

Gruppi a rischio  
aumentato: familiarità,  
genetica, densità,  
abitudini di vita

CONVEGNO NAZIONALE  
GISMa 2010

BOLOGNA, 5-6 maggio 2010  
Relais Bellaria Hotel & Congressi



**Dai dati disponibili**

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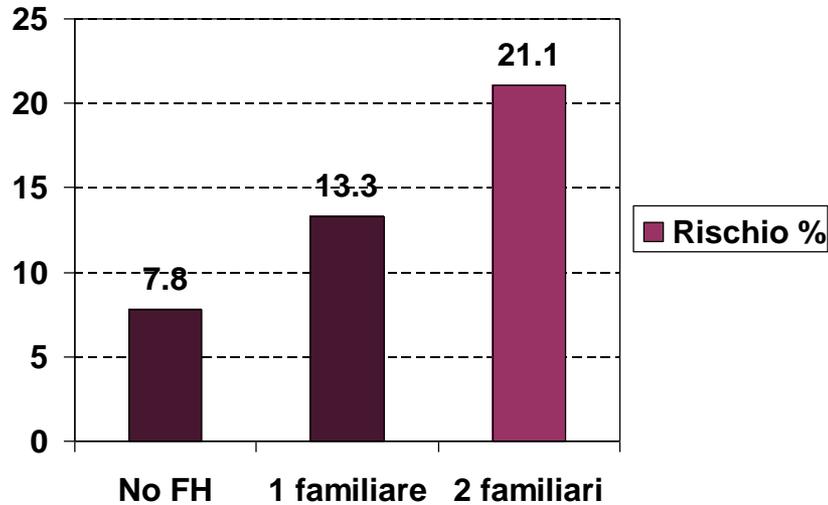
# Fattori di rischio per carcinoma mammario

Fattore	Valori di riferimento	RR
Età	Fasce d'età più avanzata vs più giovani	>10
Storia familiare	1 familiare 1° grado affetto vs nessuno	≥2
Area geografica	Paesi industrializzati vs paesi a bassa incidenza	5
Menarca precoce	<11 anni	3
Menopausa tardiva	>54 anni	2
Obesità	(>82.2 vs 58.7Kg)	2.85
Densità mammografica	Alta vs bassa densità	4.6
Alcool	4 <i>drink</i> vs nessuno	1.32
Trattamento con estro-progestinici		1.3

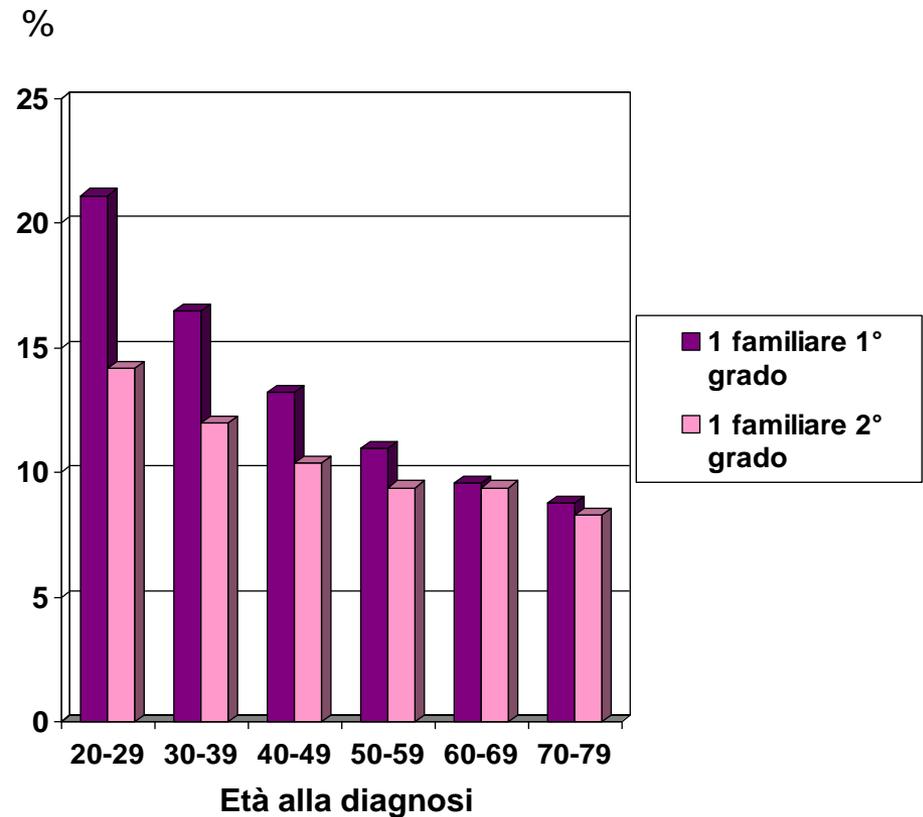
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# Rischio familiare



Collaborative Group on Hormonal Factors in Breast Cancer, 2001



Claus et al, Cancer, 1994

# Casi multipli di cancro nella famiglia

- *Cancro "ereditario"*

- Caratteristiche suggestive di predisposizione genetica
- Mutazione patogenetica in un singolo gene

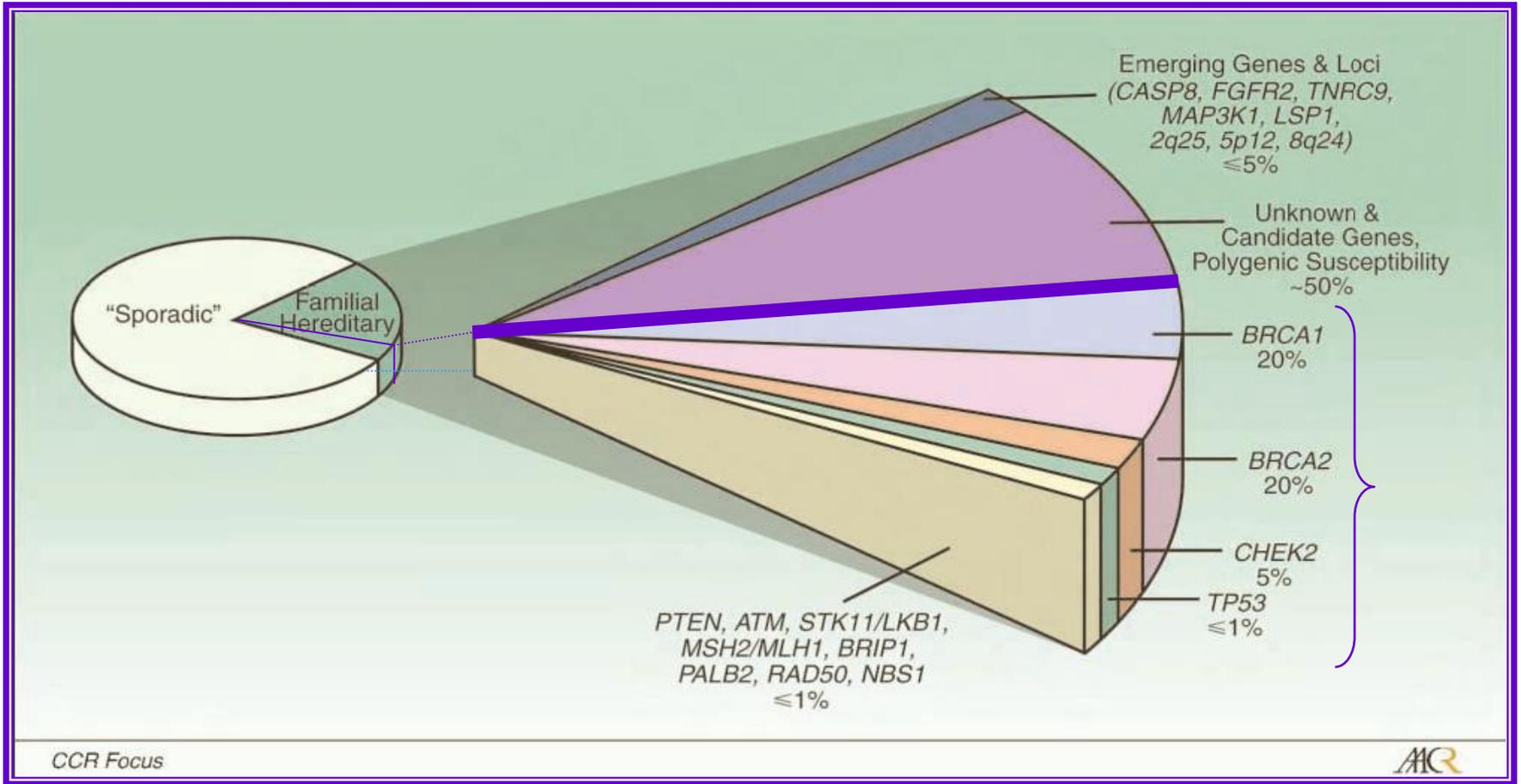
- *Cancro "familiare"*

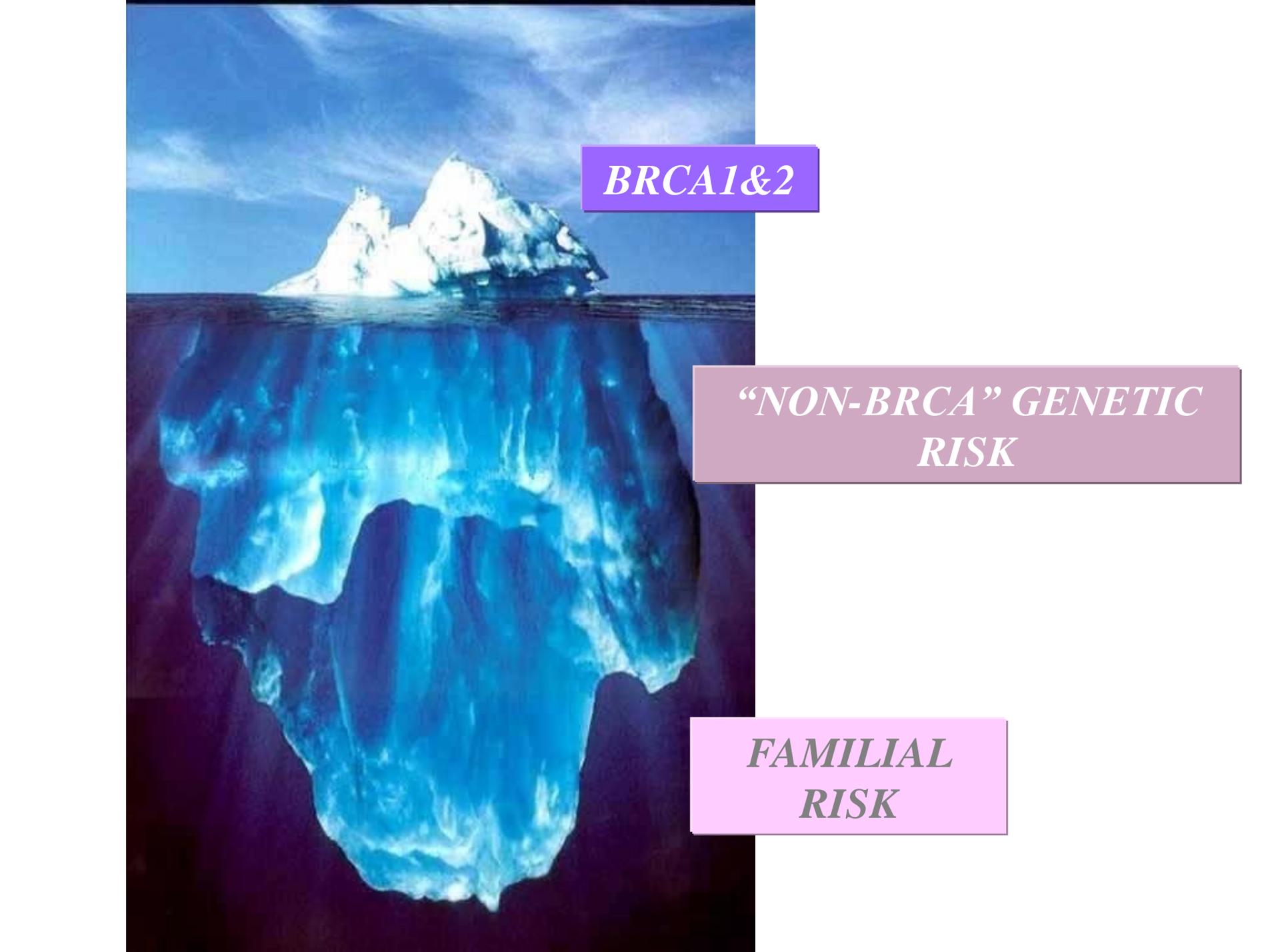
- Casi multipli dello stesso tipo di tumore senza caratteristiche suggestive di predisposizione ereditaria
- Varianti in geni a bassa penetranza
- Condivisione di fattori di rischio ambientali

- *Cancro "sporadico"*

- Frequenza compatibile con l'incidenza nella popolazione generale
- Tumori di diverso tipo
- Relazione di parentela tra gli affetti debole o assente

**Multifattoriali**

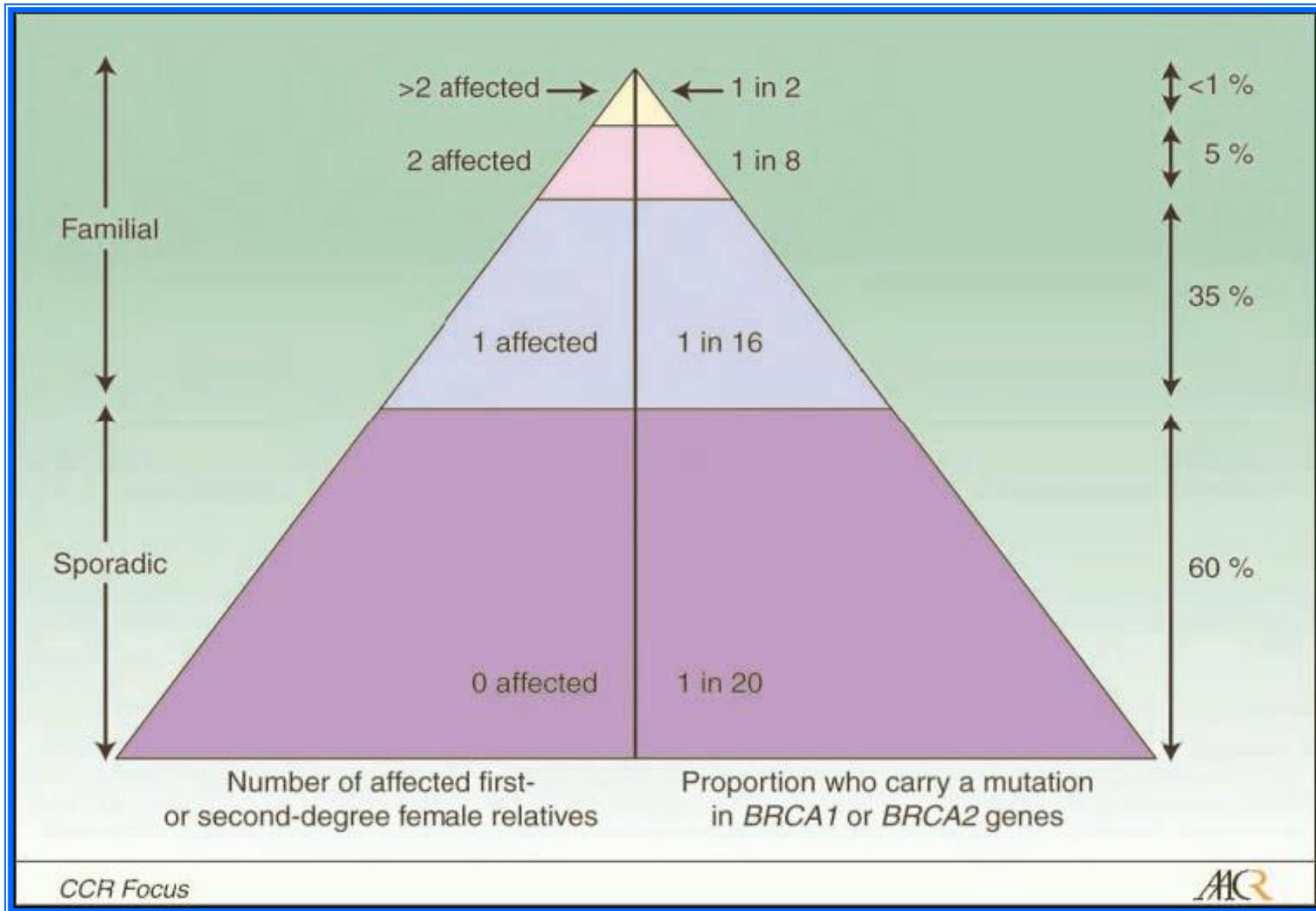


A photograph of an iceberg floating in the ocean. The tip of the iceberg is visible above the water line, while the much larger, submerged part is visible below. The sky is blue with some clouds. The water is dark blue. The iceberg is white and blue. The text is overlaid on the image in colored boxes.

*BRCA1&2*

*“NON-BRCA” GENETIC  
RISK*

*FAMILIAL  
RISK*

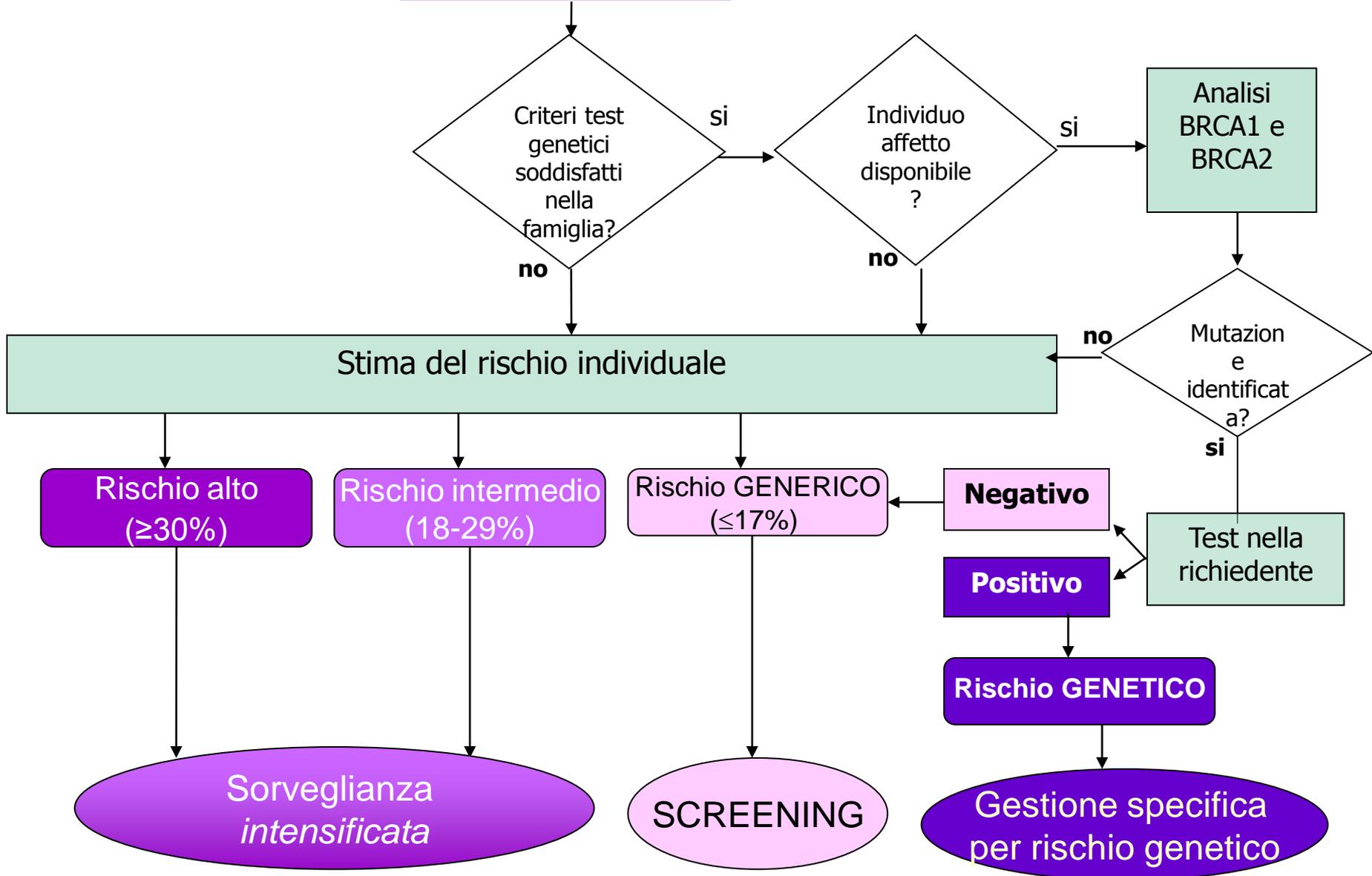


# Indicazioni alla consulenza genetica

Famiglia con:

- $\geq 3$  casi di carcinoma mammario
- 1 caso di carcinoma mammario  $< 36$  anni anche senza familiarità
- 1 caso di carcinoma mammario  $< 40$  anni +  $\geq 1$  caso di carcinoma mammario
- $\geq 1$  caso di carcinoma mammario +  $\geq 1$  carcinoma ovarico (anche nella stessa donna)
- 1 caso di carcinoma mammario maschile
- $\geq 2$  casi di carcinoma ovarico

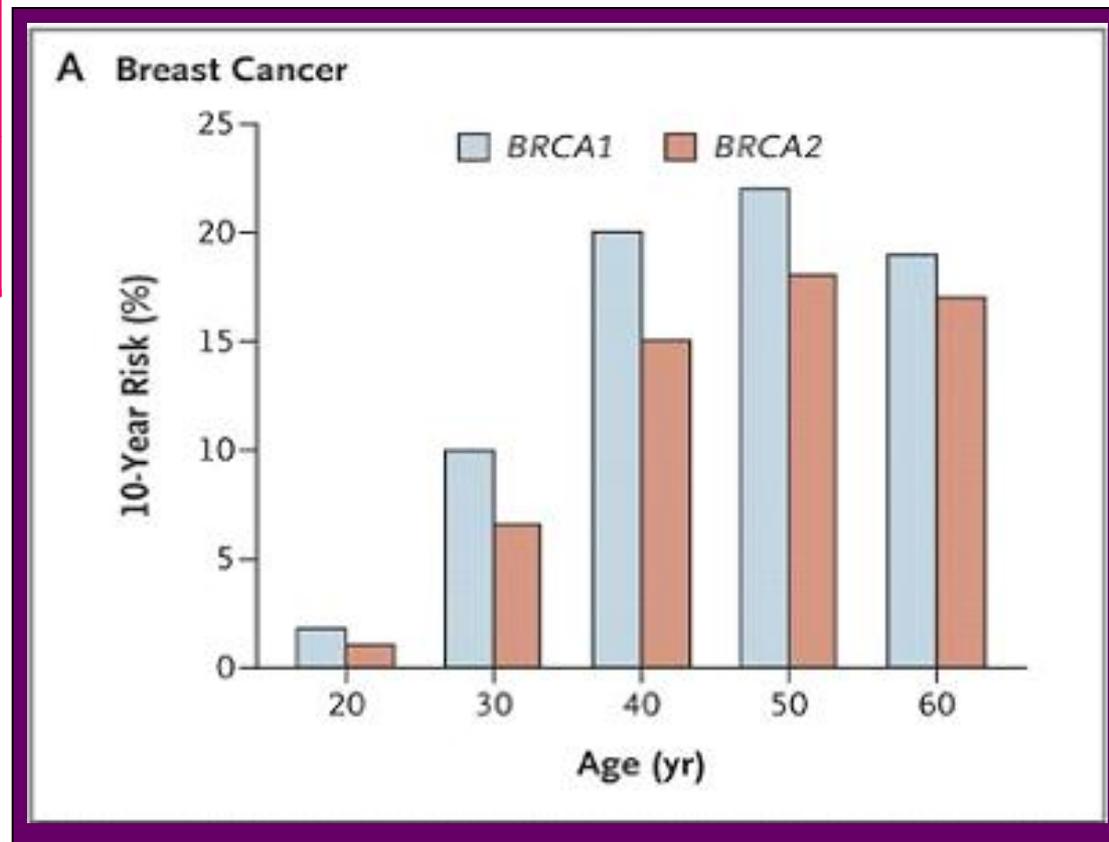
**Consulenza Genetica**



# Rischio associato a mutazioni di BRCA1/2

	BRCA1	BRCA2
Carcinoma mammario	57 %	49 %
Carcinoma ovarico	40 %	18 %

Chen and Parmigiani, JCO 2007



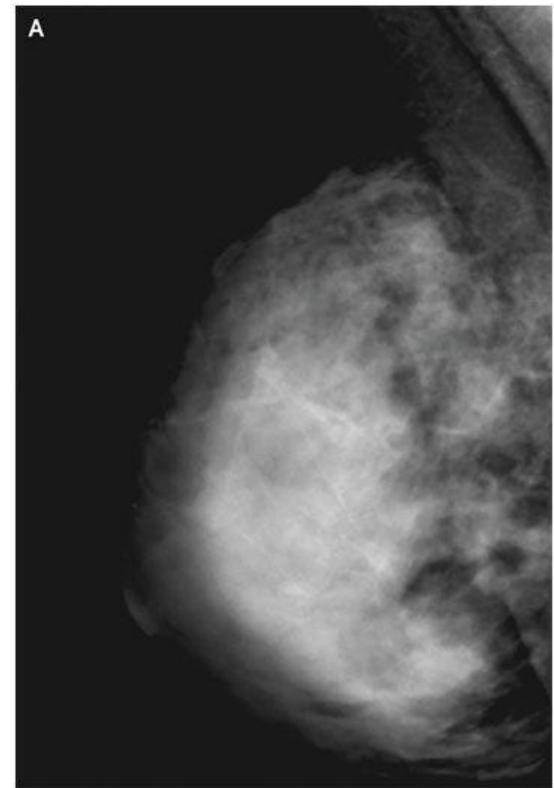
Robson M, Offit K. N Engl J Med 2007

# Sorveglianza per carcinoma mammario in portatrici di mutazioni BRCA1/BRCA2

<b>INDAGINE</b>	<b>Linee-guida "storiche" (precedenti al 2005)</b> ASCO, Cancer Genetics Consortium, French National ad Hoc Committee	<b>NICE</b> Clinical Guideline 41	<b>NCCN</b> Practice Guidelines in Oncology v.1.2009	<b>EUSOMA</b> Raccomandazioni novembre 2009 (draft)	<b>FONCAM</b> Linee guida 2008
Autopalpazione	Mensile dai 18-21 anni	Non raccomandata	Mensile dai 18 anni	Non raccomandata	Non raccomandata
Esame clinico mammario	Ogni 4-12 mesi dai 25-35 anni	Non raccomandato	Semestrale dai 25 anni	Non raccomandato	Semestrale dai 25 anni
Ecografia	Non raccomandata	Non raccomandata	Non raccomandata	Non raccomandata	Semestrale dai 25 ai 35 anni, Annuale dai 35 ai 50 anni (semestrale se seno denso)
Mammografia bilaterale	Annuale dai 25-35 anni	Annuale dai 40 ai 49 anni. Dai 50 secondo schema personalizzato	Annuale dai 25 anni (o personalizzata in base al caso più giovane verificatosi in famiglia)	Annuale dai 35 anni	Annuale dai 30 anni (a bassissima dose fino ai 35 anni, a bassa dose dai 35 ai 50, standard dai 50 in su)
Risonanza Magnetica	Nell'ambito di studi clinici controllati	Annuale dai 30 ai 49 anni - No dai 50 in poi	Annuale dai 25 anni (o personalizzata in base al caso più giovane verificatosi in famiglia)	Annuale dai 25 anni	Annuale dai 25 anni

Mammographically Occult  
Breast Cancer Detected in  
the Carrier of a BRCA2  
Mutation on Magnetic  
Resonance Imaging (MRI)

**Overall, 3391 pts, 913 BRCA+  
“MRI detects more than twice  
as many cancers as does Mx or  
US”**



# Risk of radiation-induced BC in BRCA carriers

## Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study

Steven A Narod, Jan Lubinski, Parviz Ghadirian, Henry T Lynch, Pal Moller, William D Foulkes, Barry Rosen, Charmaine Kim-Sing, Claudine Isaacs, Susan Domcheck, Ping Sun, for the Hereditary Breast Cancer Clinical Study Group\*

Lancet Oncol 2006; 7: 402-06

**No  
risk  
excess**

## Effect of Chest X-Rays on the Risk of Breast Cancer Among BRCA1/2 Mutation Carriers in the International BRCA1/2 Carrier Cohort Study: A Report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group

Nadine Andriani, Douglas F. Easton, Jerry Chang-Claude, Matti A. Rookus, Richard Brohet, Elisabeth Gardi, Antonia C. Antoniou, Teresa Wagner, Jacques Simard, Garath Evans, Susan Pook, Jean-Pierre Fricker, Catherine Nguyen, Laura Yan's Yan, Flora E. Van Leeuwen, and David E. Gelber

J Clin Oncol 24:3361-3366

**HR 1.54**

## Estimated Risk of Radiation-Induced Breast Cancer From Mammographic Screening for Young BRCA Mutation Carriers

Amy Berrington de Gonzalez, Christine D. Berg, Kala Visvanathan, Mark Robson  
J Natl Cancer Inst 2009;101:205-209

**Lifetime risk of radiation-induced BC mortality x 100000 women**  
**26 for screening at age 25-29**  
**20 for screening at age 30-34**  
**13 for screening at age 35-39**  
**Some net benefit only at age 35 or older**

# Sorveglianza per donne a rischio “intermedio”

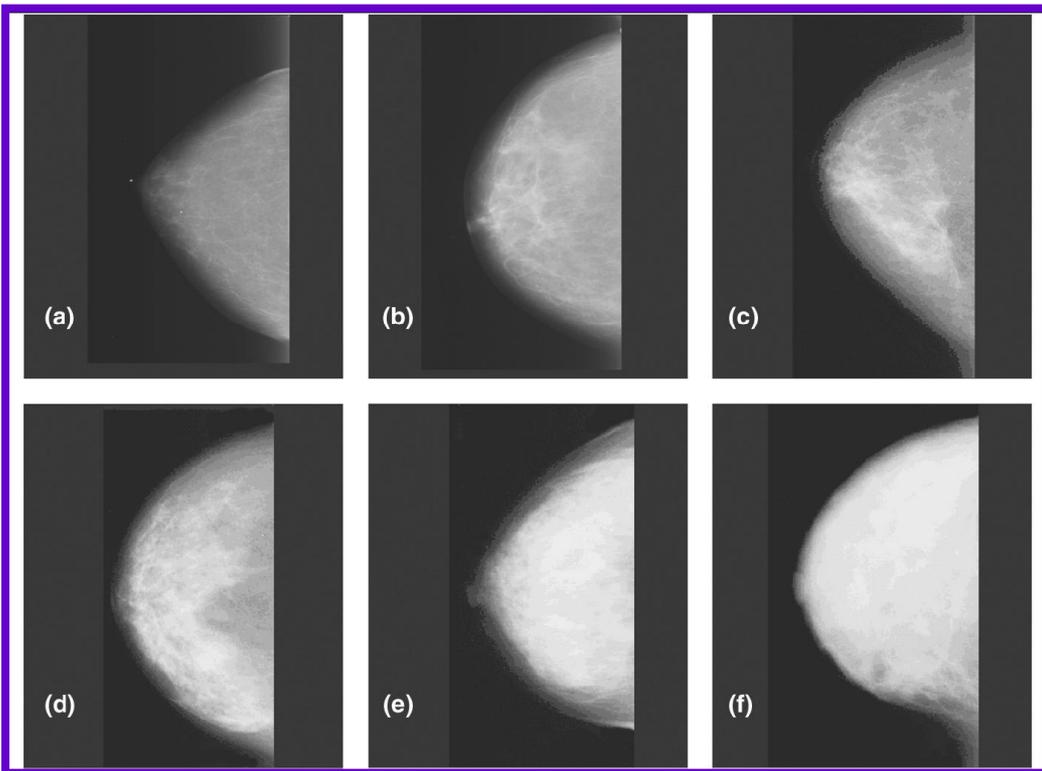
- *35-39 anni: visita + ecografia semestrale?*
- 40-44 anni: Mx annuale + eventuali altri esami a discrezione del centro di senologia sulla base del referto mammografico
- 45-49 anni: Mx annuale
- 50-74 anni: Screening

# Sorveglianza per donne a rischio “alto”

- 25-34 anni: visita + ecografia semestrale
- 35-59 anni: visita + ecografia + Mx annuale
- 60-69 anni: visita + Mx annuale
- 70-74 anni: Screening

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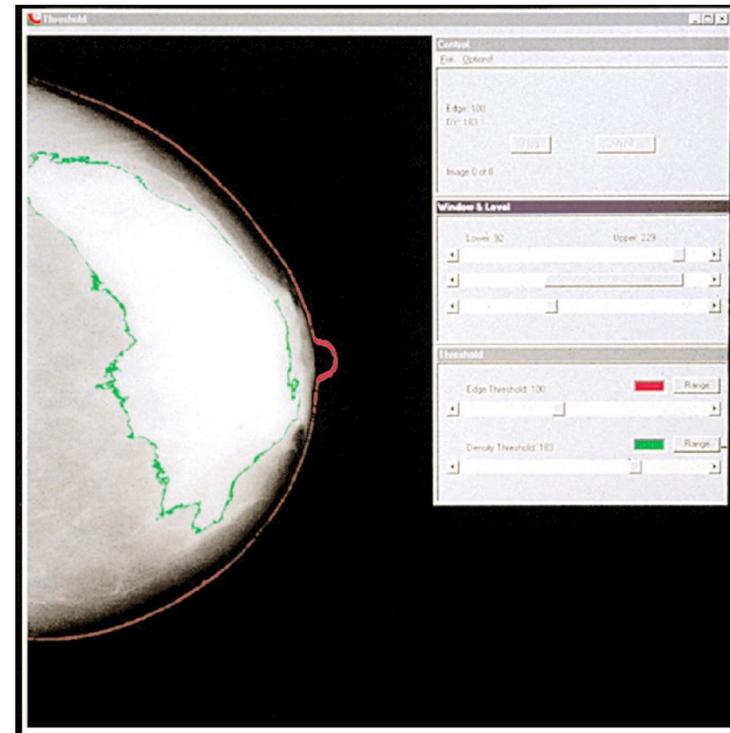


## Densità mammografica

Proporzione di area  
mammaria occupata da  
tessuto radiologicamente  
denso (stroma ed epitelio)

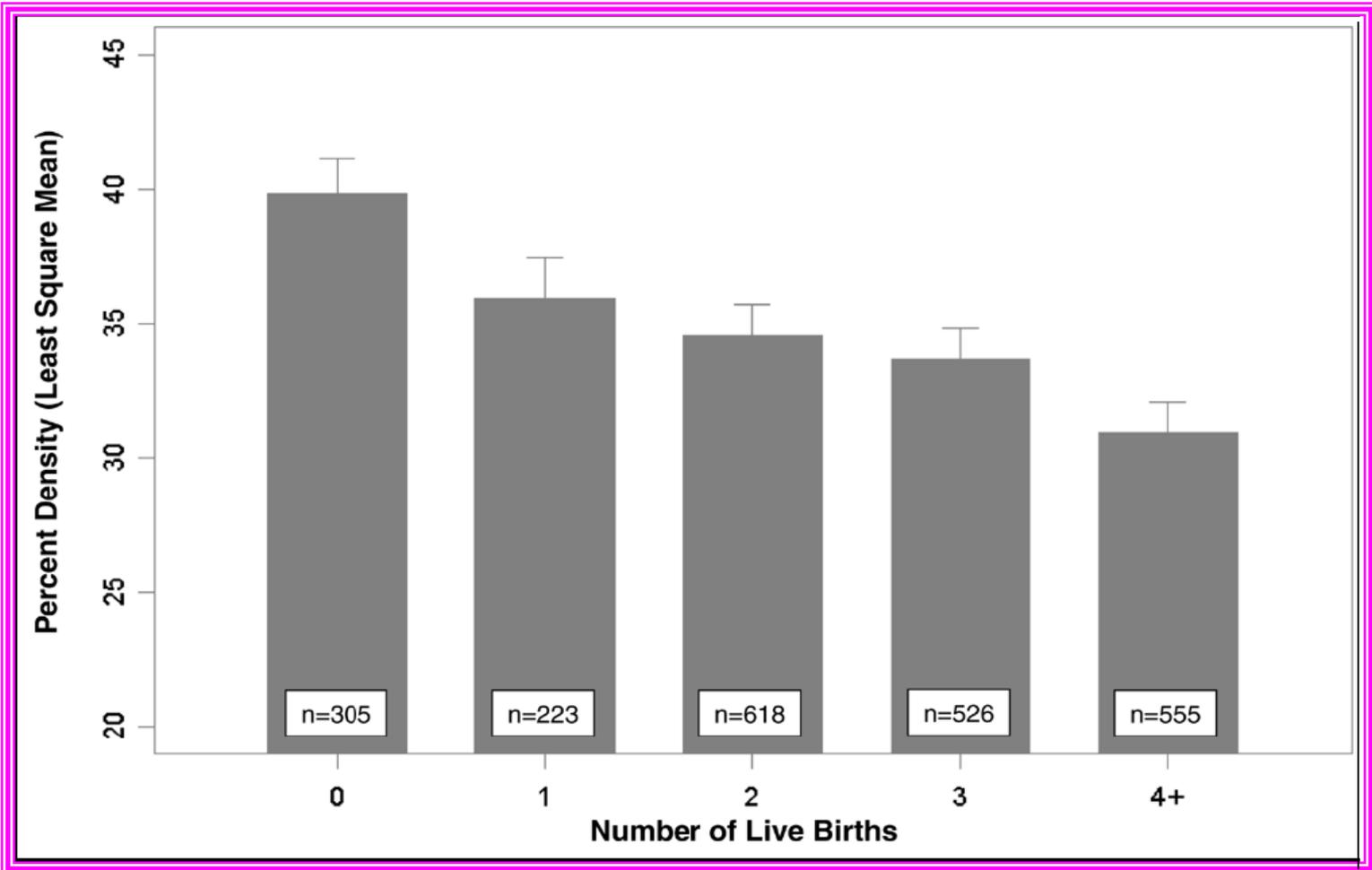
E' influenzata da:

✓ Età	}	20-30%
✓ Parità		
✓ BMI		
✓ Menopausa		
✓ Fattori ereditari		63%



# Fattori che influenzano la densità mammografica

## Parità

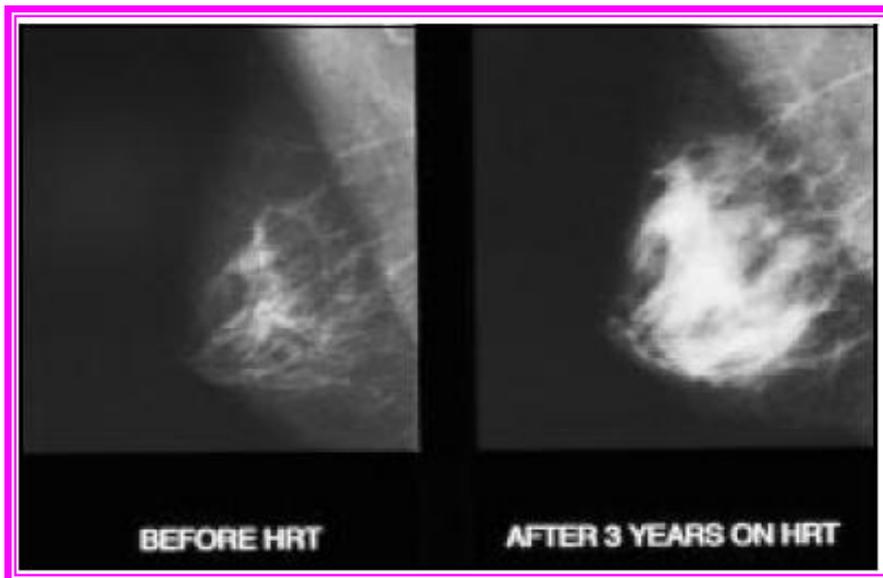


# Fattori che influenzano la densità mammografica

## Terapia ormonale

**Table 1**  
Summary of effects of hormonal interventions on quantitative measures of mammographic density from randomised trials.

Study <sup>a</sup>	Intervention	Subjects	Mean change in percent density <sup>b</sup>	Duration
Freedman 2001 [61]	Estrogen	36	+1.2% ( $p < 0.01$ )	2 years
	Raloxifene (60 mg)	45	-1.5%	
	Raloxifene (150 mg)	42	-1.7%	
	Placebo	45	-1.3%	
Greendale 2003 [62]	CEE <sup>c</sup>	99	+1.2% ( $p = 0.24$ )	1 years
	CEE + progesterone <sup>d</sup>	306	+3-5% ( $p = 0.002$ to $< 0.001$ )	
	Placebo	93	-0.1%	
McTiernan 2005 [63]	CEE + progesterone <sup>e</sup>	202	+4.9%	2 years
	Placebo	211	-0.8% ( $p < 0.001$ )	
Hofling 2007 [64]	Testosterone patch <sup>f</sup>	46	+5.4%	6 months
	Placebo patch	41	+7.4% NS	
Eilertsen 2008 [65]	Tibolone	47	0.8% ( $p < 0.01$ )	12 weeks
	Raloxifene	49	0.4 ( $p < 0.001$ )	
	Estrogen + NETA <sup>h</sup> – usual dose	49	2.3 (NS)	
	Estrogen + NETA <sup>h</sup> – low dose	48	2.6	
Vachon 2007 [69]	Letrozole	35	-0.3	1 year
	Placebo	33	-1.0 ( $p = 0.58$ )	
Brisson 2000 [71]	Tamoxifen	36	-9.4%	3.3 years
	Placebo	33	-3.6% ( $p = 0.01$ )	
Cuzick 2004 [70]	Tamoxifen	388	-13.7%	4.5 years
	Placebo	430	-7.3% ( $p < 0.001$ )	



### Relationship of HRT to breast cancer development

<b>Time on HRT</b>	<b>Breast cancers over the 20 years from age 50-70</b>	<b>Extra breast cancers in HRT users</b>	<b>Individual risk of women over 20 years</b>
Never	45 per 1000	—	1 in 22
5 years use	47 per 1000	2 per 1000	1 in 21
10 years use	51 per 1000	6 per 1000	1 in 19
15 years use	57 per 1000	12 per 1000	1 in 17-18

0

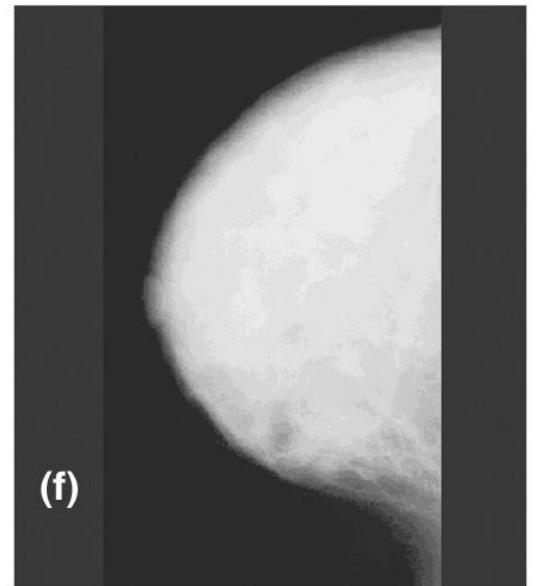
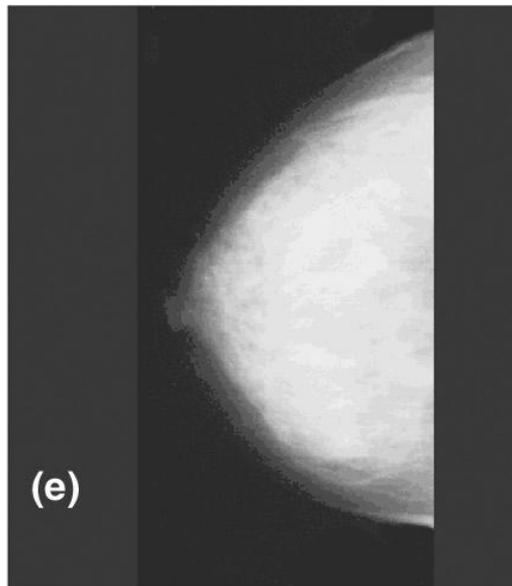
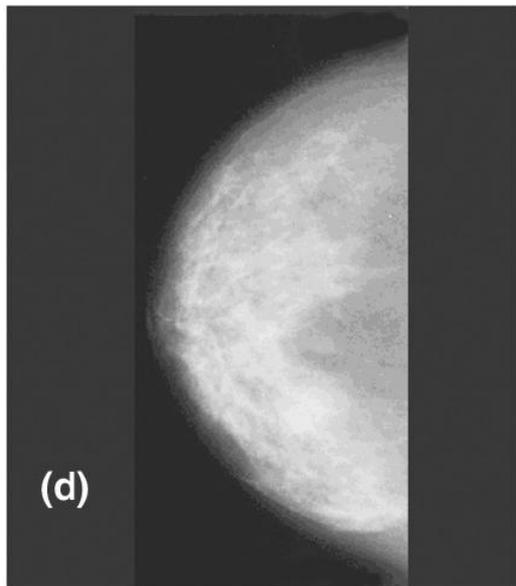
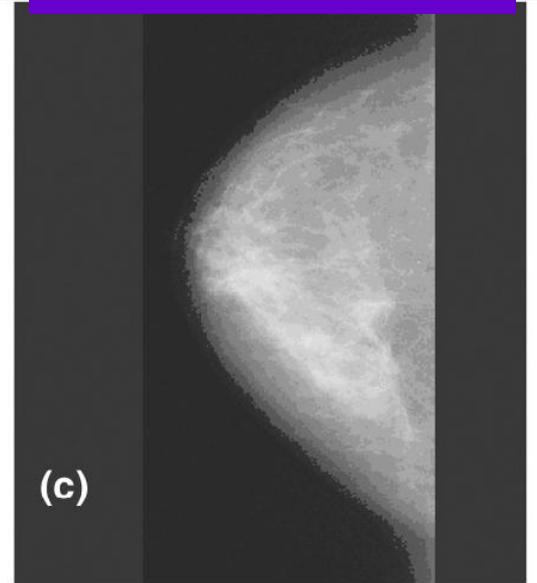
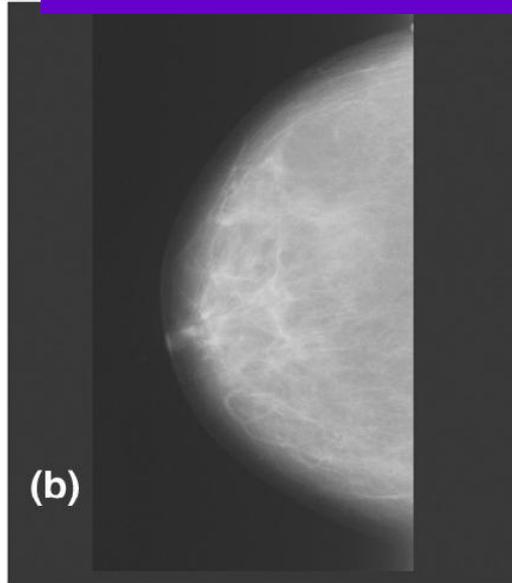
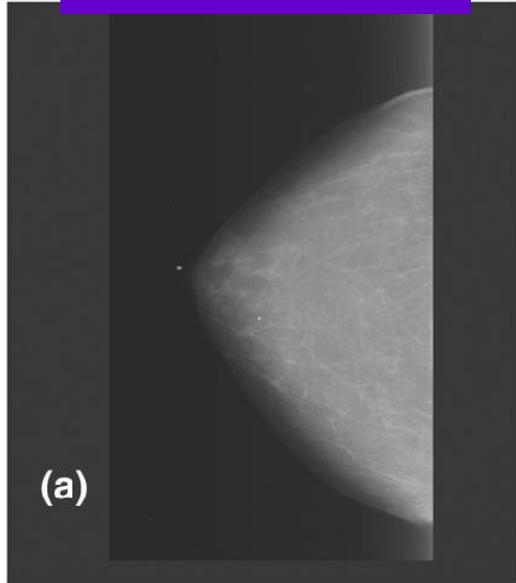
RR: 1

<10%

RR: 1.2

10-24%

RR:



26-50% RR: 2.1

51-75% RR: 2.9

>75% RR: 4.6

**Combined relative risks for breast cancer associated with different classifications of mammographic density, study designs, and study populations from meta-analysis [3]**

Classification	General population				Symptomatic population	
	Incidence studies		Prevalence studies		Cases/ Non-cases <sup>a</sup>	RR (95% CI)
	Cases/ Non-cases <sup>a</sup>	RR (95% CI)	Cases/ Non-cases <sup>a</sup>	RR (95% CI)		
<b>Wolfe parenchymal pattern</b>	2,664 /23,469 <sup>b</sup>		2,169 /32,184 <sup>b</sup>		1,857/25,394 <sup>b</sup>	
N1	181/3,613	1.0	557/15,731	1.0	428/3,318	1.0
P1	525/6,682	1.8 (1.4, 2.2)	519/9,684	1.3 (1.0, 1.5)	315/5,031	1.0 (0.77, 1.3)
P2	1,162/10,433	3.1 (2.5, 3.7)	660/4,369	2.0 (1.3, 3.0)	526/5,128	1.5 (0.91, 2.4)
DY	246/2,309	4.0 (2.5, 6.3)	294/2,216	2.4 (2.0, 3.0)	400/4,976	1.7 (1.0, 2.8)
<b>Percentage mammographic density</b>	4,508/8,342 <sup>b</sup>		2,219/4,063 <sup>b</sup>		160/160 <sup>b</sup>	
<5%	1,194/1,744 <sup>c</sup>	1.0	643/1,182 <sup>c</sup>	1.0	35/84 <sup>c</sup>	1.0
5%-24%		1.8 (1.5, 2.2)		1.4 (1.1, 1.8)		
25%-49%	1,049/1,045	2.1 (1.7, 2.6)	589/835	2.2 (1.8, 2.8)	66/35	5.5 (2.8-11)
50%-74%	1,211/999	2.9 (2.5, 3.4)	438/665	2.9 (2.3, 3.8)	34/23	4.8 (2.2-11)
75%+		4.6 (3.6, 5.9)	190/282	3.7 (2.7, 5.0)	25/18	4.3 (1.8-10)
<b>BI-RADS</b>	1,992/104,663 <sup>b</sup>	Vacek and Geller [30]	Ziv <i>et al.</i> [57]	397/1,589 <sup>b</sup>		
Fatty	62/7,550	1.0 (Ref)	0.3 (0.2, 0.4)	20/134	1.0	
Scattered density	950/52,379	2.2 (1.6, 3.0)	1.0 (Ref)	216/957	1.6 (0.9, 2.8)	
Heterogeneous density	783/36,564	3.0 (2.2, 4.1)	1.3 (1.1, 1.5)	117/407	2.3 (1.3, 4.3)	
Extremely dense	197/8,170	4.0 (2.8, 5.7)	20.1 (1.6, 2.8)	44/91	4.5 (1.9, 10.6)	

## Mammographic Density and the Risk and Detection of Breast Cancer

Norman F. Boyd, M.D., D.Sc., Helen Guo, M.Sc., Lisa J. Martin, Ph.D.,  
Limei Sun, M.Sc., Jennifer Stone, M.Sc., Eve Fishell, M.D., F.R.C.P.C.,  
Roberta A. Jong, M.D., F.R.C.P.C., Greg Hislop, M.D., F.R.C.P.C.,  
Anna Chiarelli, Ph.D., Salomon Minkin, Ph.D., and Martin J. Yaffe, Ph.D.

**Table 5. Mammographic Density and Attributable Risks of Breast Cancer.**

Age	Method of Cancer Detection	Mammographic Density $\geq 50\%$				
		No. of Case Patients	No. of Control Subjects	Prevalence*	Relative Risk (95% CI) <sup>†</sup>	Attributable Risk <sup>‡</sup>
				96		96
All ages	All	1112	1112	24.6	2.8 (2.1–3.8)	16.0
	Screening	717	717	21.5	2.3 (1.6–3.3)	12.1
	Detection <12 mo after negative screening	124	124	46.0	7.2 (2.7–19.1)	39.6
	Detection $\geq 12$ mo after negative screening	262	262	22.9	3.6 (1.9–6.9)	16.5
$\leq 56$ yr	All	561	561	37.2	3.3 (2.2–5.1)	26.1
	Screening	351	351	32.5	2.8 (1.6–4.7)	20.8
	Detection <12 mo after negative screening	84	85	58.3	7.0 (2.1–23.5)	50.0
	Detection $\geq 12$ mo after negative screening	119	118	36.1	4.7 (1.7–13.2)	28.4
>56 yr	All	551	551	11.8	2.5 (1.6–4.1)	7.2
	Screening	366	366	10.9	2.2 (1.2–4.0)	6.0
	Detection <12 mo after negative screening	40	39	20.0	8.2 (0.8–81.9)	17.6
	Detection $\geq 12$ mo after negative screening	143	144	11.9	2.9 (1.1–7.7)	7.8

# Storia familiare, densità mammografica e rischio

**Table 4.** Relative risks (RRs) comparing extreme categories of percent breast density from logistic regression in case patients and control subjects according to family history category of breast cancer\*

Family history definition	Measurement method†	No. of case patients/ No. of control subjects	RR‡	95% confidence interval
At least one first-degree relative§	Radiologist	60/45	11.14	1.54–80.39
	Computer		4.67	0.63–34.52
Two or more first- or second-degree relatives	Radiologist	40/27	2.57	0.23–28.22
	Computer		2.42	0.16–37.65
At least one first- or second-degree relative§	Radiologist	125/115	5.43	1.85–15.88
	Computer		6.83	2.02–23.14

Boyd et al, J Natl Cancer Inst, 1999

**Table 4.** Risk of breast cancer according to percent mammographic density and family history

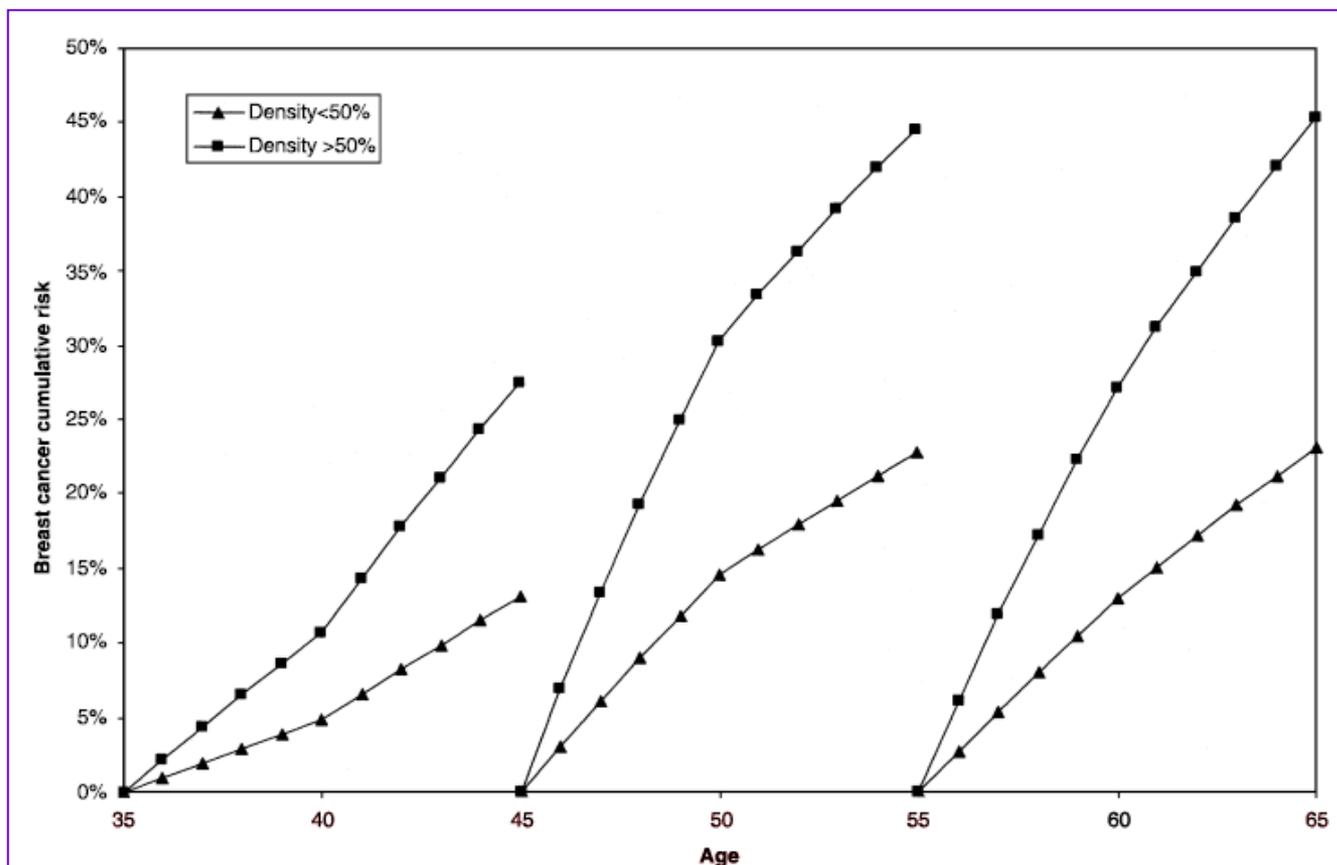
Number of affected first degree relatives		Percent mammographic density (%)				P*
		<10	10 to <25	25 to <50	≥50	
0	Cases	116	249	366	195	<0.0001
	Controls	230	294	311	143	
	OR† (95% CI)	Ref	1.77 (1.33- 2.35)	2.65 (1.98-3.53)	3.30 (2.33-4.67)	
≥1	Cases	38	61	95	44	0.06
	Controls	36	54	64	26	
	OR (95% CI)	2.12 (1.27-3.56)	2.37 (1.53-3.64)	3.39 (2.27-5.06)	4.08 (2.32-7.14)	

Martin et al, Cancer Epidemiol Biomarkers Prev, 2010

# Mammographic Density and Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers

Gillian Mitchell,<sup>1</sup> Antonis C. Antoniou,<sup>3</sup> Ruth Warren,<sup>4</sup> Susan Peock,<sup>3</sup> Judith Brown,<sup>3</sup> Russell Davies,<sup>6</sup> Jenny Mattison,<sup>3</sup> Margaret Cook,<sup>3</sup> Iqbal Warsi,<sup>4</sup> D. Gareth Evans,<sup>7</sup> Diana Eccles,<sup>8</sup> Fiona Douglas,<sup>9</sup> Joan Paterson,<sup>5</sup> Shirley Hodgson,<sup>2</sup> Louise Izatt,<sup>2</sup> Trevor Cole,<sup>10</sup> Lucy Burgess,<sup>10</sup> EMBRACE collaborators, Ros Eeles,<sup>1</sup> and Douglas F. Easton<sup>3</sup>

Cancer Res 2006; 66(3): 1866-72



**Grazie per l'attenzione!**