, high grade, whole chromosome arm aberrations and complex rearrangements, *TP53* and *PIK3CA* mutations, alterations in retinoblastoma and MAPK pathways, some are HER2+	ER+ and/or PR+ HER2− (or HER2+) Ki-67 high	Hormone therapy, chemotherapy, anti-HER2 if HER2+
HER2-enriched	ER−, most tumours show *HER2* amplification, overexpression of genes on 17q22, highly proliferative, *TP53* mutations, focal high-level amplifications	HER2+ (amplified or overexpressed) ER−	Anti-HER2, chemotherapy
Basal-like	ER−, HER2−, highly express basal keratins, express EGFR, highly proliferative, aneuploid, high grade, *TP53* mutations, complex genomic rearrangements, WNT pathway activation increased	ER−, PR−, HER2− (triple negative)	Chemotherapy
Normal-like	Express basal and myoepithelial genes, adipose tissue-specific genes	Not relevant	Not relevant

ER, oestrogen receptor; PIK3CA, phosphatidyl inositol-4,5-bisphosphate 3-kinase catalytic subunit α; PR, progesterone receptor; HER, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; EGFR, epidermal growth factor receptor.

XXV CONGRESSO NAZIONALE

015

0 novembre

Invited review

Lessons learned from the intrinsic subtypes of breast cancer in the quest for precision therapy

J. H. Norum[1,3], K. Andersen[2] and T. Sørlie[1,3]

Despite a more specific and robust breast tumour classification system being provided by gene expression profiling, heterogeneity is also evident within these molecular portraits

The luminal subtypes, comprising about two-thirds of human breast cancers, are diverse in the signalling pathways involved, and in the spectra and rate of mutations.

Basal-like breast cancers, although more homogeneous with respect to expression profiles and recurrent mutations, can be divided into several subgroups,

XXV CONGRESSO NAZIONALE

Invited review

2014

Lessons learned from the intrinsic subtypes of breast cancer in the quest for precision therapy

J. H. Norum[1,3], K. Andersen[2] and T. Sørlie[1,3]

Large-scale gene expression profiling by microarray technology is not suitable for routine clinical analysis;

therefore, **subtyping by clinico-pathological markers** is considered a **convenient approximation** for assessing risk of relapse and estimating the probable effect of specific therapies

Annals of Oncology Advance Access published June 27, 2011

special article

Annals of Oncology
doi:10.1093/annonc/mdr304

Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

A. Goldhirsch[1,*], W. C. Wood[2], A. S. Coates[3], R. D. Gelber[4], B. Thürlimann[5], H.-J. Senn[6] & Panel members[†]

Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

A. Goldhirsch[1,*], W. C. Wood[2], A. S. Coates[3], R. D. Gelber[4], B. Thürlimann[5], H.-J. Senn[6] & Panel members[†]

Intrinsic Subtype (1)	Clinico-pathologic definition	Notes
Luminal A	**'Luminal A'** ER and/or PgR positive(76) HER2 negative (77) Ki-67 low (<14%)*	This cut-point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping (7). Local quality control of Ki-67 staining is important.
Luminal B**	**'Luminal B (HER2 negative)'** ER and/or PgR positive HER2 negative Ki-67 high	Genes indicative of higher proliferation are markers of poor prognosis in multiple genetic assays (78). If reliable Ki-67 measurement is not available, some alternative assessment of tumor proliferation such as grade may be used to distinguish between 'Luminal A' and 'Luminal B (HER2 negative)'.
	'Luminal B (HER2 positive)' ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified	Both endocrine and anti-HER2 therapy may be indicated.
Erb-B2 overexpression	**'HER2 positive (non luminal)'** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	Approximately 80% overlap between 'triple negative' and intrinsic 'basal-like' subtype but 'triple negative' also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence. Staining for basal keratins (79) although shown to aid selection of true basal-like tumors, is considered insufficiently reproducible for general use.

Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

A. Goldhirsch[1,*], W. C. Wood[2], A. S. Coates[3], R. D. Gelber[4], B. Thürlimann[5], H.-J. members[†]

'Subtype'	Type of therapy
'Luminal A'	Endocrine therapy alone
'Luminal B (HER2 negative)'	Endocrine ± cytotoxic therapy
'Luminal B (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy
'HER2 positive (non luminal)'	Cytotoxics + anti-HER2
'Triple negative (ductal)'	Cytotoxics
'Special histological types'*	
A. Endocrine responsive	Endocrine therapy
B. Endocrine nonresponsive	Cytotoxics

VOLUME 28 · NUMBER 10 · APRIL 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Breast Cancer Subtypes and the Risk of Local and Regional Relapse

K. David Voduc, Maggie C.U. Cheang, Scott Tyldesley, Karen Gelmon, Torsten O. Nielsen, and Haven Kennecke

In the contemporary management of breast cancer, several possibilities exist for local and regional treatment, using various **surgical options** and the dose, volume, and technique of **radiotherapy.**

A better **understanding of the risk of local relapse** (LR) and regional relapse (RR) would facilitate therapeutic **decision making**.

The influence of breast cancer molecular subtypes on locoregional relapse.....

VOLUME 28 · NUMBER 10 · APRIL 1 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Breast Cancer Subtypes and the Risk of Local and Regional Relapse

K. David Voduc, Maggie C.U. Cheang, Scott Tyldesley, Karen Gelmon, Torsten O. Nielsen, and Haoyn Kennecke

British Columbia
2,985 tumors
median age 59 years
median follow-up time for both LR and RR 12 years

No neoadjuvant CT No trastuzumab

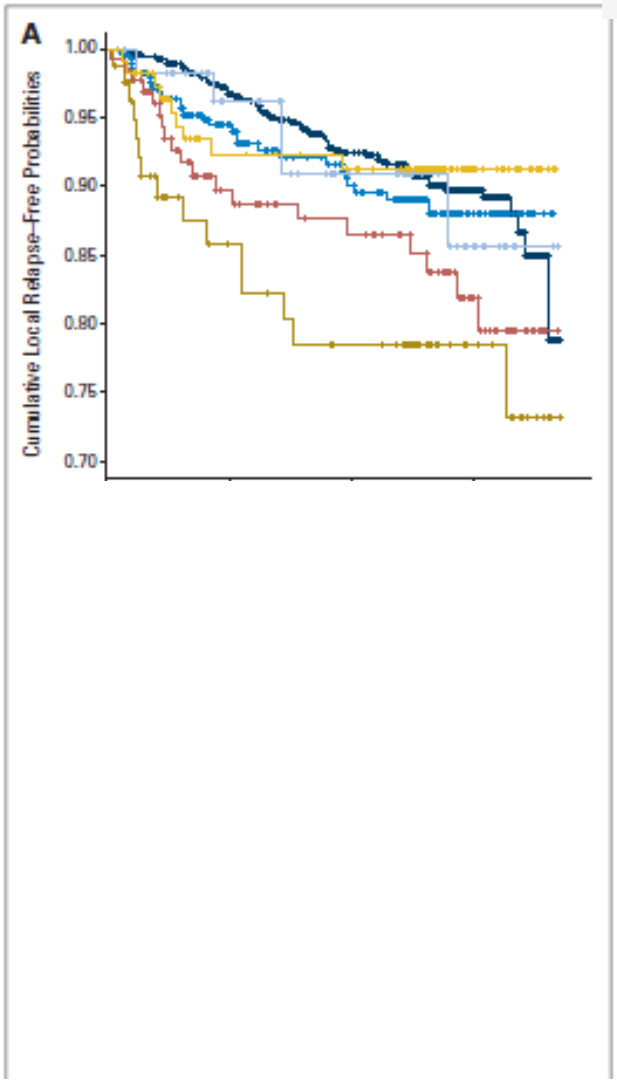
Molecular subtyping of breast tumors using a six-marker immunohistochemical panel
ER, PR, HER2, Ki-67, EGFR, CK5/

can identify pts at increased risk of local/regional recurrence

CHIR. CONSERV.

\+

RT



Luminal A→ LR a 10 years→ 8%

Basal→ LR a 10 years→ 14%

HER2 →LR a 10 years →21%

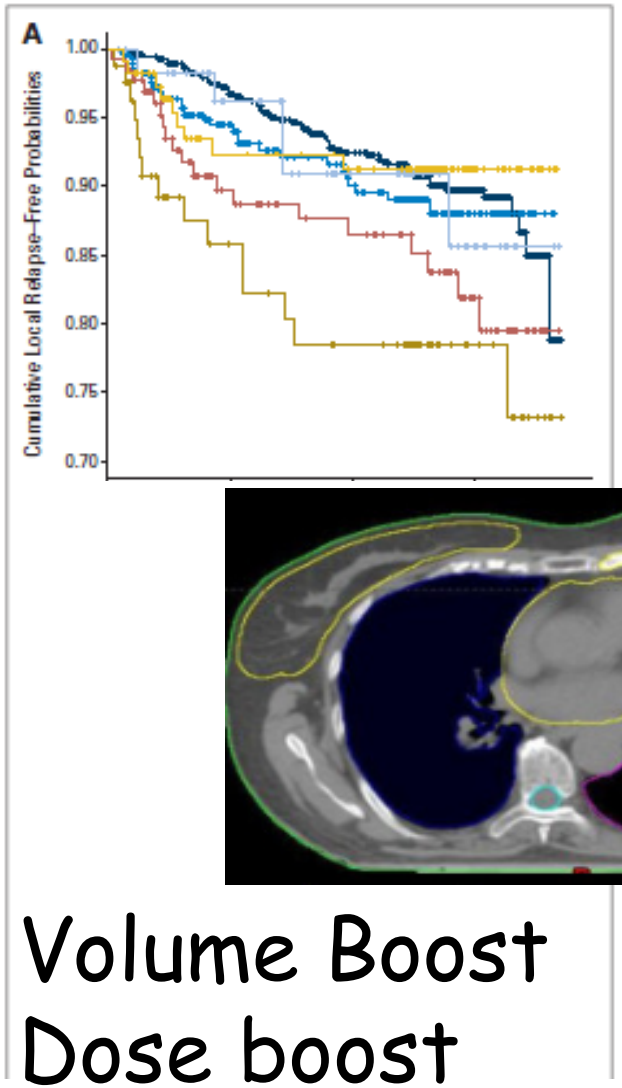
Luminal A→ RR a 10 years→ 3%

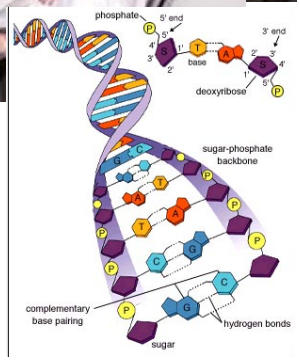
Basal→ RR a 10 years→ 14%

HER2 →RR a 10 years →16%

locoregional recurrence rate of **15% for HER2-enriched tumors** compared **with 1% for luminal A tumors at 5 years** (ss on univariable analysis)
Millar, JCO 2009

the study found that **HER2-enriched and TNP tumors** were associated with an increased risk of local recurrence on multivariable analysis
Nguyen, JCO 2008





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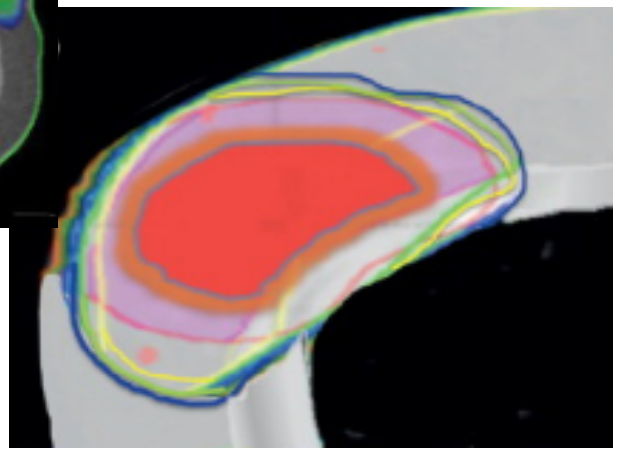
Basal→ LR a 10 years→ 14%

HER2 →LR a 10 years →21%

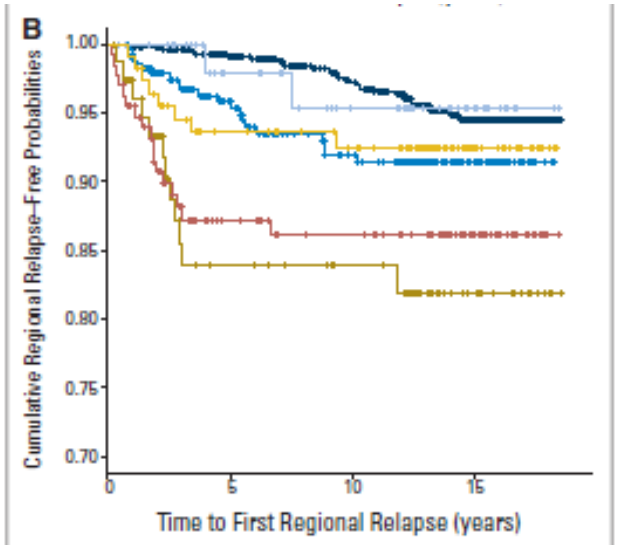


Volume Boost
Dose boost

Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

Giuliano, JAMA, 2011



Luminal A→ RR a 10 years→ 3%

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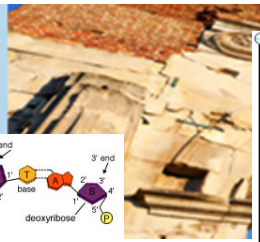
HER2 →RR a 10 years →16%

Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

Giuliano, *JAMA*, 2011



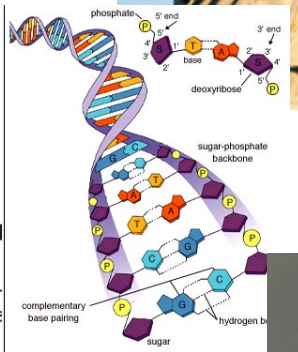
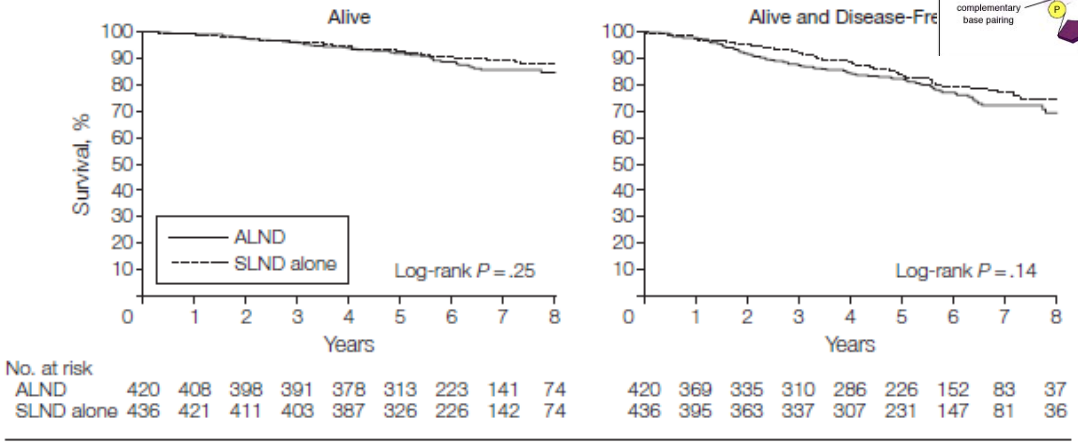


Figure 2. Survival of the ALND Group Compared With SLND-Alone Group



ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

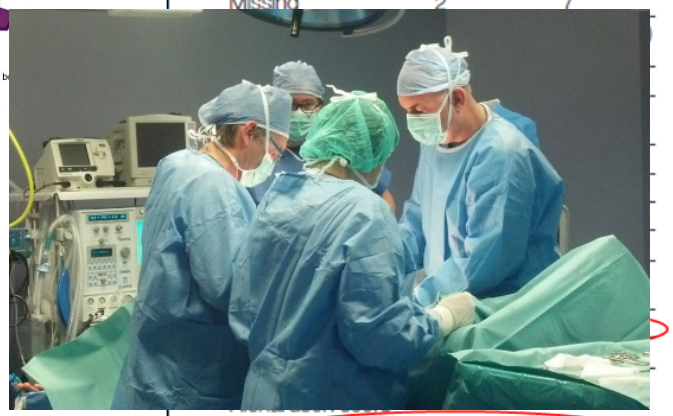
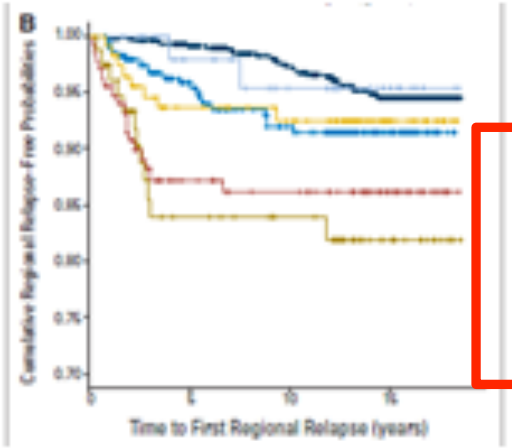


Table 1. Baseline Patient and Tumor Characteristics by Study Group

Characteristic	No. (%) ALND (n = 420)	SLND Alone (n = 436)
Age, median (range), y	56 (24-92)	54 (25-90)
Missing	7	10
Clinical T stage		
T1	284 (67.9)	303 (70.6)
T2	134 (32.1)	126 (29.4)
Missing	2	7
	71 (22.0)	81 (25.6)
2	158 (48.9)	148 (46.8)
3	94 (29.1)	87 (27.5)
Missing	97	120

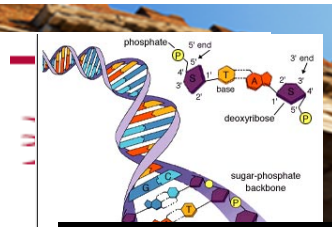


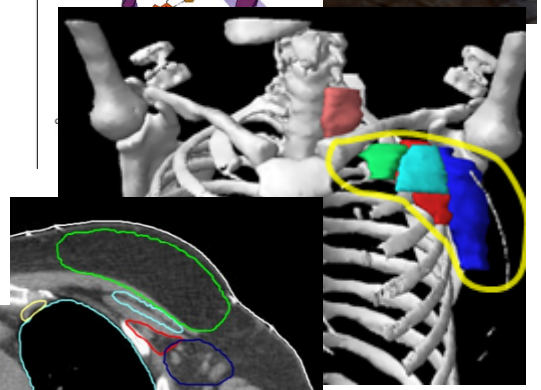
Luminal A→ RR a 10 years→ 3%

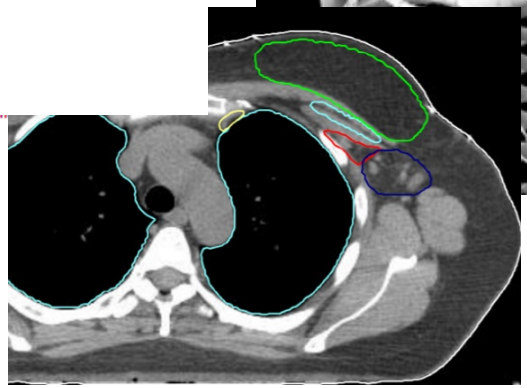
Basal→ RR a 10 years→ 14%

HER2 →RR a 10 years →16%

t cancer treated with
compared with ALND







-

Bruce G. Haffty, 2011

Clinical Scenario	No. of Positive Sentinel Nodes	Total No. of Sentinel Nodes Sampled	Probability of Four or More Nodes Involved‡ (%)	Field Design
IDC, 1.0 cm, ER positive, LVI negative	1 (IHC only)	3	< 1	Tangents only
IDC, 1.8 cm, G3, ER positive, LVI negative, unifocal	1 (macro)	2	2	High tangents
IDC, 2.0 cm, ER negative, LVI positive	2 (macro)	2	30	High tangents/consider full nodal treatment
ILC, 4.0 cm, ER positive, multifocal, LVI negative	2 (macro)	2	40	High tangents/consider full nodal treatment
IDC, 3 cm, ER negative, LVI positive, multifocal	3 (macro with ENE)	3	80	Full nodal treatment

XXV CONGRESSO NAZIONALE

VOLUME 33 · NUMBER 18 · JUNE 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Identification of a Low-Risk Luminal A Breast Cancer Cohort That May Not Benefit From Breast Radiotherapy

Fei-Fei Liu, Wei Shi, Susan J. Done, Naomi Miller, Melania Pintilie, David Voduc, Torsten O. Nielsen, Sharon Nofech-Mozes, Martin C. Chang, Timothy J. Whelan, Lorna M. Weir, Ivo A. Olivotto, David R. McCready, and Anthony W. Fyles

Classification by subtype was prognostic for IBR at 10-year

luminal A, 5.2%;
luminal B, 10.5%;
high-risk subtypes, 21.3%; *P* .001

Luminal subtypes seemed to derive less benefit from RT

luminal A hazard ratio 0.40;
luminal B HR, 0.51
high-risk subtypes HR, 0.13

Breast Cancer 2

Lancet 2011; 378: 1812–23

Gene expression profiling in breast cancer: classification, prognostication, and prediction

Jorge S Reis-Filho, Lajos Pusztai

Intrinsic molecular classification

Table 1 Characteristics, surrogate immunohistochemical definition and treatment recommendations for the intrinsic molecular subtypes of breast cancer

Intrinsic subtype	Characteristics	Immunohistochemical definition	Recommended treatment
Luminal A	ER+, highly express luminal epithelial genes, *PIK3CA* mutations, diploid, low grade, cyclin D1 overexpression, whole chromosome arm aberrations	ER+ and/or PR+ HER2– Ki-67 low	Hormone therapy
Luminal B	ER+ (low), proliferative, high grade, whole chromosome arm aberrations and complex rearrangements, *TP53* and *PIK3CA* mutations, alterations in retinoblastoma and MAPK pathways, some are HER2+	ER+ and/or PR+ HER2– (or HER2+) Ki-67 high	Hormone therapy, chemotherapy, anti-HER2 if HER2+
HER2-enriched	ER–, most tumours show *HER2* amplification, overexpression of genes on 17q22, highly proliferative, *TP53* mutations, focal high-level amplifications	HER2+ (amplified or overexpressed) ER–	Anti-HER2, chemotherapy
Basal-like	ER–, HER2–, highly express basal keratins, express EGFR, highly proliferative, aneuploid, high grade, *TP53* mutations, complex genomic rearrangements, WNT pathway activation increased	ER–, PR–, HER2– (triple negative)	Chemotherapy
Normal-like	Express basal and myoepithelial genes, adipose tissue-specific genes	Not relevant	Not relevant

ER, oestrogen receptor; PIK3CA, phosphatidyl inositol-4,5-bisphosphate 3-kinase catalytic subunit α; PR, progesterone receptor; HER, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; EGFR, epidermal growth factor receptor.

These supervised class-prediction studies, however, did not take into account the **molecular heterogeneity** of the disease and **aimed to identify multigene predictors that could be applicable to all patients with breast cancer.**

Prognostic signatures
Development of microarray-based prognostic signatures

Breast Cancer 2

Lancet 2011; 378: 1812–23

Gene expression profiling in breast cancer: classification, prognostication, and prediction

Jorge S Reis-Filho, Lajos Pusztai

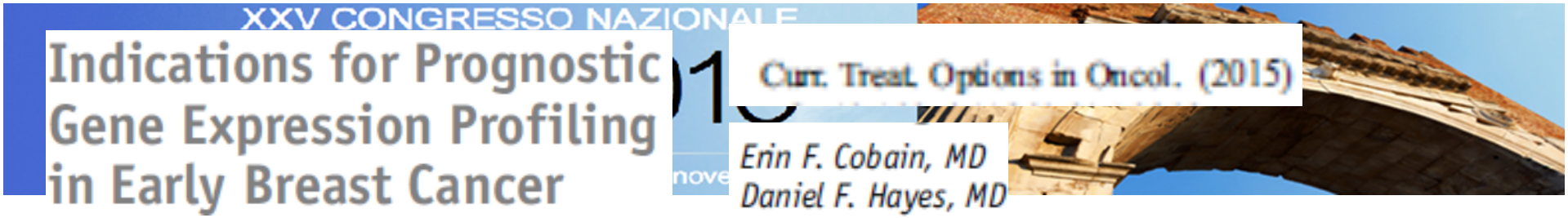
Intrinsic molecular classification

Prognostic signatures

Development of microarray-based prognostic signatures

Microarray based gene expression profiling was also used for **forecasting of outcomes for individual patients** with breast cancer,

specifically aiming to **identify patients** with disease of sufficiently good prognosis to allow the **safe omission of adjuvant chemotherapy.**



Adjuvant systemic therapy for early-stage breast cancer: a success story

Selection of Adjuvant SystemicTherapy for EBC: should all patients receive chemotherapy?

Do all breast cancers respond equally to chemotherapy?

Intrinsic subtypes: a short hand for breast cancer biology

Criteria for introduction of tumor biomarker tests into routine clinical practice

Gene expression profiles for use in EBC: a critical analysis

Erin F. Cobain, MD
Daniel F. Hayes, MD

Curr. Treat. Options in Oncol. (2015)

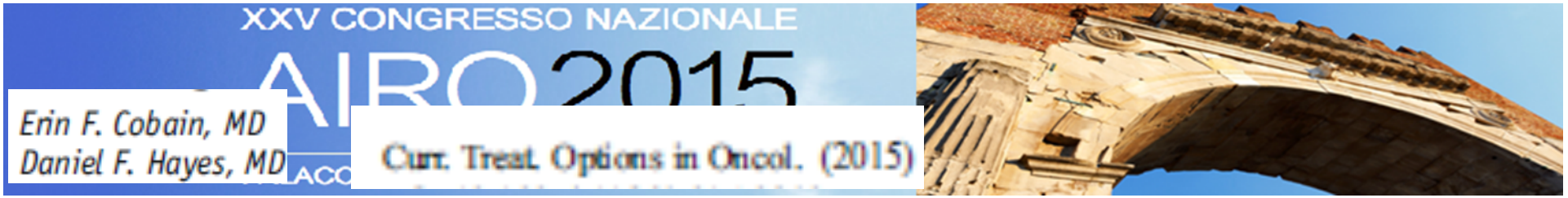
Adjuvant systemic therapy for early-stage breast cancer: a success story

broad implementation of screening

primary surgery and radiotherapy if necessary

delivery of effective Adjuvant Sistemic Therapy

a substantial decline in breast cancer mortality over the past 30 years



Adjuvant systemic therapy for early-stage breast cancer: a success story

Current guidelines indicate that following local treatment early breast cancer pts

ER/PGR positive→ at least 5 years (or more) of OT

HER2-positive → trastuzumab + chemotherapy

Determining which patients should receive adjuvant chemotherapy is more complex, as serious side effects can occur and many patients may not benefit.

Selection of Adjuvant SystemicTherapy for EBC: should all patients receive chemotherapy?

Adjuvant CT to women with EBC reduces mortality
EBCTCG, 2012

Almost 100 % of patients receiving chemotherapy suffer bothersome side effects (i.e., hair loss, fatigue, nausea).

Selection of Adjuvant SystemicTherapy for EBC: should all patients receive chemotherapy?

Serious and even life-threatening toxicities (neutropenic fever, bleeding, transfusion requirement, secondary malignancy, congestive heart failure, and peripheral neuropathy) occur in approximately 1– 2 % of patients.

These considerations highlight the importance for the clinician to determine whether the absolute benefit of chemotherapy outweighs the 1–2 % absolute risk of serious toxicity.

Selection of Adjuvant SystemicTherapy for EBC: should all patients receive chemotherapy?

to identify patients for whom we can recommend adjuvant chemotherapy, it is important to consider ……

Prognostic markers →pts at high risk of metastatic relapse
tumor stage and grade

Predictive markers to estimate which therapies will benefit specific patient groups
ER
HER-2

Do all breast cancers respond equally to chemotherapy?

response may not be uniform

particularly for those patients with low-grade, well-differentiated tumors and high expression of hormone receptors

Fisher B, 2004
Berry DA, 2006

Lippman and colleagues first suggested this relative chemotherapy effect in 1978 when they reported that…. patients with low or absent ER expression had greater objective responses to treatment

Intrinsic subtypes: a short hand for breast cancer biology

Over a decade ago, Perou and colleagues demonstrated that breast cancer could be subdivided into four distinct categories based upon unsupervised patterns of gene expression.

Table 1 Characteristics, surrogate immunohistochemical definition and treatment recommendations for the intrinsic molecular subtypes of breast cancer

Intrinsic subtype	Characteristics	Immunohistochemical definition	Recommended treatment
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HER2-enriched	ER–, most tumours show *HER2* amplification, overexpression of genes on 17q22, highly proliferative, *TP53* mutations, focal high-level amplifications	HER2+ (amplified or overexpressed) ER–	Anti-HER2, chemotherapy
Basal-like	ER–, HER2–, highly express basal keratins, express EGFR, highly proliferative, aneuploid, high grade, *TP53* mutations, complex genomic rearrangements, WNT pathway activation increased	ER–, PR–, HER2– (triple negative)	Chemotherapy
Normal-like	Express basal and myoepithelial genes, adipose tissue-specific genes	Not relevant	Not relevant

ER, oestrogen receptor; PIK3CA, phosphatidyl inositol-4,5-bisphosphate 3-kinase catalytic subunit α; PR, progesterone receptor; HER, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; EGFR, epidermal growth factor receptor.

Erin F. C
Daniel F.

Criteria for introduction of tumor biomarker tests into routine clinical practice

Evaluation of Genomic Applications in Practice and Prevention Initiative coined three semantics to guide phisician

analytic validity →how accurately and reliably the assay detects the analyte(s) of interest

clinical validity → how well the assay can predict the clinical outcome of interest

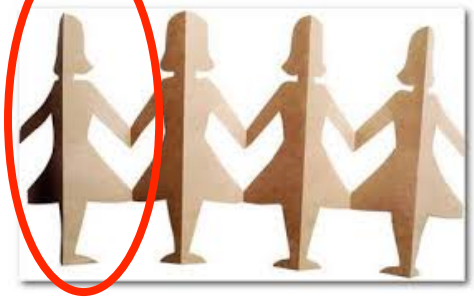
clinical utility →whether there are high levels of evidence demonstrating that the results of the assay provide information that contributes to and improves current optimal management of the patient's disease

Gene expression profiles for use in EBC: a critical analysis

Prognostic gene expression profiles have been developed primarily to identify those EBC patients with such favorable prognosis that the benefits of adjuvant chemotherapy do not clearly outweigh the risks.

Genomica:
studio dell'espressione di gruppi di geni per definire una caratterizzazione
della biologia del tumore
e
del suo comportamento clinico

Gene expression profiles for use in EBC: a critical analysis



Test Genomici:

basati sull'epressione di geni correlati ad attività biologiche rilevanti come la proliferazione o l'espressione dei recettori ormonali

forniscono il profilo molecolare personalizzato del tumore,

definire la probabilità di risposta alle terapia

il rischio di recidiva a distanza

Erin F. Cobain, MD
Daniel F. Hayes, MD

Table 1. Characteristics of gene expression profiles intended for use in patients with early breast cancer (EBC)

	21-gene RS (Oncotype Dx®)	Amsterdam 70-gene signature (MammaPrint®)	PAM50 (Prosigna™)	Rotterdam 76-gene signature	Genomic grade index	Breast cancer index	Endopredict®
Relevant EBC Population	ER+ HER2− Node−	Node− Tumor size ≤5 cm	ER+	Node−	ER+	ER+ Node−	ER+ HER2−
Tissue Required for Assay	FFPE	FFPE or frozen	FFPE	FFPE	FFPE or frozen	FFPE	FFPE
Assay Technique	qRT-PCR	Microarray	qRT-PCR	Microarray	Microarray	qRT-PCR	qRT-PCR
Demonstrated Analytic Validity	✓	✓	✓				✓
Demonstrated Clinical Validity	✓	✓	✓	✓	✓	✓	✓
Demonstrated Clinical Utility	✓		✓			✓	✓
Level of Evidence	IB	III	IB	III	III	IB	IB
Ongoing Studies	TAILORx, RxPONDER	MINDACT					

Levels of evidence are measured on a scale of I (strongest) to IV (weakest) [21]
FFPE formalin-fixed paraffin-embedded, *qRT-PCR* quantitative reverse-transcriptase polymerase chain reaction, *TAILORx* Trial Assigning Individualized Options for Treatment, *RxPONDER* Rx for Positive Node, Endocrine Responsive Breast Cancer, *MINDACT* Microarray in Node Negative and 1–3 Positive Lymph Node Disease May Avoid Chemotherapy

VOLUME 26 · NUMBER 5 · FEBRUARY 10 2008

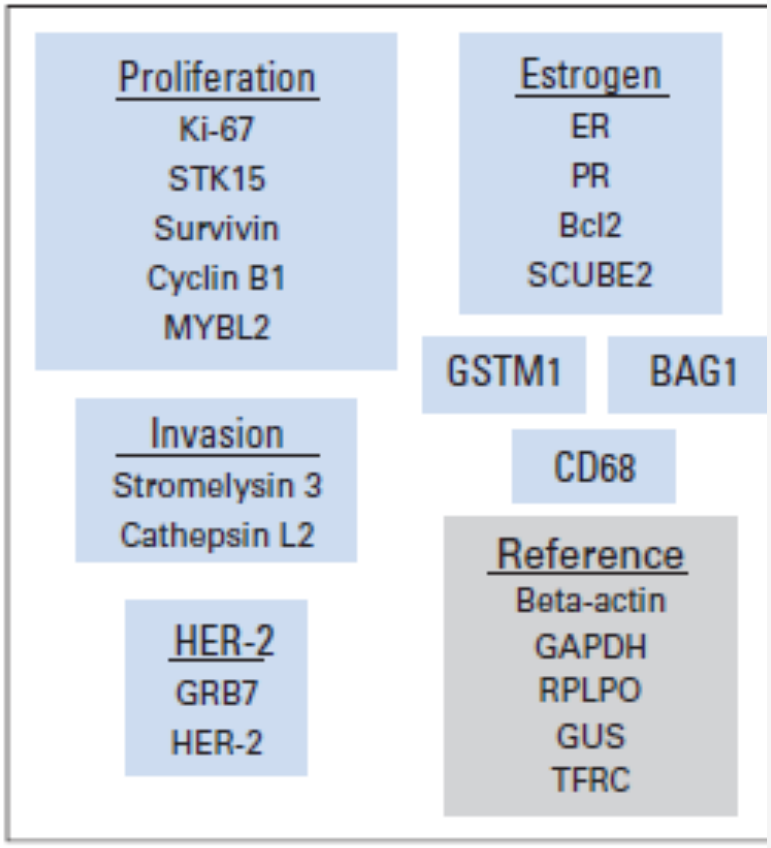
JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Oncotype DX

Development of the 21-Gene Assay and Its Application in Clinical Practice and Clinical Trials

Joseph A. Sparano and Soonmyung Paik



21 GENI

16 geni specifici del tumore
- patway della risposta ormonale
- proliferazione
- invasività
- apoptosi
- risposta immune
- recettore HER2

5 come controllo

VOLUME 26 · NUMBER 5 · FEBRUARY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Development of the 21-Gene Assay and Its Application in Clinical Practice and Clinical Trials

Joseph A. Sparano and Soonmyung Paik

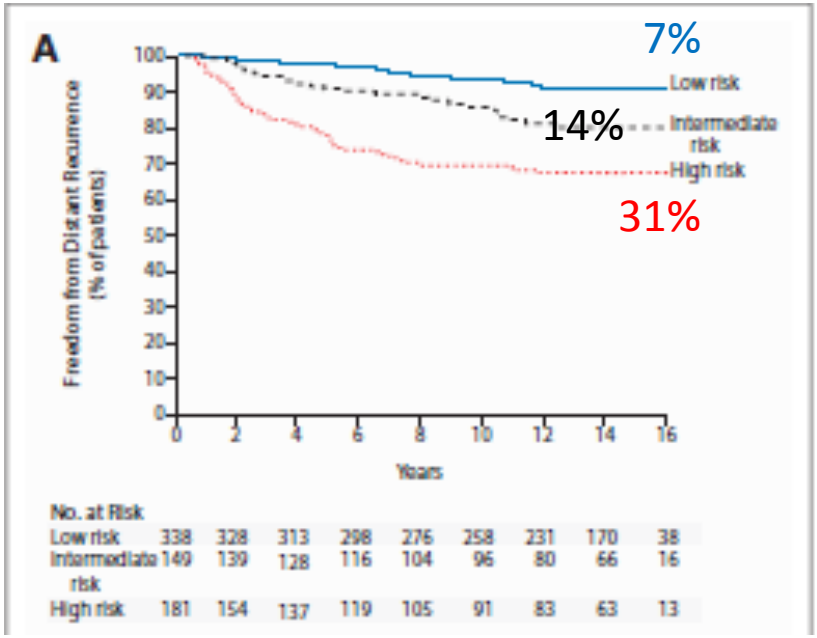
21 GENI

utilizzati per l'algoritmo del Recurrence Score

Test con un modello matematico che "pesa" alcuni geni più di altri e consente di suddividere le pazienti in categorie di rischio

Serious and even life-threatening toxicities (neutropenic fever, bleeding, transfusion requirement, secondary malignancy, congestive heart failure, peripheral neuropathy) occur in approximately 1- 2 % of patients.

Paik S 2004



CT→ risk reduction → one third

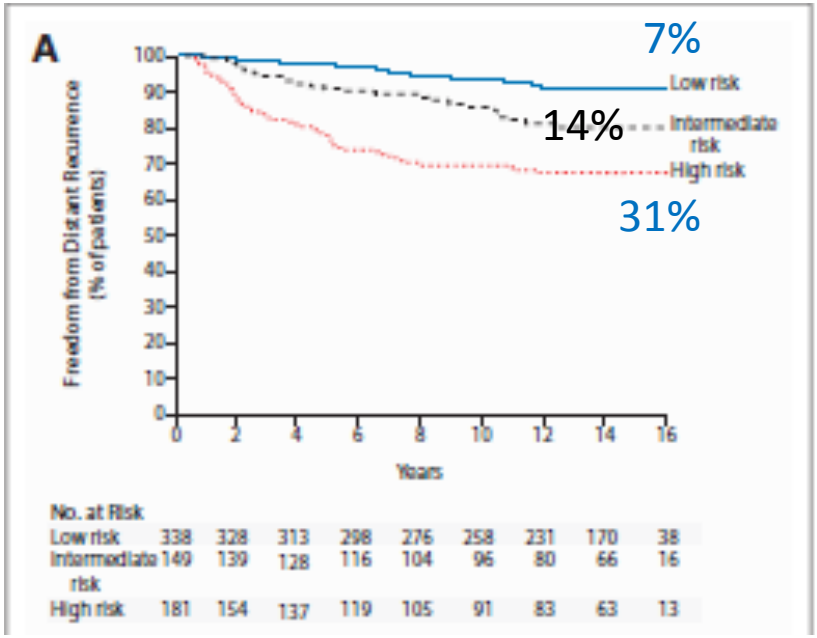
2% of LR pts→ avoid recurrence M+ with CT

≥5 % of pts (ER+, HER2-, N-) with high RS will benefit from CT,

(>1-2 % of significant toxicity to justify its application.)

CT→ risk reduction → one third

Paik S 2004



controversial whether or not patients with an intermediate RS have a sufficiently high risk of recurrence to justify CT

TAILORx
randomized pts with RS of 11-25 to ET alone vs ET plus CT

VOLUME 24 · NUMBER 23 · AUGUST 10 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor–Positive Breast Cancer

Soonmyung Paik, Gong Tang, Steven Shak, Chungyeul Kim, Joffre Baker, Wanseop Kim, Maureen Cronin, Frederick L. Baehner, Drew Watson, John Bryant, Joseph P. Costantino, Charles E. Geyer Jr, D. Lawrence Wickerham, and Norman Wolmark

tam vs tam + CT CMF/MF)
NSABP B20 trial

All pts **LR**

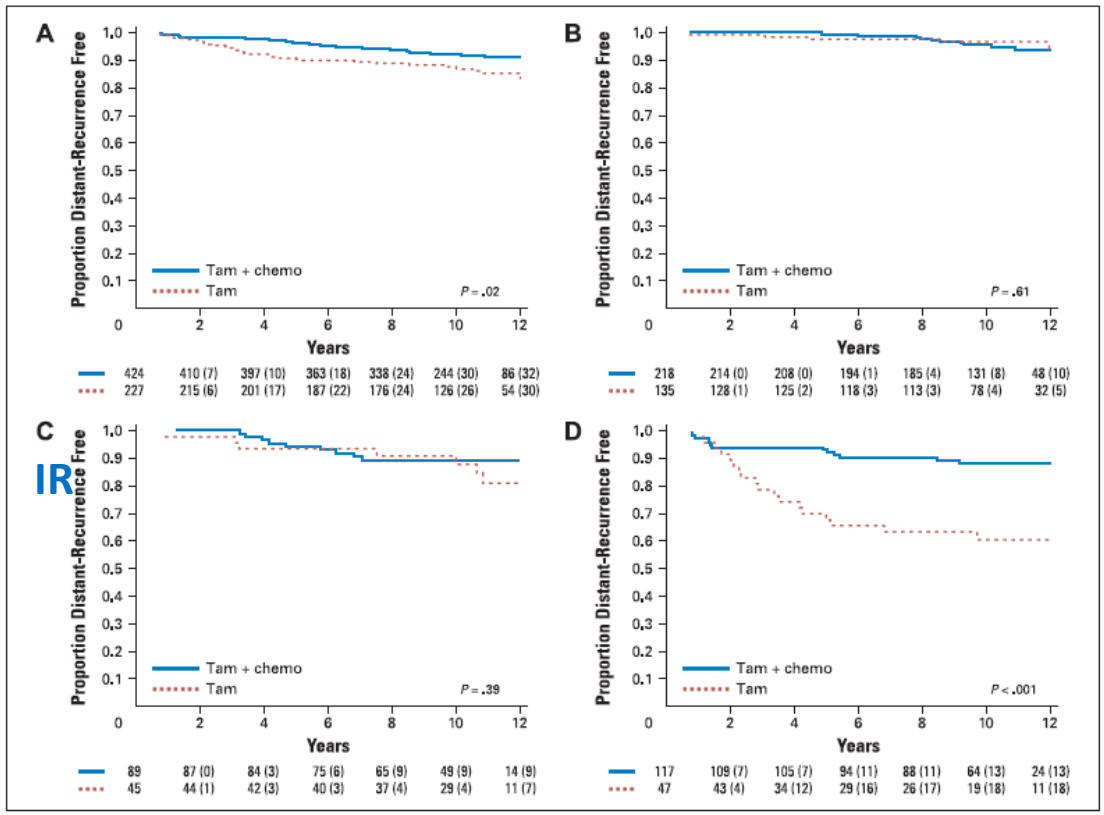


Fig 2. Kaplan-Meier plots for distant recurrence comparing treatment with tamoxifen (Tam) alone versus treatment with tamoxifen plus chemotherapy (Tam + chemo). (A) All patients; (B) low risk (recurrence score [RS] < 18); (C) intermediate risk (RS 18-30); (D) high risk (RS ≥ 31). The number of patients at risk and the number of distant recurrences (in parentheses) are provided below each part of the figure.

HR

OT+CT →
S libera da M+ a 10 anni

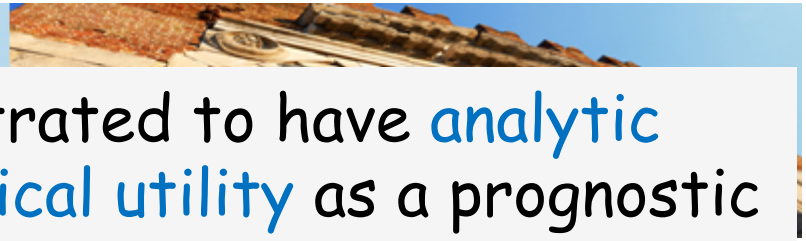
OT 60%→OT+CT 88%

Beneficio assoluto 28%

Numerous studies have confirmed the **clinical validity** and utility of the 21-gene RS in node-negative, ER-positive, HER2-negative patients as a prognostic Tool

NSAPB B-14
NSABP-B20
Kaiser Permanente
TransATAC
SWOG 8814
……

Studi prospettici in pts N+/N0 a rischio intermedio
TAILORx
RxPONDER



the 21-gene RS has been demonstrated to have analytic validity, clinical validity, and clinical utility as a prognostic tool in patients with ER positive, HER2-negative, node-negative tumors treated with ET.

Linee guida e indicazioni	Oncotype DX

Indications for Prognostic Gene Expression Profiling in Early Breast Cancer

Erin F. Cobain, MD
Daniel F. Hayes, MD*

2015

Given this, these tests are indicated in patients with ER+/PR +, HER2-negative, node-negative EBC.

Clinical trials are underway to determine if the 21-gene RS or other assays of intrinsic subtype may also be used to identify those women with ER-positive, HER2-negative breast cancer with positive axillary lymph nodes who may not benefit from adjuvant chemotherapy.

Finally, several studies have begun to assess whether one or more of these assays can identify patients who have received 5 years of adjuvant ET and do not require further, extended therapy.

Association Between the 21-Gene Recurrence Score Assay and Risk of Locoregional Recurrence in Node-Negative, Estrogen Receptor–Positive Breast Cancer: Results From NSABP B-14 and NSABP B-20

Eleftherios P. Mamounas, Gong Tang, Bernard Fisher, Soonmyung Paik, Steven Shak, Joseph P. Costantino, Drew Watson, Charles E. Geyer Jr, D. Lawrence Wickerham, and Norman Wolmark

The 21-gene Oncotype*DX recurrence score assay quantifies the risk of distant recurrence in* tamoxifen-treated patients with N-, ER+ breast cancer.

We investigated the association between **RS and risk for locoregional recurrence** (LRR) in patients with node-negative, ER-positive breast cancer from two National Surgical Adjuvant Breast and Bowel Project (NSABP) trials (NSABP B-14 and B-20).

XXV CONGRESSO NAZIONALE
AIRO 2015

VOLUME 28 · NUMBER 10 · APRIL 1 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

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The **21-gene OncotypeDX recurrence score** was available for

895 tamoxifen-treated pts (from both trials),
355 placebo-treated pts (from B-14),
424 chemotherapy + tamoxifen-treated pts (from B-20).

The primary end point was time to first LRR.

XXV CONGRESSO NAZIONALE

2015

i, 7-10 novembre

VOLUME 28 · NUMBER 10 · APRIL 1 2010

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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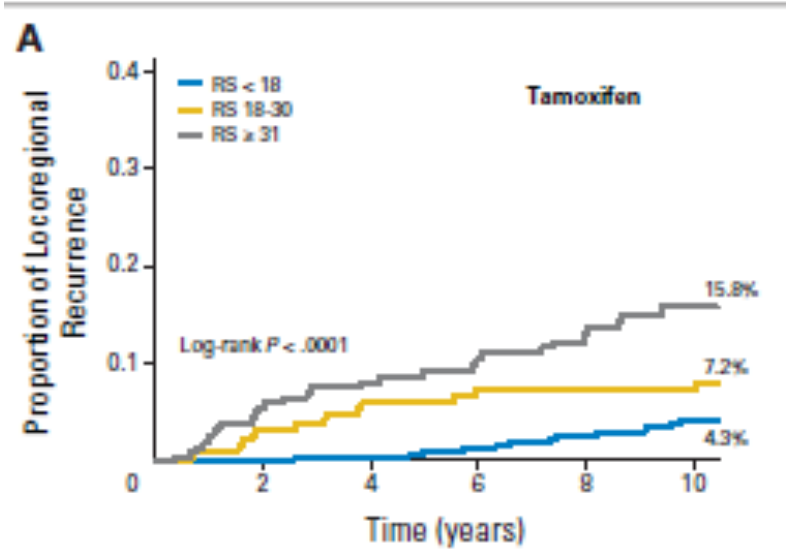


Chirurgia cons. + RT (390 pts)

LRR for the RS low 6.8%

intermediate 10.8%

high 14.6

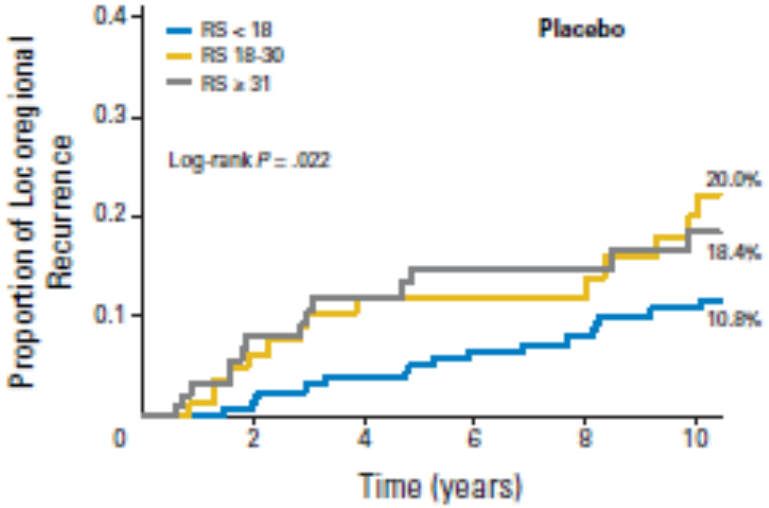
Mastectomia (505 pts)

LRR for the RS low 2.3%

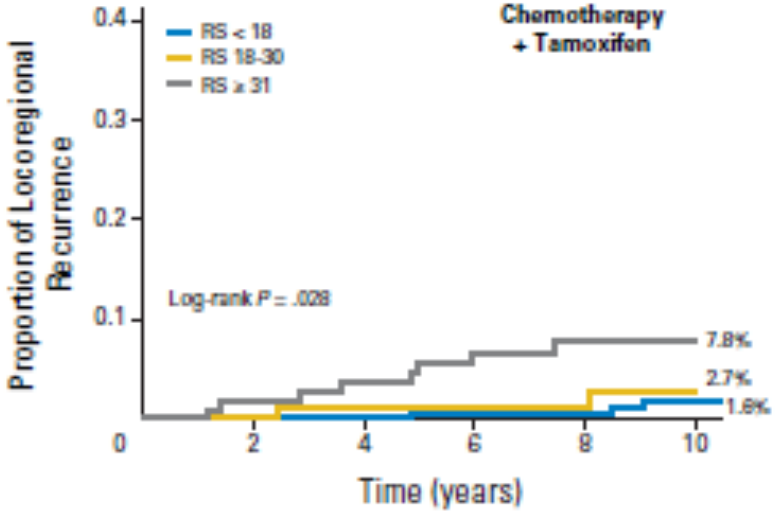
intermediate 4.7%

high 16.8%

B


Placebo
RS < 18
RS 18-30
RS ≥ 31
Log-rank P = .022
20.0%
18.4%
10.8%
Proportion of Locoregional Recurrence
0.4
0.3
0.2
0.1
0
2
4
6
8
10
Time (years)

C


Chemotherapy + Tamoxifen
RS < 18
RS 18-30
RS ≥ 31
Log-rank P = .028
7.8%
2.7%
1.6%
Proportion of Locoregional Recurrence
0.4
0.3
0.2
0.1
0
2
4
6
8
10
Time (years)

XXV CONGRESSO NAZIONALE

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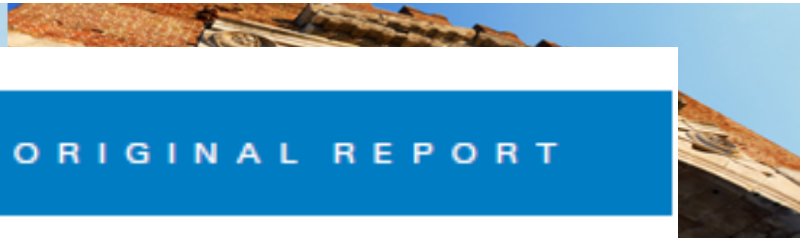
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



Association Between the 21-Gene Recurrence Score Assay and Risk of Locoregional Recurrence in Node-Negative, Estrogen Receptor–Positive Breast Cancer: Results From NSABP B-14 and NSABP B-20

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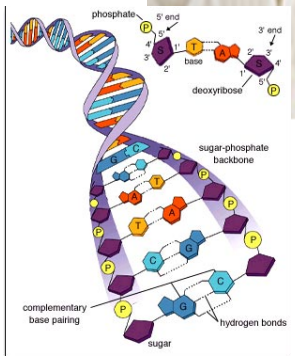
Conclusion

This information has **biologic consequences and potential clinical implications relative to locoregional therapy** decisions for patients with node-negative and ER + pts and could become important in identifying subgroups with one to three or four positive nodes at low versus high risk for LRR who may or may not need chest wall and/or regional radiotherapy.



GENETICA E CANCRO DELLA MAMMELLA

RIFLESSIONI CONCLUSIVE....

In about **5%** of all the breast cancer cases, the disease is part of a **hereditary cancer** syndrome,

caused by mutations **in high penetrance susceptibility genes.**

XXV CONGRESSO NAZIONALE

AIRO 2015

PALACONGRESSI - Rimini, 7-10 novembre

E' necessario individuare le pazienti in cui eseguire lo studio del patrimonio genetico

- Breast cancer diagnosed before age 50 years
- Cancer in both breasts in the same woman
- Both breast and ovarian cancers in either the same woman or the same family
- Multiple breast cancers
- Two or more primary types of *BRCA1*- or *BRCA2*-related cancers in a single family member
- Cases of male breast cancer
- Ashkenazi Jewish ethnicity

Enhanced screening

Mammografia annuale+/-US
MRI→ >sensibile, <specifica

Prophylactic surgery

- Mastectomia profilatticay →riduce rischio di ca mammario

- Ovariectomia →riduce il rischio di
  cancro ovarico,
  cancro mammella,
  mortalità,
  mortalità mammaria,
  mortalità ovarica

Chemoprevention→ non dati certi disponibili

Chirurgia Conservativa +RT
Mastectomia

Controllo locale →sec solo AA >IBLR→ secondi tumori

Rischio di neoplasia controlaterale → ⬆

Sopravvivenza→ non differenze in base
al trattamento locale
alla presenza di mutazione

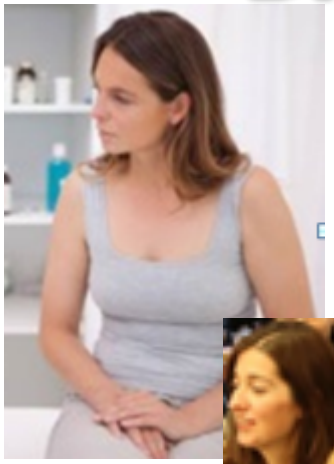
Tossicità RT su tessuti sani → non aumento
tox acuta/tardiva
cancerogenesi…

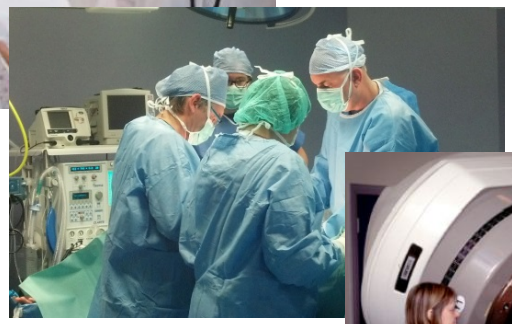
XXV CONGRESSO NAZIONALE

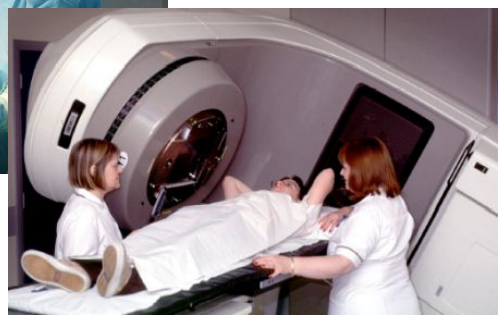
A

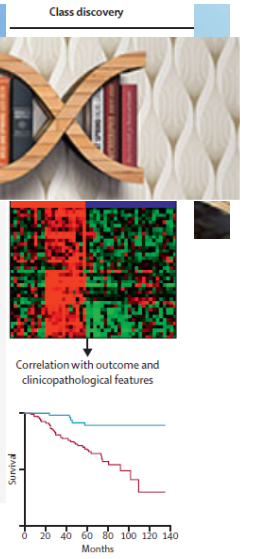
PALAC

BRCA







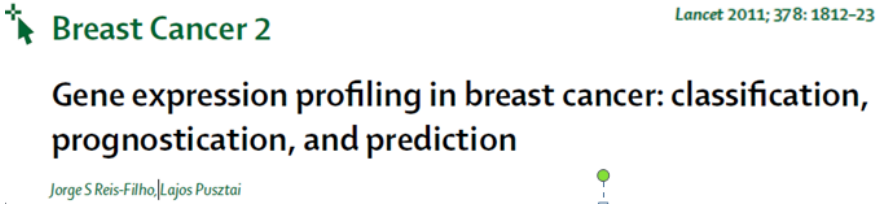


I risultati degli studi disponibili sul profilo genico hanno modificato la visione del carcinoma mammario….

Perou CM, Nature 2000

Sorlie T, 2001

diverse neoplasie che originano dalla stessa struttura anatomica e si sviluppano nello stesso organo ma…



con diverse caratteristiche biologiche, prognostiche e capacità di risposta al trattamento

Invited review

Lessons learned from the intrinsic subtypes of breast cancer in the quest for precision therapy

J. H. Norum[1,3], K. Andersen[2] and T. Sørlie[1,3]

2014

L'analisi del profilo genico ci ha fornito la possibilità di una classificazione immuno-istochimica (espressione fenotipica).....

Table 1 Characteristics, surrogate immunohistochemical definition and treatment recommendations for the intrinsic molecular subtypes of breast cancer

Intrinsic subtype	Characteristics	Immunohistochemical definition	Recommended treatment
Luminal A	ER+, highly express luminal epithelial genes, *PIK3CA* mutations, diploid, low grade, cyclin D1 overexpression, whole chromosome arm aberrations	ER+ and/or PR+ HER2− Ki-67 low	Hormone therapy
Luminal B	ER+ (low), proliferative, high grade, whole chromosome arm aberrations and complex rearrangements, *TP53* and *PIK3CA* mutations, alterations in retinoblastoma and MAPK pathways, some are HER2+	ER+ and/or PR+ HER2− (or HER2+) Ki-67 high	Hormone therapy, chemotherapy, anti-HER2 if HER2+
HER2-enriched	ER−, most tumours show *HER2* amplification, overexpression of genes on 17q22, highly proliferative, *TP53* mutations, focal high-level amplifications	HER2+ (amplified or overexpressed) ER−	Anti-HER2, chemotherapy
Basal-like	ER−, HER2−, highly express basal keratins, express EGFR, highly proliferative, aneuploid, high grade, *TP53* mutations, complex genomic rearrangements, WNT pathway activation increased	ER−, PR−, HER2− (triple negative)	Chemotherapy
Normal-like	Express basal and myoepithelial genes, adipose tissue-specific genes	Not relevant	Not relevant

ER, oestrogen receptor; PIK3CA, phosphatidyl inositol-4,5-bisphosphate 3-kinase catalytic subunit α; PR, progesterone receptor; HER, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; EGFR, epidermal growth factor receptor.

con implicazioni sul rischio di ricaduta sistemica e sulla strategia medica sistemica

Ma anche informazioni sul possibile rischio di ricaduta loco regionale….

Luminal A →low risk of local or regional recurrence.
Voduc DK, 2010

Luminal A→ Locoregional recurrence rate 1%
HER2- henriched → Locoregional recurrence rate 5%
Millar JCO 2009

HER2-enriched and TNP tumors were associated with an increased risk of local recurrence on multivariable analysis
Nguyen JCO 2008

XXV CONGRESSO NAZIONALE

AIRO 2015

ovembre

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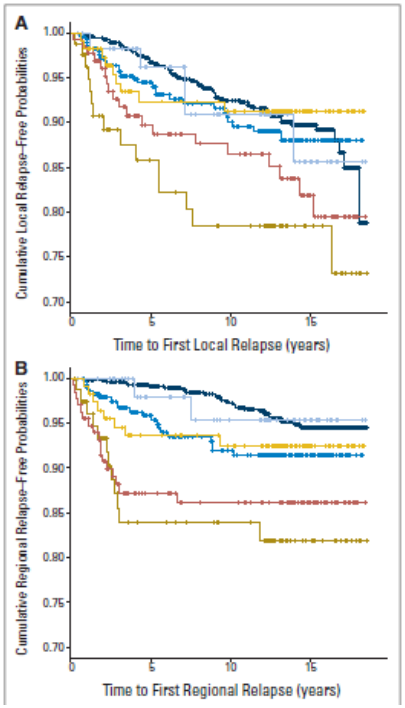
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Breast Cancer Subtypes and the Risk of Local and Regional Relapse

K. David Voduc, Maggie C.U. Cheang, Scott Tyldesley, Karen Gelmon, Torsten O. Nielsen, and Haoyn Kennecke

Questo suggerisce modulazioni trattamento loco regionale in termini di…



volume e dose del boost

…non solo lo stato dei margini

estensione loco-regionale della RT

…..non guidata esclusivamente dal TNM

Breast Cancer 2

Gene expression profiling in breast cancer: classification, prognostication, and prediction

Lancet 2011; 378: 1812–23

Jorge S Reis-Filho, Lajos Pusztai

Prognostic signatures

Development of microarray-based prognostic

La possibilità di studiare il profilo genico del tumore della singola paziente particolarmente in neoplasie a prognosi favorevole….

Table 1. Characteristics of gene expression profiles intended for use in patients with early breast cancer (EBC)

	21-gene RS (Oncotype Dx®)	Amsterdam 70-gene signature (MammaPrint®)	PAM50 (Prosigna™)	Rotterdam 76-gene signature	Genomic grade index	Breast cancer index	Endopredict®
Relevant EBC Population	ER+ HER2– Node–	Node– Tumor size ≤5 cm	ER+	Node–	ER+	ER+ Node–	ER+ HER2–
Tissue Required for Assay	FFPE	FFPE or frozen	FFPE	FFPE	FFPE or frozen	FFPE	FFPE
Assay Technique	qRT-PCR	Microarray	qRT-PCR	Microarray	Microarray	qRT-PCR	qRT-PCR
Demonstrated Analytic Validity	✓	✓	✓				✓
Demonstrated Clinical Validity	✓	✓	✓	✓	✓	✓	✓
Demonstrated Clinical Utility	✓		✓			✓	✓
Level of Evidence	IB	III	IB	III	III	IB	IB
Ongoing Studies	TAILORx, RxPONDER	MINDACT					

Levels of evidence are measured on a scale of I (strongest) to IV (weakest) [21]
FFPE formalin-fixed paraffin-embedded, *qRT-PCR* quantitative reverse-transcriptase polymerase chain reaction, *TAILORx* Trial Assigning Individualized Options for Treatment, *RxPONDER* Rx for Positive Node, Endocrine Responsive Breast Cancer, *MINDACT* Microarray in Node Negative and 1–3 Positive Lymph Node Disease May Avoid Chemotherapy

VOLUME 24 · NUMBER 23 · AUGUST 10 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor–Positive Breast Cancer

Soonmyung Paik, Gong Tang, Steven Shak, Chungyeul Kim, Joffre Baker, Wanseop Kim, Maureen Cronin, Frederick L. Baehner, Drew Watson, John Bryant, Joseph P. Costantino, Charles E. Geyer Jr, D. Lawrence Wickerham, and Norman Wolmark

Ci fornisce indicazioni per modulare la terapia medica sistemica, sulla base del rischio di ricaduta e della possibile risposta ai trattamenti

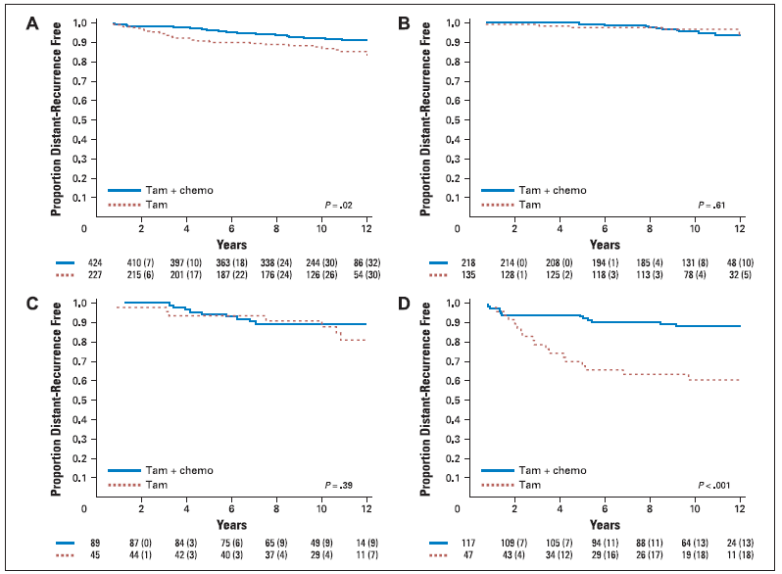


Fig 2. Kaplan-Meier plots for distant recurrence comparing treatment with tamoxifen (Tam) alone versus treatment with tamoxifen plus chemotherapy (Tam + chemo). (A) All patients; (B) low risk (recurrence score [RS] < 18); (C) intermediate risk (RS 18-30); (D) high risk (RS ≥ 31). The number of patients at risk and the number of distant recurrences (in parentheses) are provided below each part of the figure.

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AIRO

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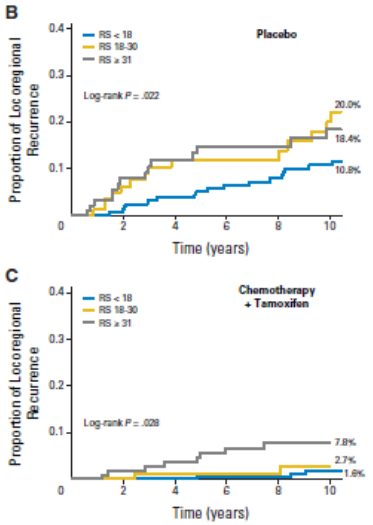
ma i test ci possono fornire dati sulla correlazione tra Risk Score e ricaduta loco-regionale



e pertanto

indicazioni alla estensione del trattamento loco regionale

Non solo TNM

Non solo numero di N+

Molecular Biology and Genetics of Breast Cancer Development: A Clinical Perspective

Thomas A. Buchholz and David E. Wazer

Seminars in Radiation Oncology, Vol 12, No 4 (October), 2002: pp 285-295

Breast Cancer Is a Genetic Disease

Breast cancer results from a series of complex **genetic and epigenetic events** that result in a **malignant transformation** of a normal epithelial cell.

GENETICA E CANCRO DELLA MAMMELLA

Marina Guenzi

Genova