

Comunidad de Madrid



AGERS
Asociación Española de
Gerencia de Riesgos y Seguros

MUTUALIDAD DE LA
ABOGACIA

Foro Riesgos Personales

Mitigación y medida del Riesgo en
Cáncer de Mama y de Ovario



Cáncer de mama y cáncer de ovario

Cristina Grávalos

Oficina Regional de Coordinación Oncológica

19 octubre 2016

Introducción

- El cáncer de mama supone un importante problema socio-sanitario
 - por su elevada incidencia y prevalencia
 - por las implicaciones que tiene para las mujeres y sus familias
 - por los recursos humanos y materiales que requiere
- El cáncer de ovario es menos frecuente y se asocia al riesgo de cáncer de mama en mujeres portadoras de mutaciones BRCA

Incidencia y mortalidad de cáncer de mama en España

Tendencia

INCIDENCIA	2012	2015	2030
< 65 años	15.675	16.097	17.098
≥ 65 años	9.590	10.190	13.483
Total	25.265	26.282	30.581
Incremento respecto a 2012	--	+1.067	+5.366

Tendencia

MORTALIDAD	2012	2015	2030
< 65 años	3.188	3.770	5.577
≥ 65 años	3.887	4.111	5.381
Total	6.075	6.381	7.908
Incremento respecto a 2012	--	+ 306	+1.833

Cáncer de mama en la Comunidad de Madrid

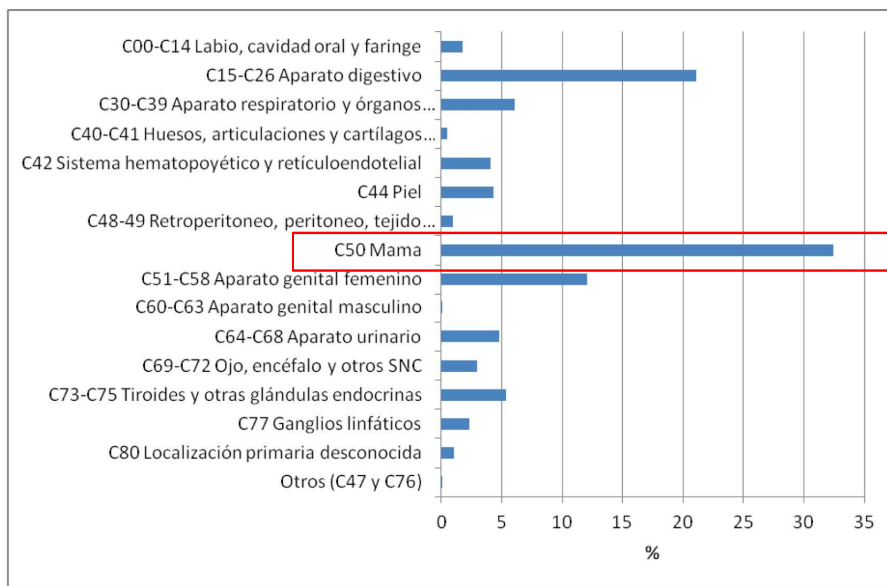
Registro de Tumores de Madrid RTMAD*

Incidencia

	2012	2013	2014	2015
Mujeres	3.313 (3?,?%)	3.577 (3?,5%)	3.911 (3?,?%)	3.871 (30,?%)
Hombres	64	39	35	?8
Total	3.383 (14,8%)	3.616 (14,7%)	3.946 (14,9%)	3.899 (13,6%)

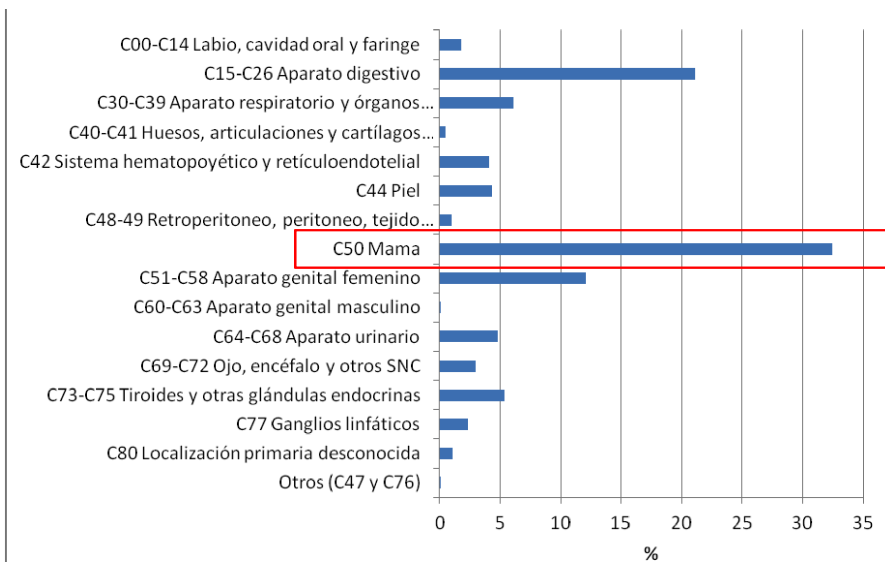
*RTMAD: Registro de hospitales públicos

Donación de AGERS al Centro de Documentación de Fundación MAPFRE

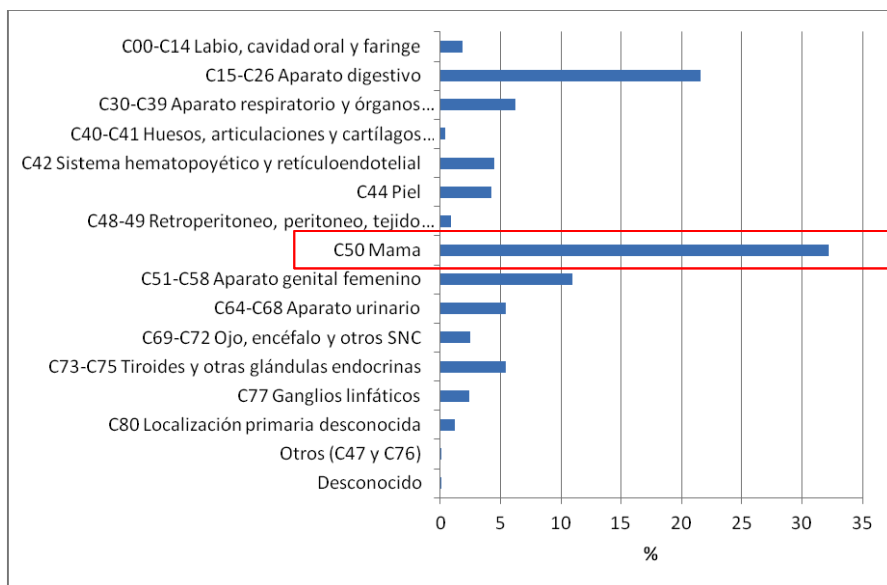


2011

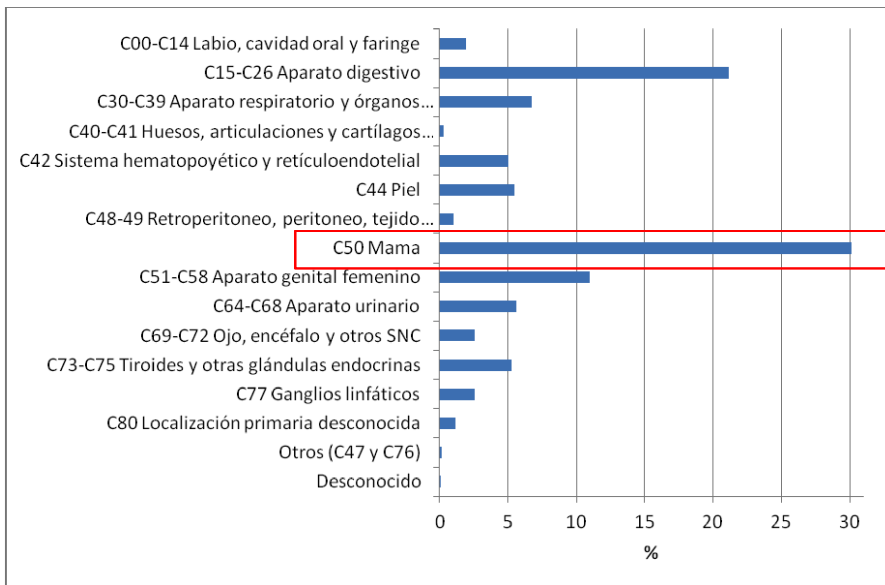
Incidencia en mujeres



2013

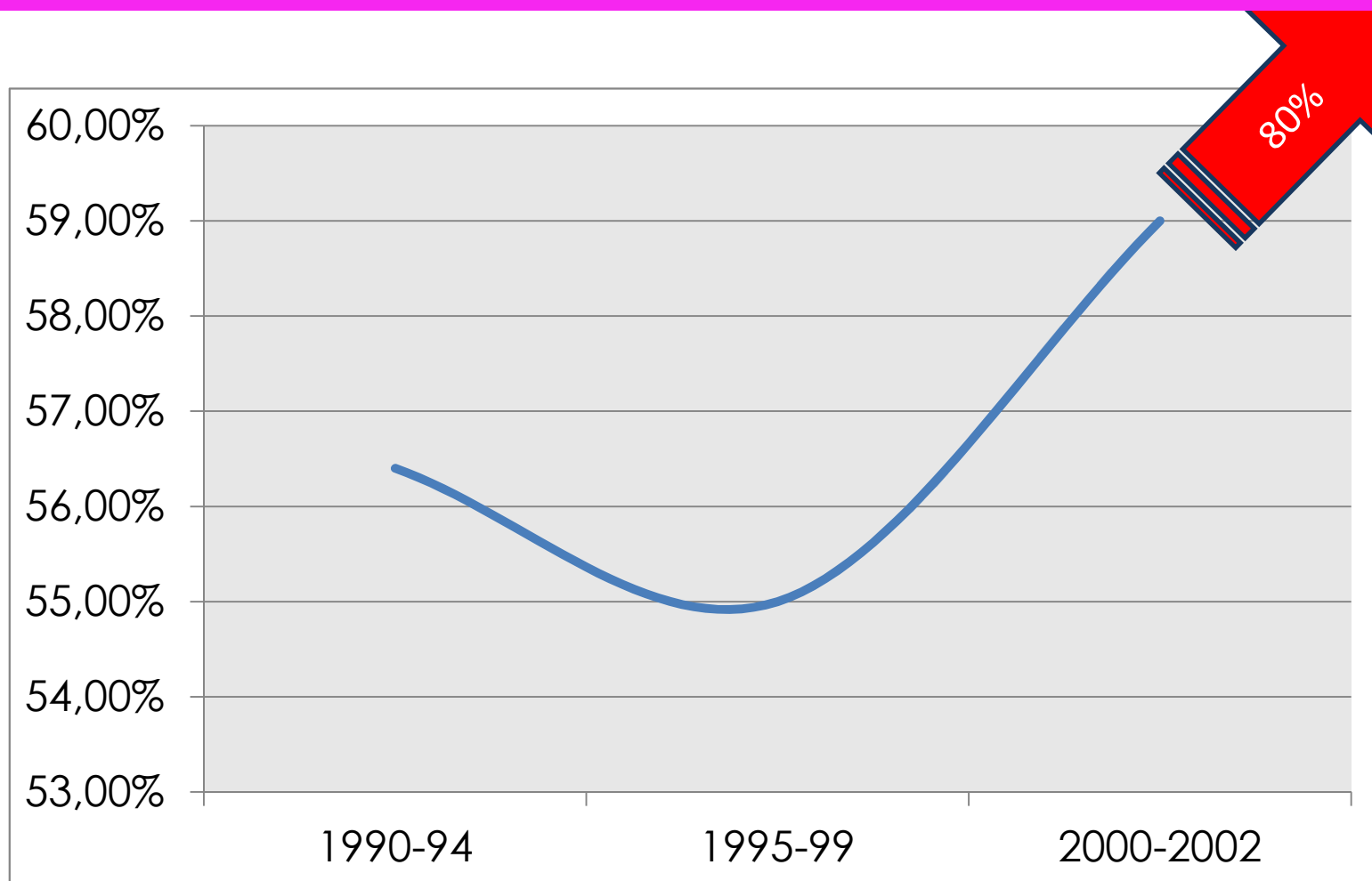


2014



2015

Evolución de la supervivencia del cáncer de mama



European Journal of Cancer (2015) 51, 2191–2205



ELSEVIER

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

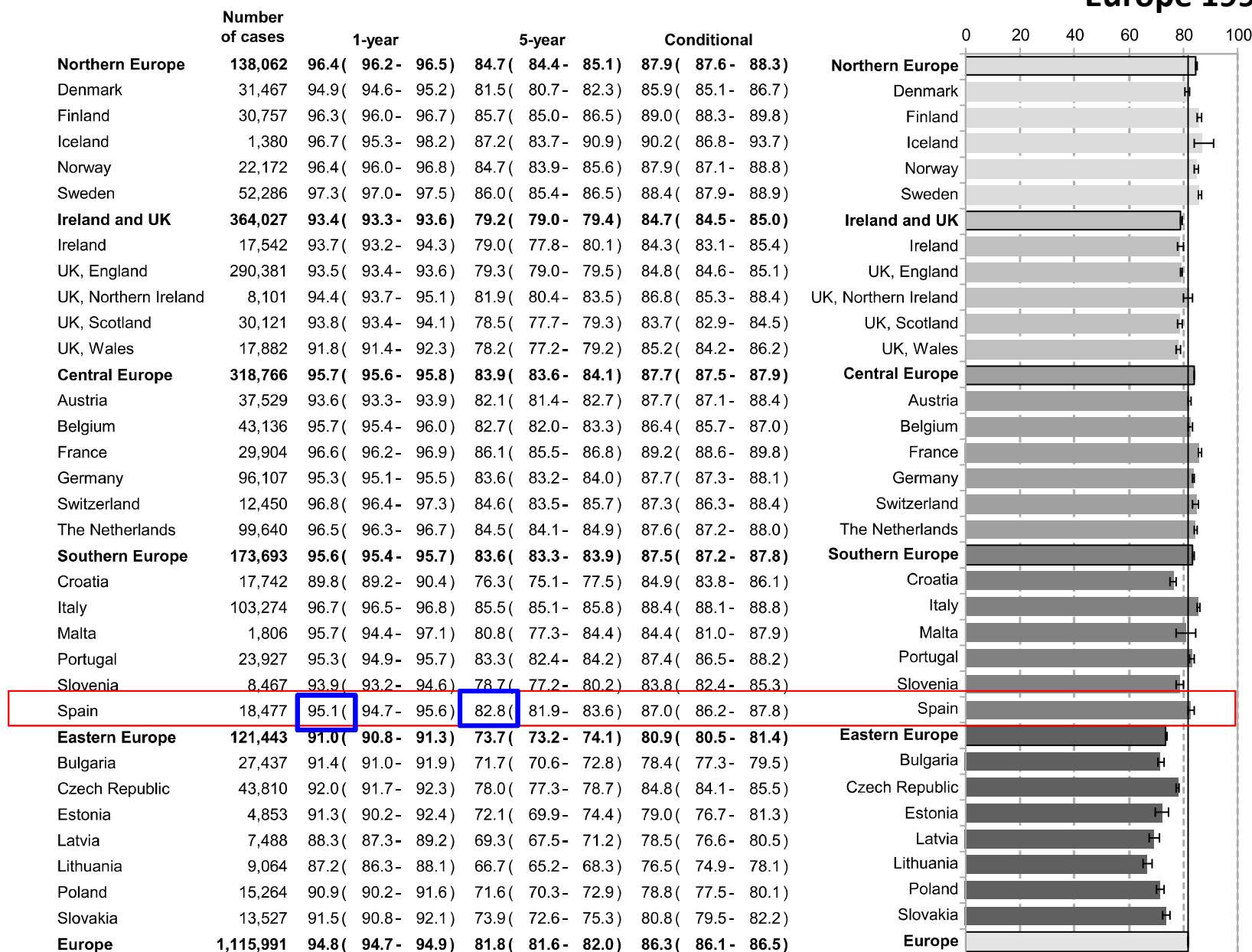
Survival of women with cancers of breast and genital organs in Europe 1999–2007: Results of the EURO CARE-5 study

Milena Sant^{a,*}, Maria Dolores Chirlaque Lopez^{b,c}, Roberto Agresti^d,
Maria José Sánchez Pérez^{e,c}, Bernd Holleczeck^f, Magdalena Bielska-Lasota^g,
Nadya Dimitrova^h, Kaire Innosⁱ, Alexander Katalinic^j, Hilde Langseth^k,
Nerea Larrañaga^{l,c}, Silvia Rossi^m, Sabine Siesling^{n,o}, Pamela Minicozzi^a,
The EURO CARE-5 Working Group¹

Age-standardised 1-year, 5-year relative survival, and 5-year relative survival conditional to surviving 1 year, with 95% confidence intervals in parentheses

Age-standardised 5-year relative survival (%)

Europe 1999-2007



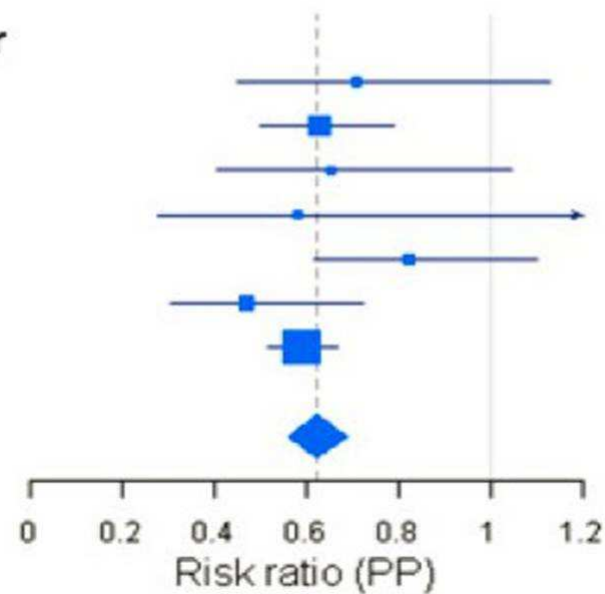
Principales factores de aumento de la supervivencia

- Diagnóstico precoz
 - Programas de cribado: Mamografía
 - Seguimiento específico en alto riesgo
- Clasificación de los subtipos de cáncer de mama
- Tratamiento neo/adyuvante
 - Quimioterapia
 - Hormonoterapia
 - Terapias dirigidas
 - Radioterapia

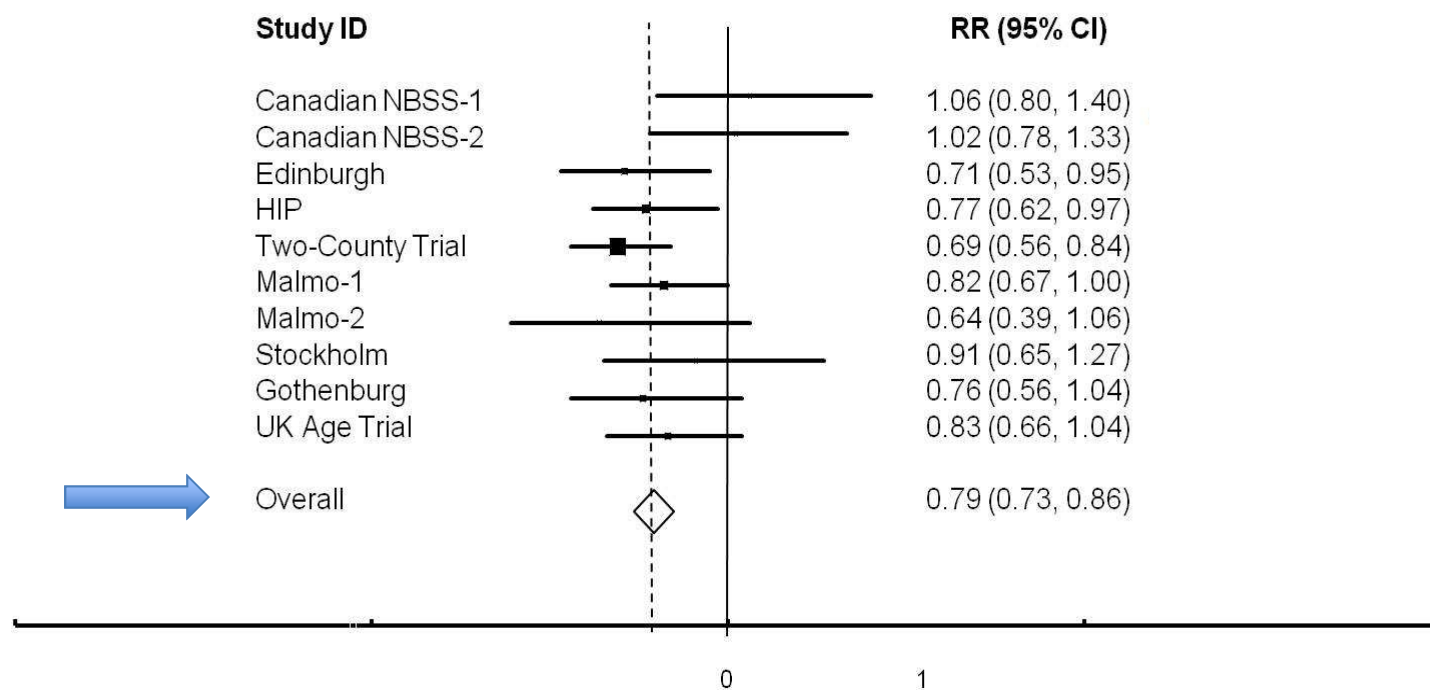
EUROSCREEN Incidence-based mortality estimates for breast cancer mortality reduction in women ages 50-69, **exposed versus not-exposed** to screening

(b) Study	RR	Lower	Upper
Hakama, (1997) ³⁹	0.71	0.45	1.13
Olsen, (2005) ³²	0.63	0.5	0.79
Sarkeala, (2008) ³⁶	0.65	0.41	1.05
Paci, (2002) ⁴²	0.58	0.28	1.22
Kalager, (2010) ⁵¹	0.82	0.62	1.1
Ascunce, (2007) ⁵³	0.47	0.31	0.73
SOSSEG, (2006) ⁵⁹	0.59	0.52	0.67
Summary (random)	0.62	0.56	0.69

J Med Screen 2012;19 Suppl1:14-25

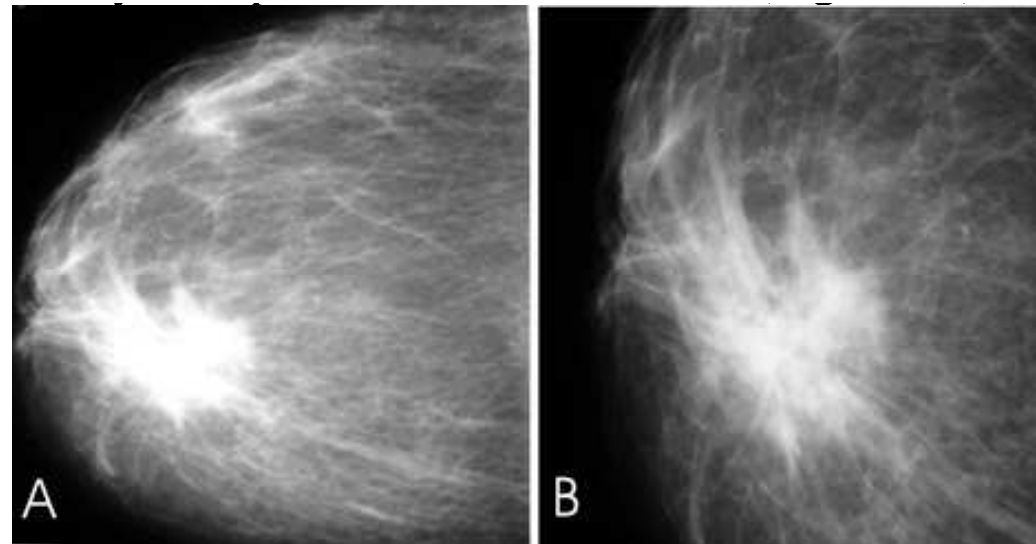


RCTs of screening mammography: Overall results in terms of breast cancer mortality



Overall RR = 0.79 (95% CI: 0.73, 0.86)

Detección de lesiones en mamografía



Programa de cribado de cáncer de mama en Comunidad de Madrid DEPRECAM

- El diagnóstico precoz permite aplicar tratamientos eficaces, antes de la aparición de síntomas, ofreciendo la posibilidad de mejorar el pronóstico
- Población diana: mujeres de 50-69 años (aprox 780.000)
- Técnica: Mamografía digital
- Periodicidad: bienal
- Desde el inicio de DEPRECAM en 1998, se han estudiado más de dos millones de mujeres

Cribado/seguimiento de mujeres de alto riesgo

- Antecedentes de cáncer de mama y/o de ovario
- Mutaciones BRCA 1 o BRCA 2
- Otros síndromes hereditarios asociados a cáncer de mama
- Probabilidad \geq 5% de desarrollar un cáncer de mama a lo largo de la vida

- Diferencias con el cribado poblacional
 - Edad de inicio más temprana
 - Mamografía +/- Resonancia mamaria...
 - Unidades específicas

- Valoración de cirugía profiláctica

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v103–v110, 2016
doi:10.1093/annonc/mdw327

Prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening[†]

S. Paluch-Shimon¹, F. Cardoso², C. Sessa³, J. Balmana⁴, M. J. Cardoso², F. Gilbert⁵ & E. Senkus⁶,
on behalf of the ESMO Guidelines Committee^{*}

¹Division of Oncology and the Dr Pinchas Borenstein Talpiot Medical Leadership Program, Sheba Medical Center, Ramat Gan, Israel; ²Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal; ³Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland; ⁴Vall d'Hebron University Hospital Institut d'Oncologia, Barcelona, Spain; ⁵School of Clinical Medicine, University of Cambridge, Cambridge, UK; ⁶Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland

Table 1. Prevention and screening strategies for specific mutations

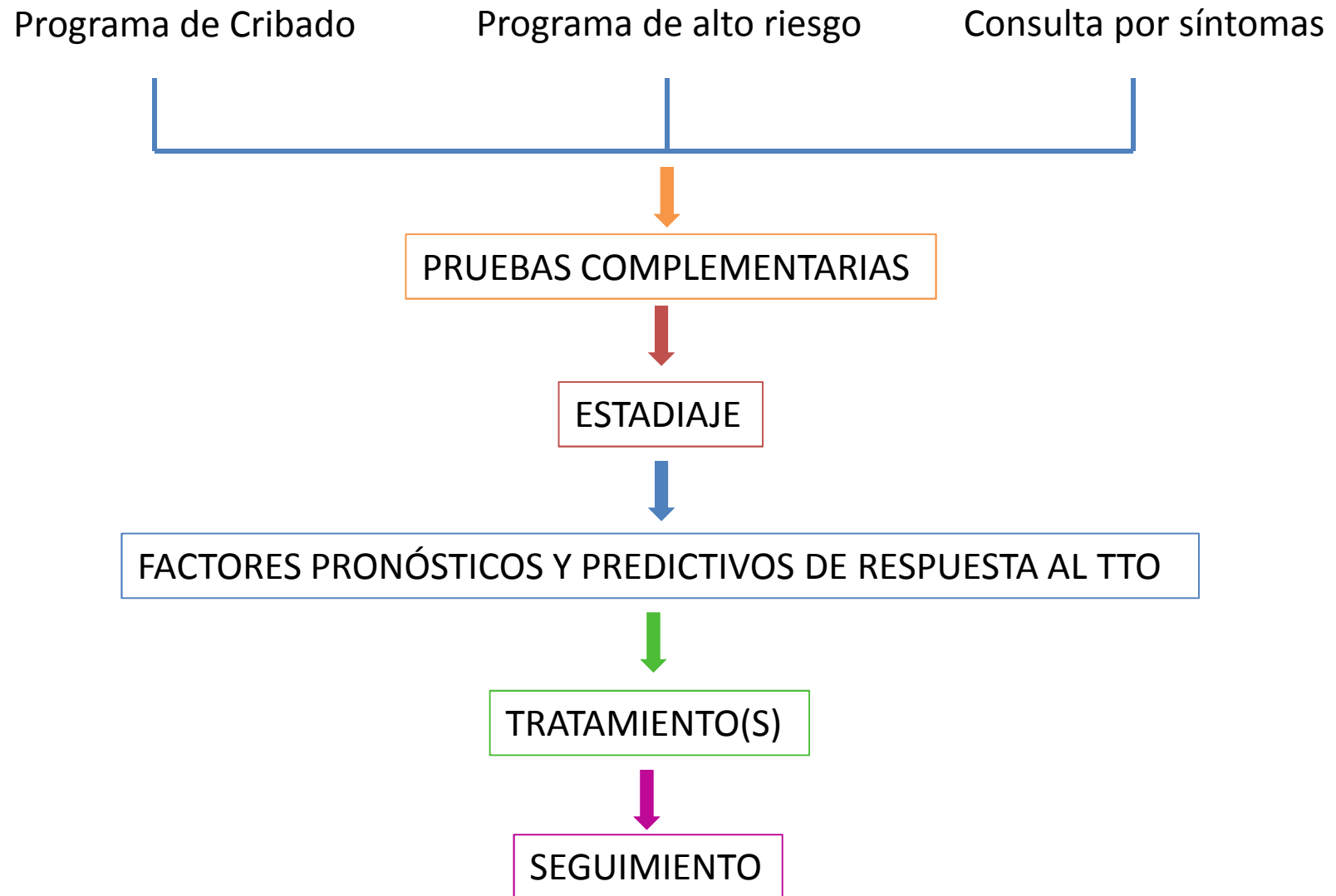
	Screening	Prevention/risk reduction
Li Fraumeni Syndrome - <i>p53</i> mutation	<ol style="list-style-type: none"> 1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI at age 20–75. If MRI is not available, mammography may be considered [V] 3) Colonoscopy every 5 years from the age of 25 or as clinically indicated 4) Annual dermatological and neurological examination 5) Consider annual whole-body MRI and 6-monthly complete blood count 	<ol style="list-style-type: none"> 1) Avoid ionising radiation, e.g. CT 2) Consider offering PGD before pregnancies 3) Consider risk-reducing mastectomy
<i>PTEN</i> /Cowden Syndrome	<ol style="list-style-type: none"> 1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI and/or mammogram at age 30–75 [V] 3) Annual endometrial ultrasound ± biopsies from age 30–35 	<ol style="list-style-type: none"> 1) Consider risk-reducing mastectomy 2) Consider risk-reducing hysterectomy 3) Consider offering PGD before pregnancies
<i>ATM</i> mutation	<ol style="list-style-type: none"> 1) Consider annual breast MRI (no evidence regarding the age of onset) 	
Lynch Syndrome - <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>EPCAM</i> and <i>PMS2</i> mutations	<ol style="list-style-type: none"> 1) Annual colonoscopy from age 20–25 2) Annual neurological examination for screening of CNS tumours may be considered 3) Annual endometrial ultrasound ± biopsies from age 30–35 may be considered 	<ol style="list-style-type: none"> 1) Consider risk-reducing hysterectomy and RRSO after completion of childbearing
<i>RAD51</i> mutation		<ol style="list-style-type: none"> 1) Consider RRSO after the age of 45
<i>BRIP1</i> mutation		<ol style="list-style-type: none"> 1) Consider RRSO after the age of 45
<i>PALB2</i> mutation	<ol style="list-style-type: none"> 1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI from age 20–29 3) Annual breast MRI and/or mammogram at age 30–75 [V] 	<ol style="list-style-type: none"> 1) Consider risk-reducing mastectomy
<i>CHEK2</i> mutation	<ol style="list-style-type: none"> 1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI from age 20–29 3) Annual breast MRI and/or mammogram at age 30–75 [V] 	
<i>STK11</i> mutation (Peutz–Jeghers Syndrome)	<ol style="list-style-type: none"> 1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI from age 20–29 3) Annual breast MRI and/or mammogram at age 30–75 [V] 4) Upper endoscopy and colonoscopy every 2–3 years from late teens 5) Screening for pancreatic cancer with EUS or MRI from the age of 30 6) Annual testicular examination from childhood 7) Routine annual gynaecological surveillance 8) Counselling to reduce lung cancer risk 	<ol style="list-style-type: none"> 1) Consider risk-reducing mastectomy
<i>CDH1</i> mutation	<ol style="list-style-type: none"> 1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI from age 20–29 3) Annual breast MRI and/or mammogram at age 30–75 [V] 	<ol style="list-style-type: none"> 1) Consider risk-reducing mastectomy

MRI, magnetic resonance imaging; CT, computed tomography; PGD, pre-implantation genetic diagnosis; CNS, central nervous system; RRSO, risk-reducing salpingo-oophorectomy; EUS, endoscopic ultrasound.

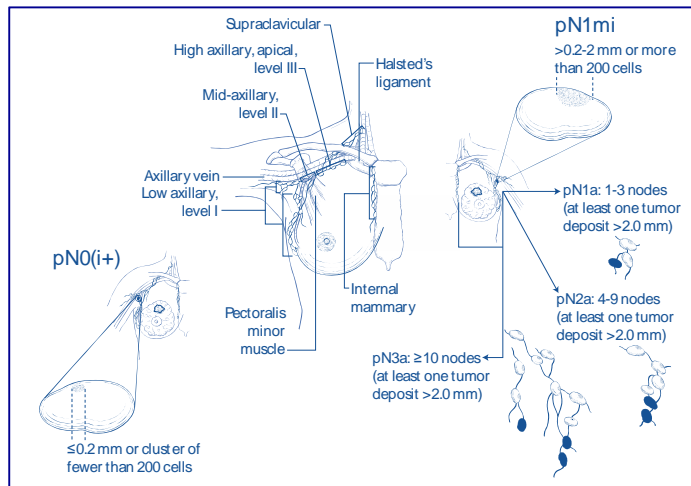
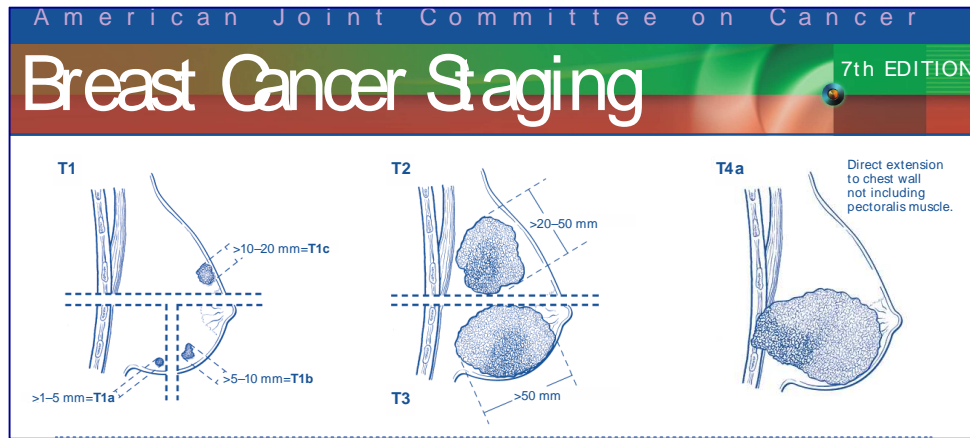
Table 2. Summary of recommendations

Recommendations	LOE, GOR
Initial counselling and follow-up of BRCA mutation carriers	
Follow-up counselling outlining options for screening for early detection, risk-reducing measures and issues pertaining to fertility in women who have not completed their family is fundamental	V, B
Discussion with individuals should address issues of quality of life and the psychosocial impact of risk-reducing interventions	V, B
For individuals above the age of 25 years from a family known to harbour a <i>BRCA1/2</i> mutation, until mutation status has been assessed or in women declining genetic testing or risk-reduction measures, screening recommendations as for known mutation carriers should be followed	V, B
If available, carriers should be encouraged to participate in dedicated high-risk follow-up clinics that specifically focus on follow-up and screening of individuals with a known hereditary cancer syndrome	V, B
Breast cancer risk reduction	
Lifestyle modifications	
Breastfeeding should be encouraged	IV, B
Regular exercise, maintaining healthy body weight and limiting alcohol consumption should be encouraged and HRT should be avoided	V, B
Screening	
Clinical breast examination every 6–12 months is recommended from the age of 25 or 10 years before the youngest breast cancer diagnosis in the family, whichever is earlier	V, B
All carriers should be encouraged to be 'breast-aware' and to seek immediate medical attention if they perceive any changes in their breast or lumps in the axilla	V, B
Annual screening MRI should be commenced from the age of 25 with the addition of annual mammography from the age of 30	II, A
If MRI screening is not available, annual mammography should be utilised from age 30	III, B
Breast ultrasonography can be considered if MRI is unavailable and may also be used as an adjunct to mammography	IV, B
Risk-reducing agents	
Tamoxifen as primary prevention may be considered, although the level of evidence is weak	IV, C
Risk-reducing surgery	
Bilateral RRM is the most effective method for reducing breast cancer risk among <i>BRCA1/2</i> mutation carriers	III, B
SSM and NSM are accepted alternatives to total mastectomy	III, C
Immediate breast reconstruction should be offered	V, C
CRRM among patients with a previous breast cancer diagnosis can be considered	III, B
Ovarian cancer risk reduction	
Lifestyle modifications/exposures	
The use of the OCP may be considered as a risk-reducing measure for ovarian cancer	II, C
Screening	
Before RRSO, 6-monthly, trans-vaginal ultrasound and measures of serum Ca125 may be considered from the age of 30; however, the limited value of these tools as an effective screening measure should be communicated to individuals	V, C
Risk-reducing surgery	
The most effective measure for reducing the risk of ovarian cancer is RRSO (combined removal of ovaries and the fallopian tubes)	I, A
RRSO should be carried out at age 35–40	II, B
Risk-reducing salpingectomy alone is not recommended, outside the setting of a clinical trial	V, C
Screening recommendations following risk-reducing surgery	
There is no currently recommended routine surveillance schedule following RRS	V, C
Reproductive considerations in BRCA mutation carriers	
<i>BRCA1/2</i> carriers can be reassured that there is no convincing evidence that mutation carriers have reduced ovarian reserve or fertility	IV, C
All women harbouring a <i>BRCA1/2</i> mutation should be encouraged to complete childbearing before planned RRSO	V, C
For women who wish to undergo RRSO and have not yet completed childbearing fertility preservation options should be discussed	V, C
<i>BRCA1/2</i> mutation carriers (male and female) planning to conceive should be made aware of the options of prenatal diagnosis (via chorionic villous or amniotic fluid sampling in week 11–20 of gestation) and PGD	V, C
Women harbouring a <i>BRCA1/2</i> mutation who have been diagnosed with a malignancy should be counselled about options for fertility preservation before the commencement of oncology treatment	V, B
Appropriate counselling should be available and vaginal moisturisers and lubricants should be prescribed to all women following RRS	V, C
Short-term use of HRT to alleviate menopausal symptoms following RRSO is safe among healthy <i>BRCA1/2</i> mutation carriers	III, B
No safety data are available about the use of HRT among <i>BRCA1/2</i> carriers with a previous diagnosis of breast cancer. The relationship between hormonal influences and the development of different breast cancer subtypes, including triple negative breast cancers, has not been fully elucidated, thus HRT in the setting of a past breast cancer diagnosis should be strongly discouraged—irrespective of endocrine status of the initial tumour	V, B

PROCESO DE DIAGNÓSTICO Y TRATAMIENTO DEL CÁNCER DE MAMA



Estadíaaje: Clasificación TNM



ANATOMI C STAGE/ PROGNOSTI C GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Factores pronósticos y predictivos

Factores pronósticos



¿Que tratamiento es necesario?

Factores predictivos



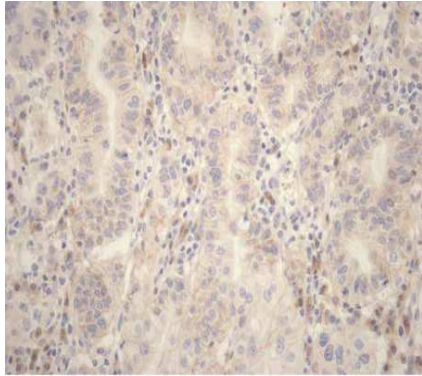
¿Qué tratamiento es el mejor?

Factores pronósticos y predictivos (II)

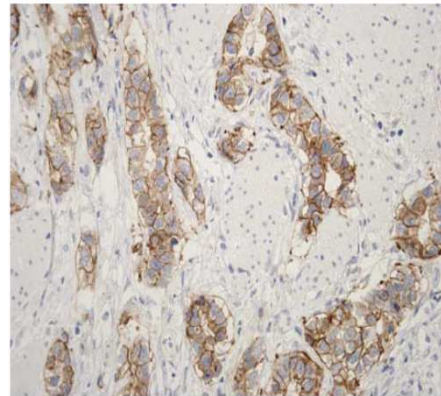
- Tumor
 - TNM
 - Grado
 - Tipo histológico
 - Ca ductal
 - Ca lobulillar
 - Estado HER2*
 - RE* y RP*
 - Perfil genómico
- Paciente
 - Edad
 - Estado menopáusico

* Son factores pronósticos y predictivos al mismo tiempo

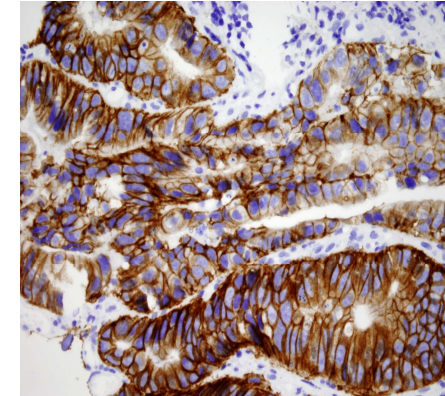
Positividad de HER2



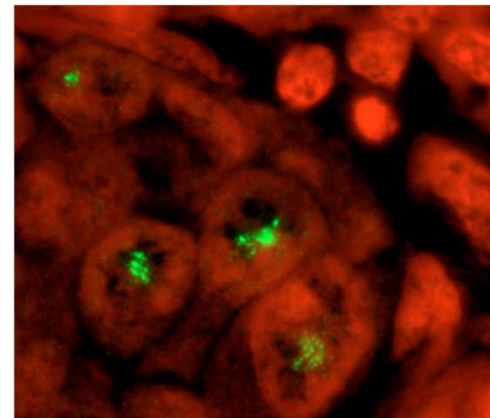
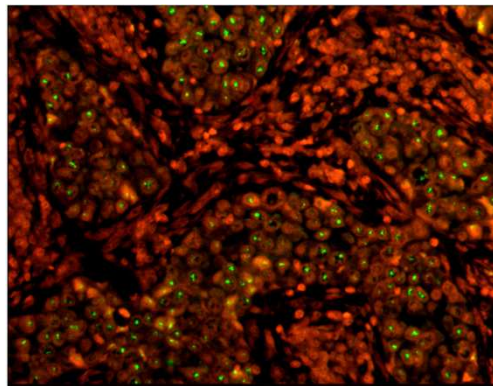
IHQ Tinción débil 1+



Tinción moderada 2+

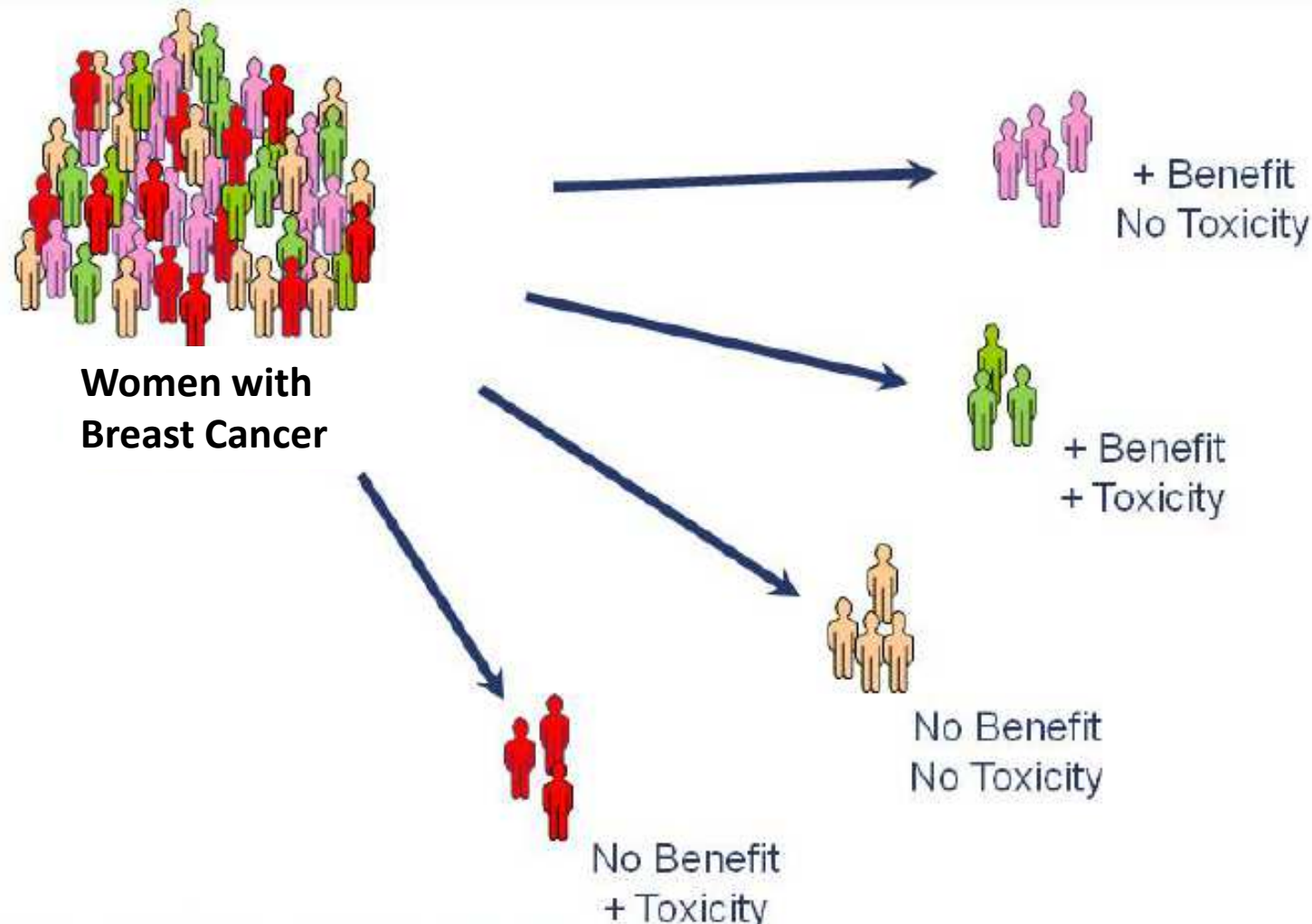


Tinción intensa 3+



FISH amplification of HER2

¿Podemos identificar pacientes de bajo riesgo que no se beneficien de quimioterapia?



¿De que test genómicos disponemos?

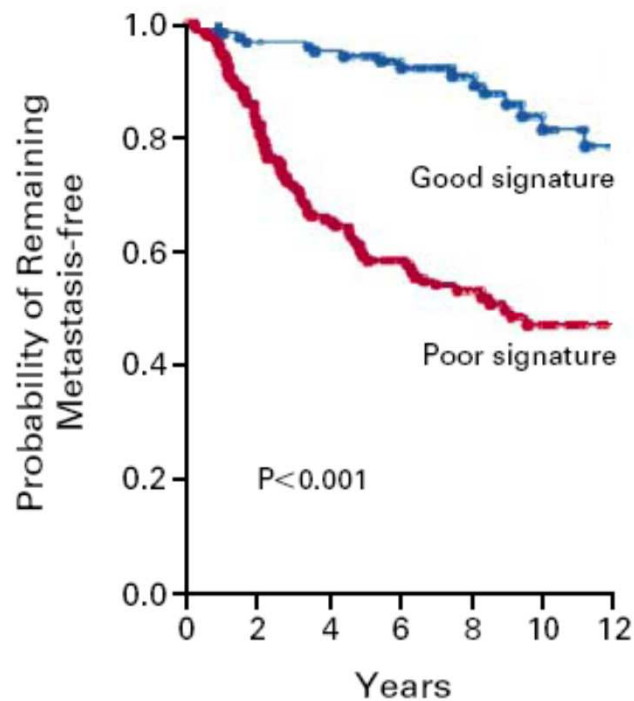
- Test genómicos de expresión que clasifican pacientes en alto, intermedio o bajo riesgo de recaída
- Según ello se aplica tratamiento adyuvante: quimioterapia seguido de hormonoterapia, o hormonoterapia sola

- Mamaprint (70-gene)
- Oncotype DX (21-gene)
- PAM50 (50-gene)
- **No sustituyen a los factores pronósticos clásicos**

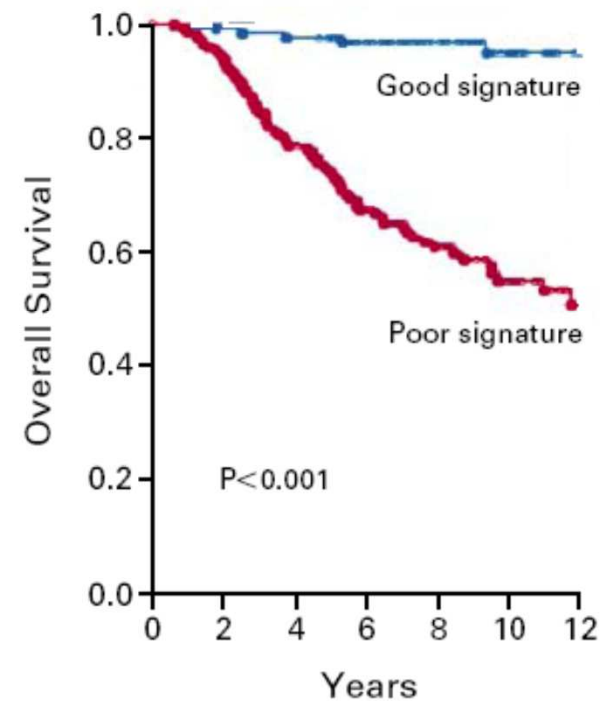
Un perfil de expresión génica como factor pronóstico de la supervivencia en cáncer de mama

- Total de pacientes (295)
 - ✓ Probabilidad de no desarrollar metástasis
 - ✓ Sobrevida total

A All Patients



B All Patients



Principales factores de aumento de la supervivencia

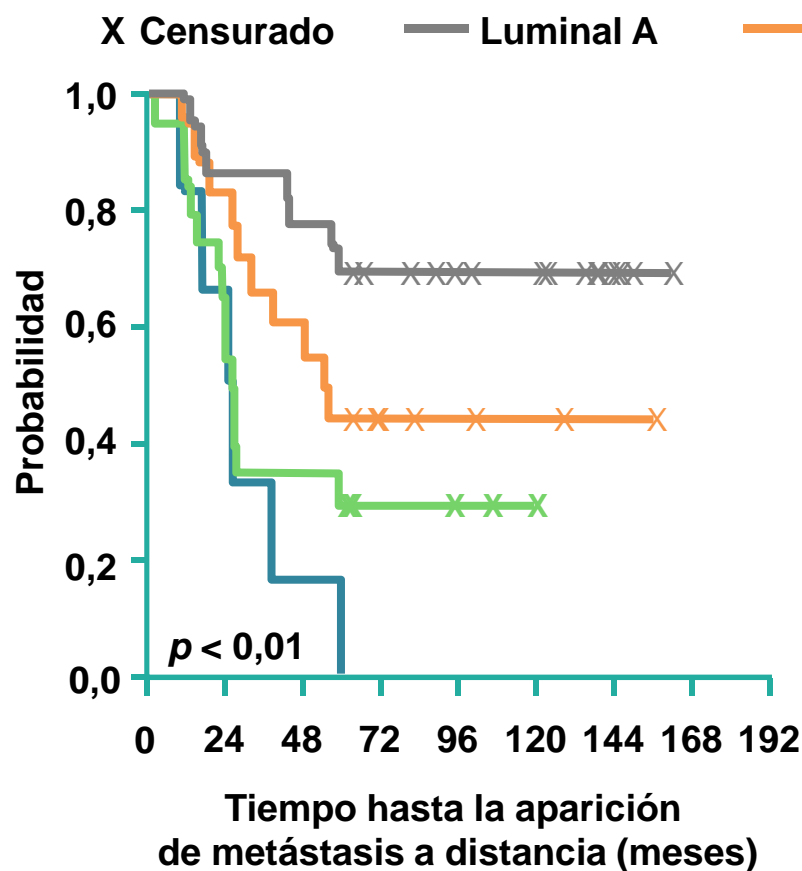
- Diagnóstico precoz
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- Tratamiento neo/adyuvante
 - Quimioterapia
 - Hormonoterapia
 - Terapias dirigidas
 - Radioterapia

Fenotipos en cáncer de mama

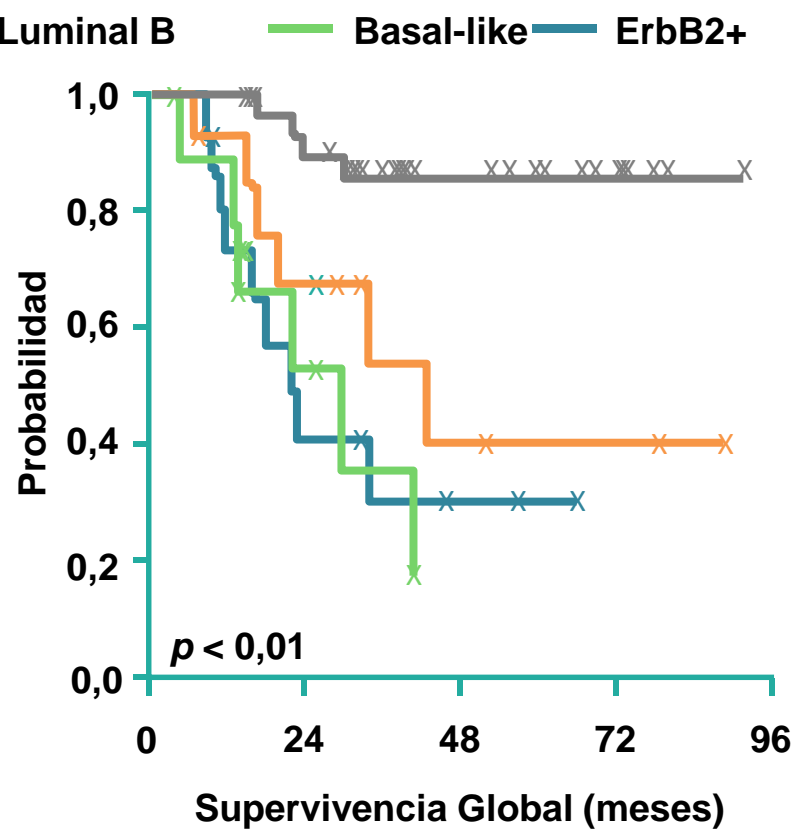
Fenotipo	Receptor de estrógenos	Receptor de progesterona	HER2	MIB1 otros
Luminal A	+	+	-	< 14%
Luminal B	+	+/-	+/-	>13%
HER2	-	-	+	
Triple negativo (basal)	-	-	-	

Supervivencia libre de recaída y supervivencia global

(A) Tiempo hasta la recaída a distancia



(B) Supervivencia



special article

Annals of Oncology 2013; 24: 1-10
doi:10.1093/annonc/mdt003



Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013

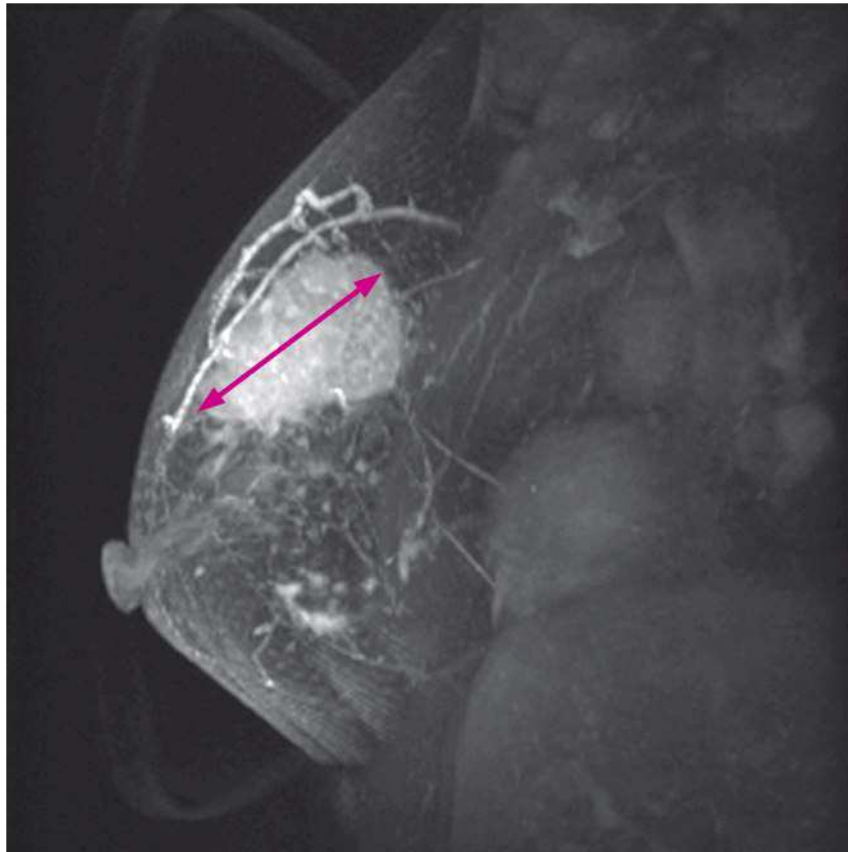
A. Goldhirsch^{1*}, E. P. Winer², A. S. Coates³, R. D. Gelber⁴, M. Pocock-Gebhart⁵, B. Thürlimann⁶ & H.-J. Senn⁷ Panel members[†]

Category	IHQ	Therapy
Luminal A	RE and RP +ve HER2 -ve Ki-67 < 20 %	Hormonal therapy and CT if: RS high, Grade 3 or ≥ 4 +ve nodes
Luminal B (HER2 -ve)	RE+ve and HER2-ve and: RP -ve and/or Ki-67 ≥ 20%	Hormonal therapy Chemotherapy for most
Luminal B (HER2 +ve)	RE+ve and any RP HER2 +ve Ki-67 any	Hormonal therapy Anti-HER2 therapy Chemotherapy
HER2 “enriched”	RE and RP -ve HER2 +ve	Anti-HER2 therapy Chemotherapy
Triple negative	RE and RP -ve HER2 -ve	Chemotherapy

Principales factores de aumento de la supervivencia

- Diagnóstico precoz
 - Programas de cribado: Mamografía
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- Tratamiento neo/adyuvante
 - Quimioterapia
 - Hormonoterapia
 - Terapias dirigidas
 - Radioterapia

Quimioterapia neoadyuvante (preoperatoria)



**pre-chemotherapy
longest dimension = 47 mm**

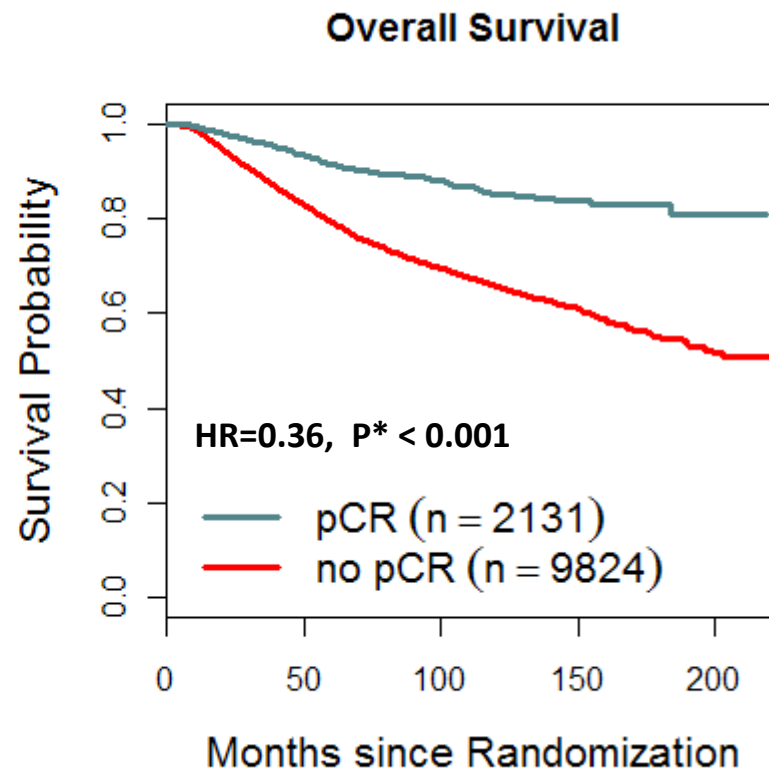
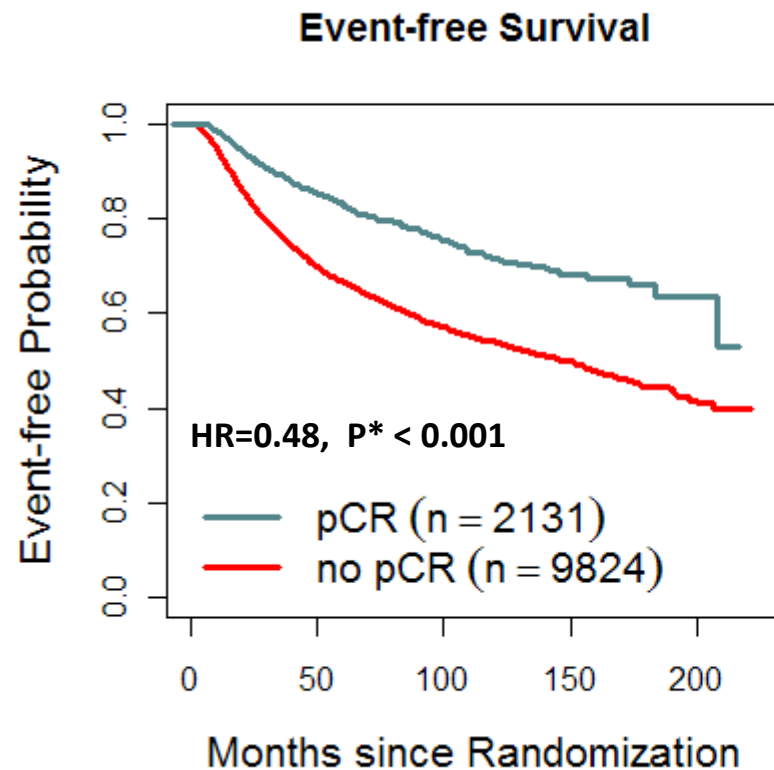


**post-chemotherapy
longest dimension = 16 mm**

Taken from Biology of Cancer

Asociación de pCR con supervivencia libre de enfermedad y supervivencia global

pCR: respuesta completa patológica



pCR=ypT0/is ypN0

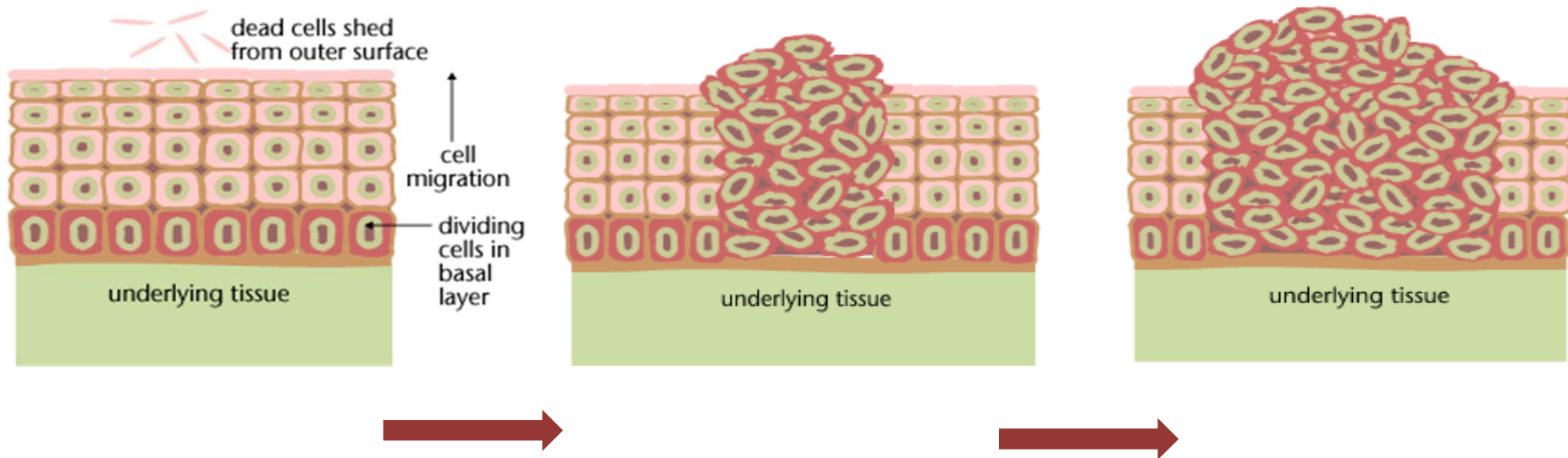
* Nominal p-value

FDA, SABCS 2012



Terapias dirigidas: Proceso del cáncer (conocimiento antiguo)

El cáncer es un proceso que tiene múltiples etapas

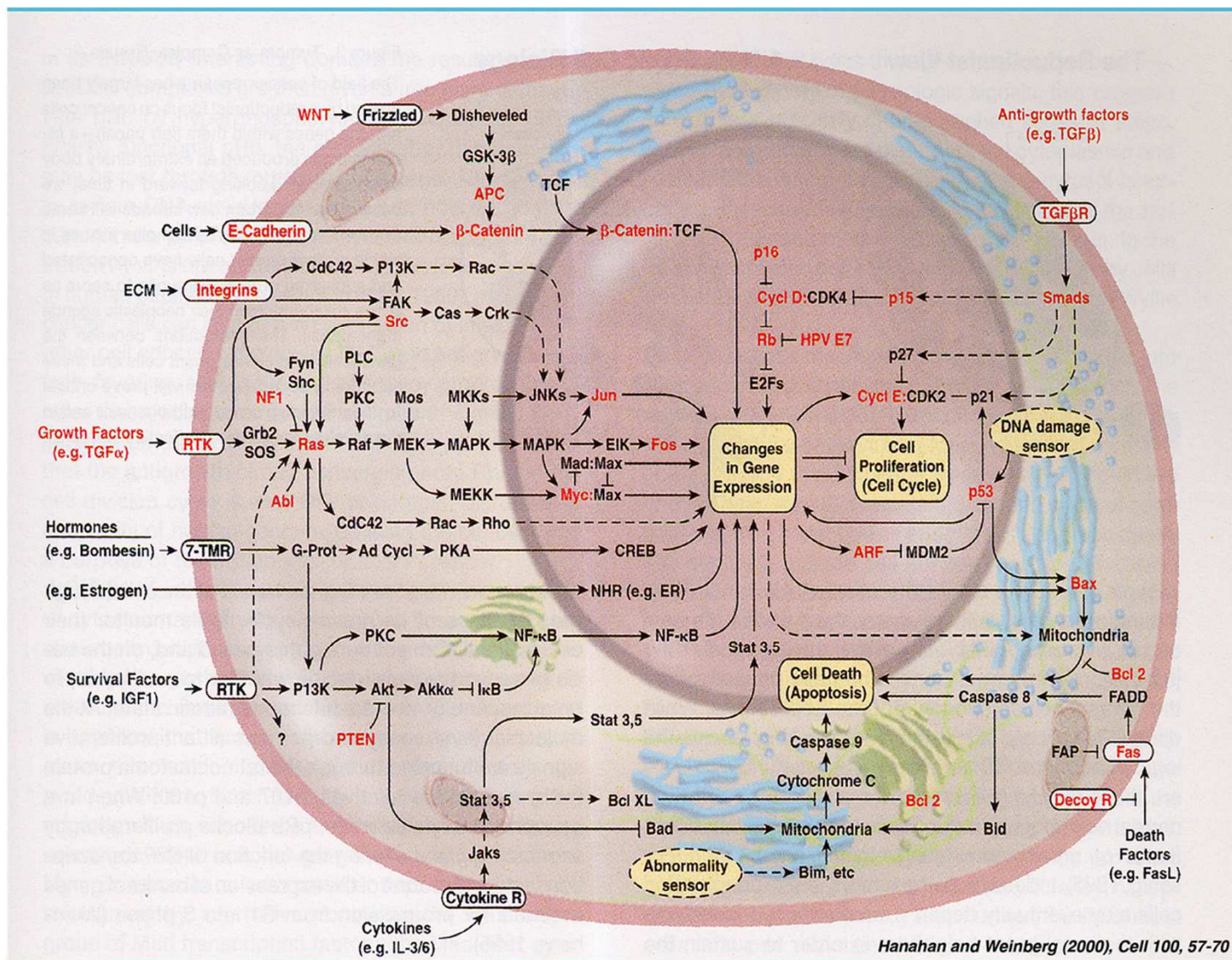


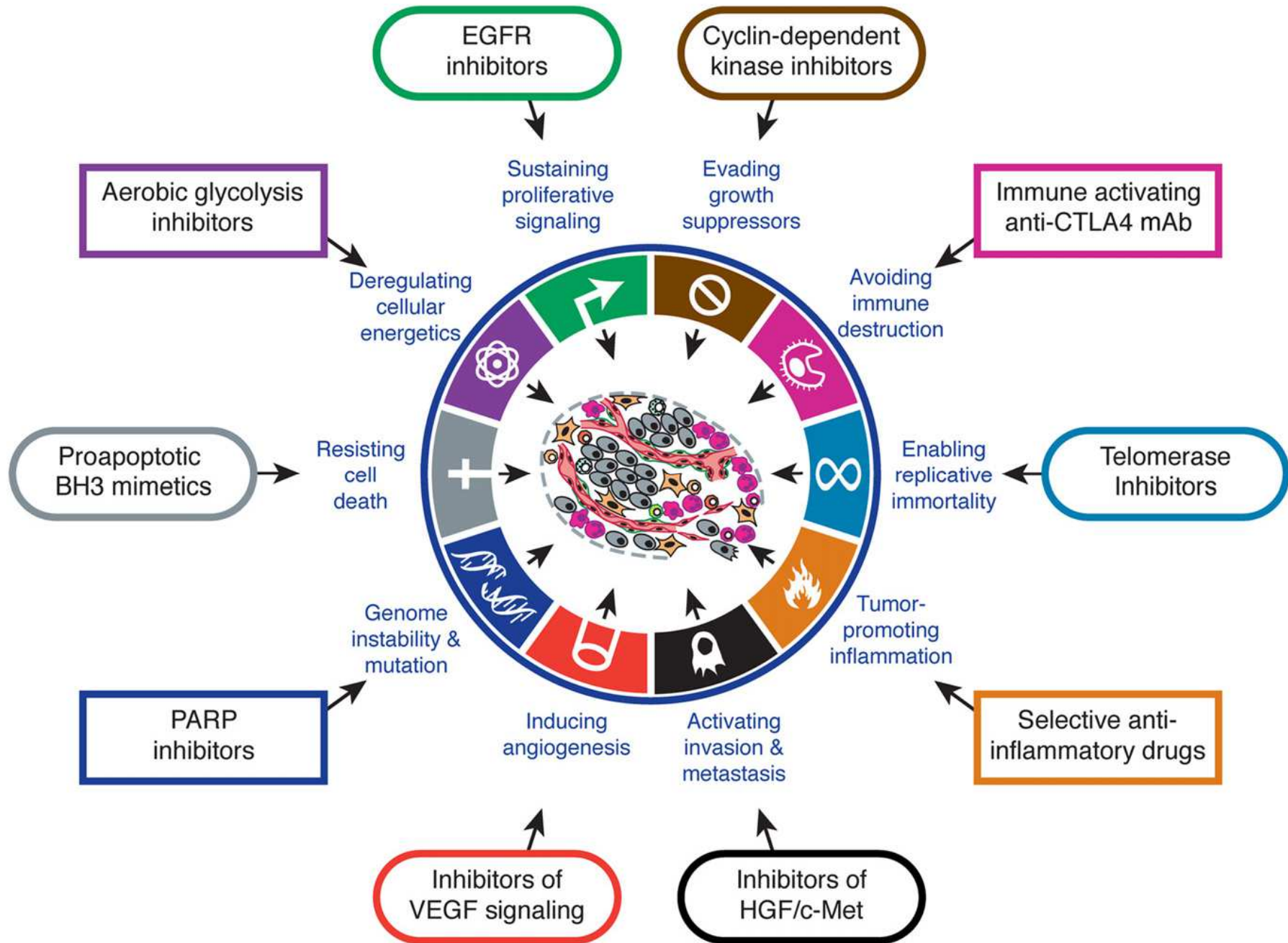
Se produce cuando existe un crecimiento descontrolado de células
(por mayor multiplicación y/o menor muerte celular)

Proceso del cáncer (conocimiento actual)

- Producción de factores de crecimiento
- Insensible a las señales antiproliferativas
- Mecanismos de evasión de la apoptosis
- Capacidad de replicación no controlada
- Angiogénesis
- Invasión de tejidos y formación de metástasis
- Resistencia primaria o adquirida a fármacos
- Inestabilidad genómica, alteraciones genéticas
- Inmunidad

Vías de señalización intracelular





Conclusiones sobre cáncer de mama

- Existen distintos tipos de cáncer de mama
- Disminución de riesgo de aparición: Prevención primaria
 - Dieta, ejercicio
 - Mastectomía profiláctica bilateral en mujeres de alto riesgo
 - Quimioprevención de cáncer de mama contralateral
- Disminución de riesgo de recaída/mortalidad
 - Cribado poblacional y de mujeres de alto riesgo
 - Tratamiento adyuvante/neoadyuvante con terapias dirigidas si indicado
 - Terapias dirigidas (si diana celular)
 - Seguimiento de mujeres con cáncer de mama

Cáncer de ovario

- Los estadios iniciales son poco frecuentes porque no suele producir síntomas hasta que no está avanzado
- Tratamiento:
 - Cirugía y/o quimioterapia
 - Terapias dirigidas

Incidencia y mortalidad de cáncer de ovario en España

Tendencia

INCIDENCIA	2012	2015	2030
< 65 años	1.613	1.671	1.859
≥ 65 años	1.623	1.724	2.280
Total	3.236	3.395	4.139
Incremento respecto a 2012	--	+159	+902

Tendencia

MORTALIDAD	2012	2015	2030
< 65 años	663	661	777
≥ 65 años	1.245	1.320	1.739
Total	1.878	1.981	2.516
Incremento respecto a 2012	--	+ 103	+638

Cáncer de ovario en la Comunidad de Madrid

Registro de Tumores de Madrid RTMAD*

INCIDENCIA	2012	2013	2014	2015
Mujeres (% sobre total casos registrados en RTMAD)	345 (3,3%)	370 (3,3%)	333 (2,7%)	410 (3,2%)
Total (hombres y mujeres) (% sobre total casos registrados en RTMAD)	345 (1,5%)	370 (1,5%)	333 (1,2%)	410 (1,3%)

Aproximadamente el **12%** del total de casos diagnosticados en España

*RTMAD: Registro de hospitales públicos

Conclusiones sobre reducción de riesgo de cáncer de ovario

- Población riesgo estándar: No existe cribado

clinical practice guidelines

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Prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening[†]

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- Población alto riesgo:
 - Modificar estilo de vida/exposición: anticonceptivos
 - Cribado: Ecografía transvaginal + CEA 125 c/6 meses desde los 30 años (valor limitado)
 - Cirugía de reducción de riesgo: Anexectomía bilateral a partir de 35-40 años



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