RESULTADOS PRELIMINARES DE FRECUENCIA DE MUTACIONES GERMINALES EN BRCA 1 Y BRCA 2 EN MUJERES CON CARCINOMA EPITELIAL DE OVARIO ESPORÁDICO, SIN ANTECEDENTES FAMILIARES Y SU RELACIÓN CON EL FENOTIPO TUMORAL

A. Aránzazu y Cols.

Discusor:

Dr. Ignacio Blanco
Coordinador,
Programa de Asesoramiento y Genética Clínica
Hospital Germans Trias I Pujol

03/ SIMPOSIO SEOM

RESULTADOS PRELIMINARES DE FRECUENCIA DE MUTACIONES GERMINALES EN BRCA 1 Y BRCA 2 EN MUJERES CON CARCINOMA EPITELIAL DE OVARIO ESPORÁDICO, SIN ANTECEDENTES FAMILIARES Y SU RELACIÓN CON EL FENOTIPO TUMORAL

Aránzazu Manzano, Pedro Pérez-Segura, Amelia Asturias, Isabel Díaz, Trinidal Caldés, Antonio Casado, Eduardo Díaz-Rubio, Miguel de la Hoya

IdISSC INSTITUTO de INVESTIGACIÓN SANITARIA Hospital Clínico San Carlos

Hospital Clínico San Carlos Madrid

VNIVERSITAS COMPLVTENSIS MATRITENSIS

SEOM Sociedad Española de Oncología Médica

03/ SIMPOSIO SEOM

Objetivos

- Determinar la prevalencia de mutaciones germinales en BRCA1 y 2 en una cohorte de pacientes con carcinoma epitelial de ovario esporádico

- Estimar la prevalencia en función de características fenotípicas del tumor: subtipo y grado histológico

SEOM Sociedad Española de Oncología Médica

03/ SIMPOSIO SEOM

COE cáncer de ovario epitelial
AF: antecedentes familiares

Métodos I

Registro Sº Oncología Médica HCSC 2006-2013

242 COE

94 fallecidas

Contacto prospectivo

148 COE

63 AF
12 perdidas

***CO esporádico**: aquel caso de cáncer de ovario sin antecedentes de CM y/o CO en familiares de primer/segundo grado

73 COE sin AF

11 rechazan el estudio

62 COE sin AF

ESTUDIO GENETICO tras firma de CI

* ***44 estudiadas***
* 18 mujeres pendientes de estudio genético

SEOM Sociedad Española de Oncología Médica

03/ SIMPOSIO SEOM

Resultados

PREVALENCIA DE MUTACIONES PATOGÉNICAS EN FUNCIÓN DE LA HISTOLOGÍA Y GRADO

PREVALENCIA
11.4%
(5/44)

(4 BRCA1 y 1 BRCA2)

Edad (años)	Familia informativa	Histología	Grado	Gen
50	si	seroso	AG	BRCA1
49	si	seroso	AG	BRCA1
56	si	seroso	AG	BRCA1
75	si	seroso	AG	BRCA2
37	no	seroso*	AG	BRCA1

PREVALENCIA MUTACIONES EN SEROSOS ALTO GRADO	PREVALENCIA MUTACIONES EN RESTO HISTOLOGIAS	p
5/18 **(27.8%)**	0/26 (0%)	***0.008***

SEOM Sociedad Española de Oncología Médica

03/ SIMPOSIO SEOM

Conclusiones

- La prevalencia de mutaciones en mujeres con histología serosa de alto grado justifica la realización de estudio genético en este subgrupo de pacientes, con independencia de antecedentes familiares y/o edad de diagnóstico
- La histología podría ser considerada un predictor de mutaciones en *BRCA1/2* en CO y debería ser incorporada a las guías
- El caracter retrospectivo del estudio podría condicionar un sesgo de selección y sobreestimar la prevalencia

SEOM Sociedad Española de Oncología Médica

Journal of Clinical Oncology, Vol 14, 1730-1736, Copyright © 1996 by American Society of Clinical Oncology

ARTICLES

Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adopted on February 20, 1996

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility

Adopted on March 1, 2003, by the American Society of Clinical Oncology

VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility

Mark E. Robson, Courtney D. Storm, Jeffrey Weitzel, Dana S. Wollins, and Kenneth Offit

- ASCO still recommended that, outside of a research protocol, genetic testing for cancer susceptibility only be offered when the following three criteria are met:
  - *the individual being tested has a personal or family history suggestive of genetic cancer susceptibility;*
  - *the genetic test can be adequately interpreted; and*
  - *the test results have accepted clinical utility.*

- ASCO still recommended that, outside of a research protocol, genetic testing for cancer susceptibility only be offered when the following three criteria are met:
  - *the individual being tested has a personal or family history suggestive of genetic cancer susceptibility;*
  - *the genetic test can be adequately interpreted; and*
  - *the test results have accepted clinical utility.*

- ASCO still recommended that, outside of a research protocol, genetic testing for cancer susceptibility only be offered when the following three criteria are met:
  - *the individual being tested has a personal or family history suggestive of genetic cancer susceptibility;*
  - *the genetic test can be adequately interpreted; and*
  - *the test results have accepted clinical utility.*

Seminar

Lancet 2014; 384: 1376–88

Ovarian cancer

Gordon C Jayson, Elise C Kohn, Henry C Kitchener, Jonathan A Ledermann

Seminar

Lancet 2014; 384: 1376–88

Ovarian cancer

Gordon C Jayson, Elise C Kohn, Henry C Kitchener, Jonathan A Ledermann

Epithelial ovarian cancer

High-grade serous	Low-grade serous	Endometrioid	Clear cell	Mucinous
TP53 BRCA1/2 NF1 CDK12 Homologous Recombination Repair genes Pathway alterations PI3/Ras/Notch/ FoxM1	BRAF KRAS NRAS ERBB2	ARID1A PI3KCA PTEN PPP2R1A MMR deficiency	ARID1A PI3KCA PTEN CTNNB1 PP2R1A	KRAS ERBB2 ampl

Seminar

Lancet 2014; 384: 1376–88

Ovarian cancer

Gordon C Jayson, Elise C Kohn, Henry C Kitchener, Jonathan A Ledermann

Epithelial ovarian cancer

High-grade serous	Low-grade serous	Endometrioid	Clear cell	Mucinous
TP53 BRCA1/2 NF1 CDK12 Homologous Recombination Repair genes Pathway alterations PI3/Ras/Notch/ FoxM1	BRAF KRAS NRAS ERBB2	ARID1A PI3KCA PTEN PPP2R1A MMR deficiency	ARID1A PI3KCA PTEN CTNNB1 PP2R1A	KRAS ERBB2 ampl

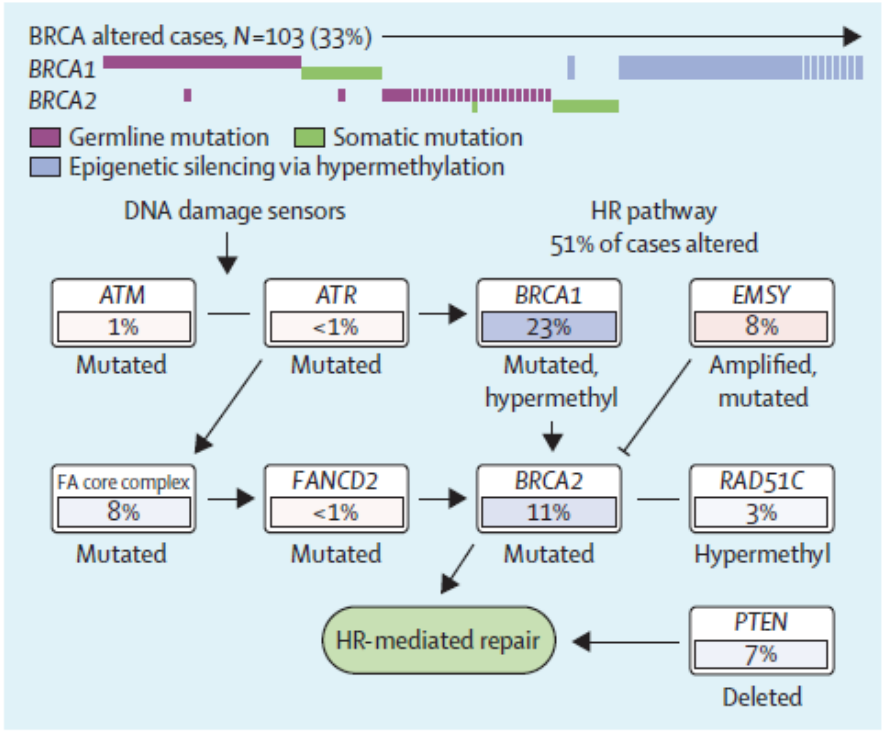
Seminar

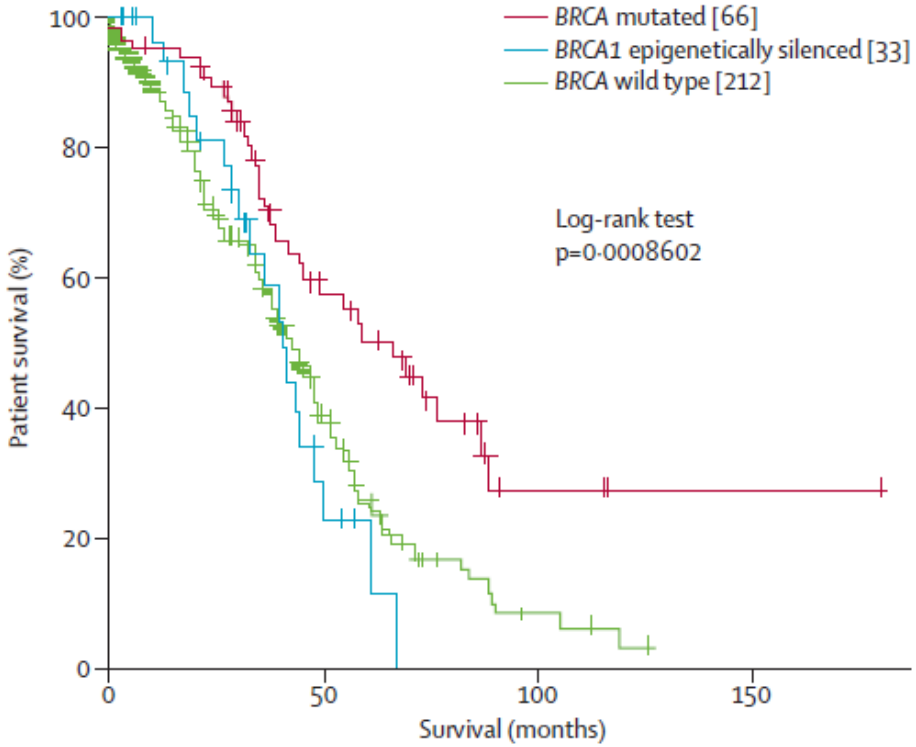
Lancet 2014; 384: 1376–88

Ovarian cancer

Gordon C Jayson, Elise C Kohn, Henry C Kitchener, Jonathan A Ledermann

C HR alterations





SCIENTIFIC REPORTS

SCIENTIFIC REPORTS | 4 : 4026 | DOI: 10.1038/srep04026

OPEN

SUBJECT AREAS:
OVARIAN CANCER
DISEASES

Clinical Characteristics of Ovarian Cancer Classified by *BRCA1*, *BRCA2*, and *RAD51C* Status

Table 2 | Summary of germline mutations, somatic mutations, and methylation of *BRCA1*, *BRCA2* and *RAD51C*

		Gene, n			
	N Tested	*BRCA1*	*BRCA2*	*RAD51C*	Combined HRD
Germline deleterious mutation	899	32	28	26	83
Somatic deleterious mutation	279	6	4	0	10
Methylated	482	45	-	7	52
No deleterious mutation, not methylated	NA	237	261	263	NA
No deleterious germline mutation, unknown somatic mutation and/or tumor methylation status	NA	592	606	604	NA
Not methylated, germline and somatic mutation status unknown	NA	151	164	163	NA
Total		1063	1063	1063	143

- The HRD phenotype was most common in **high grade serous EOC**.
- Identification of EOC patients with an **HRD phenotype** may help **tailor** specific therapies.

frontiers in ONCOLOGY

REVIEW ARTICLE
published: 27 February 2014
doi: 10.3389/fonc.2014.00019

BRCA 1/2-mutation related and sporadic breast and ovarian cancers: more alike than different

*Melissa Burgess and Shannon Puhalla**

September 2014 | Volume 9 | Issue 9 | e107643

OPEN ACCESS Freely available online

PLOS | ONE

Molecular Subtyping of Serous Ovarian Tumors Reveals Multiple Connections to Intrinsic Breast Cancer Subtypes

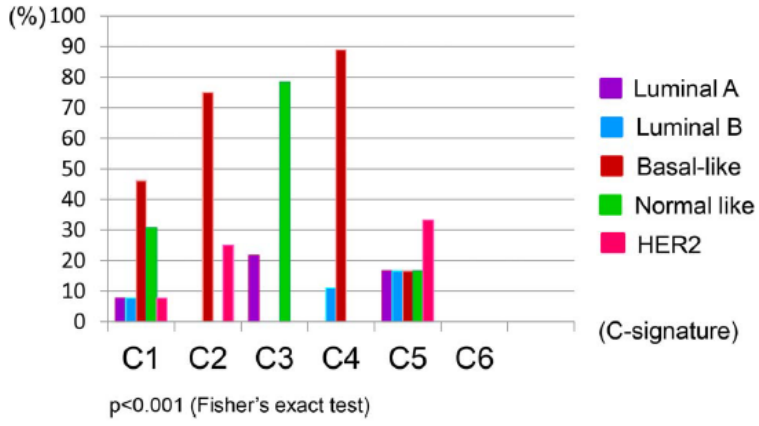


Figure 2. Correlations between ovarian and breast cancer molecular subtypes. Correlations between specific ovarian cancer C-

The similarities between molecular subtypes of ovarian and breast cancer may be of potential interest for further studies regarding **targeted therapies** and the use of chemotherapeutic agents in ovarian cancer, as well as biomarker studies.

- *the individual being tested has a personal or family history suggestive of genetic cancer susceptibility;*
- *the genetic test can be adequately interpreted; and*
- *the test results have accepted clinical utility.*

VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility

Mark E. Robson, Courtney D. Storm, Jeffrey Weitzel, Dana S. Wollins, and Kenneth Offit

http://carlosgallego.com/wp-content/uploads/2014/09/o-.jpg

VOLUME 32 · NUMBER 12 · APRIL 20 2014

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Underestimation of Risk of a *BRCA1* or *BRCA2* Mutation in Women With High-Grade Serous Ovarian Cancer by BRCAPRO: A Multi-Institution Study

Molly S. Daniels, Sheri A. Babb, Robin H. King, Diana L. Urbauer, Brittany A.L. Batte, Amanda C. Brandt, Christopher I. Amos, Adam H. Buchanan, David G. Mutch, and Karen H. Lu

Annals of Oncology Advance Access published October 3, 2014

The Performance of BRCA1 Immunohistochemistry for Detecting Germline, Somatic, and Epigenetic *BRCA1* Loss in High-Grade Serous Ovarian Cancer

J.L. Meisel[1,*], D.M. Hyman[1,2,8,*], K. Garg[3], Q. Zhou[4], F. Dao[5], M. Bisogna[5], J. Gao[6], N.D. Schultz[6], R.N. Grisham[1,8], M. Phillips[5], A. Iasonos[4], N. D. Kauff[1,5,7,8], D.A. Levine[5,8], R.A. Soslow[3,8,], D.R. Spriggs[1,2,8,**]**

Table 2: Performance of BRCA IHC by Mechanism of Loss

		BRCA1 Loss (Germline Only)		*BRCA1* Loss (Germline/Somatic/Methylation)	
		No	Yes	No	Yes
BRCA1 IHC Results	Normal	83	4	83	4
	Abnormal	23	25	5	35

		Rate	95% CI	Rate	95% CI
BRCA1 IHC Performance	Sensitivity	86.2%	73.7 - 98.8%	89.7%	80.2 - 99.3%
	Specificity	78.3	70.5 - 86.2%	94.3%	89.5 - 99.2%
	PPV	52.1%	38.0 - 66.2%	87.5%	77.3 - 97.8%
	NPV	95.4%	91.0 - 99.8%	95.4%	91.0 - 99.8%
	OCCR	80.0%	73.3 - 86.8%	92.9%	88.5 - 97.4%

PPV, positive predictive value; NPV, negative predictive value; OCCR, overall correct classification rate.

BioMed Research International
Volume 2014, Article ID 787143, 11 pages
http://dx.doi.org/10.1155/2014/787143

Review Article

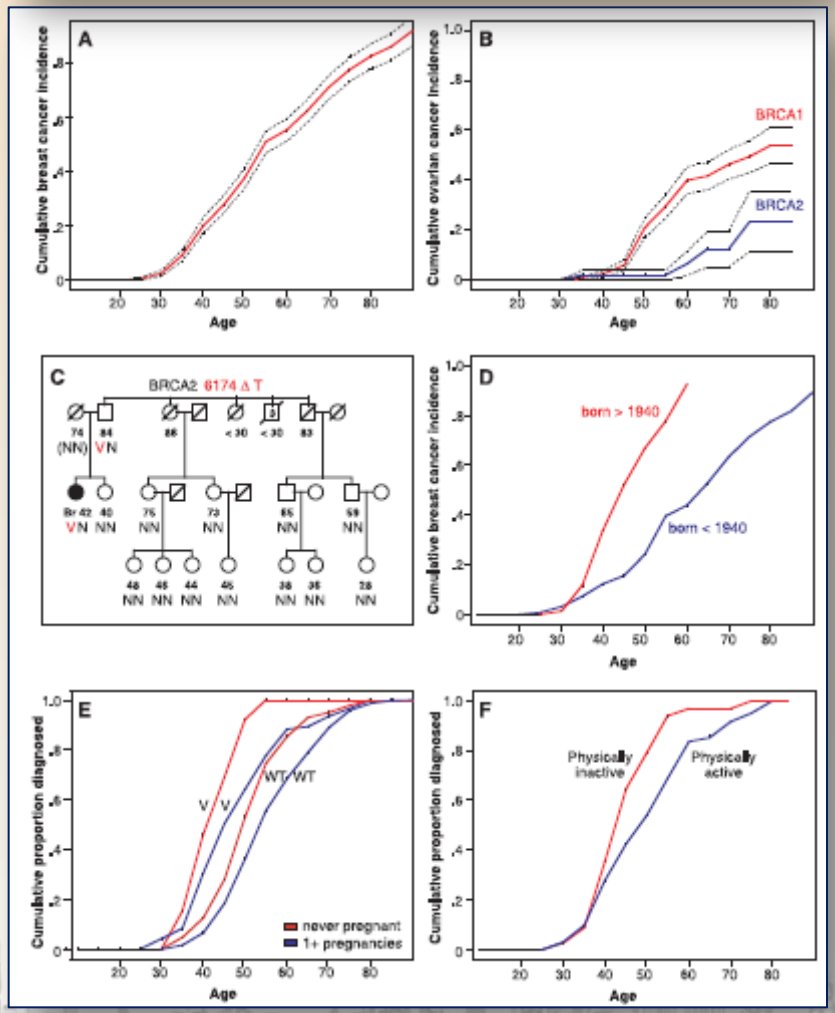
BRCA-Associated Ovarian Cancer: From Molecular Genetics to Risk Management

- Ovarian Cancer arising in *BRCA1/2* mutation carriers have peculiar molecular, pathological, and clinical features.
- Since a non-negligible proportion of newly diagnosed OC patients are expected to carry such mutations, ***BRCA1/2* mutational analysis would help**, in the future, to tailor OC management according to BRCA status.
- In addition, this would allow the subsequent identification of asymptomatic carriers who would benefit from targeted interventions for high-risk women.

SCIENCE VOL 302 24 OCTOBER 2003

Breast and Ovarian Cancer Risks Due to Inherited Mutations in *BRCA1* and *BRCA2*

Mary-Claire King,[1]* Joan H. Marks,[2] Jessica B. Mandell[2]* for The New York Breast Cancer Study Group[3]



28 MARCH 2014 VOL 343 SCIENCE

PERSPECTIVE

"The Race" to Clone *BRCA1*

Mary-Claire King

verely affected families (*36*). Identification of cancer-causing mutations in *BRCA1* and *BRCA2* has clear and actionable implications for prevention. *BRCA1* and *BRCA2* screening as part of routine health care for young adult women is sensible and feasible. As in any population-screening program, genetic or otherwise, few participants will prove positive, but for women who learn that they carry mutations in *BRCA1* or *BRCA2*, the consequences are enormous, addressable, and life-saving.

Until there are no more breast or ovarian cancers among women with *BRCA1* or *BRCA2* mutations, the real race is not over.

28 MARCH 2014 VOL 343 SCIENCE

PERSPECTIVE

"The Race" to Clone *BRCA1*

Mary-Claire King

verely affected families (*36*). Identification of cancer-causing mutations in *BRCA1* and *BRCA2* has clear and actionable implications for prevention. *BRCA1* and *BRCA2* screening as part of routine health care for young adult women is sensible and feasible. As in any population-screening program, genetic or otherwise, few participants will prove positive, but for women who learn that they carry mutations in *BRCA1* or *BRCA2*, the consequences are enormous, addressable, and life-saving.

Until there are no more breast or ovarian cancers among women with *BRCA1* or *BRCA2* mutations, the real race is not over.

JAMA September 17, 2014 Volume 312, Number 11

Opinion

VIEWPOINT

Population-Based Screening for *BRCA1* and *BRCA2*

2014 Lasker Award

Mary-Claire King, PhD

Based on our 20 years' experience working with families with cancer-predisposing mutations in *BRCA1* and *BRCA2*, it is time to offer genetic screening of these genes to every woman

JAMA September 17, 2014 Volume 312, Number 11

Opinion

VIEWPOINT

Mary-Claire King, PhD

Population-Based Screening for *BRCA1* and *BRCA2*
2014 Lasker Award

PNAS | September 30, 2014 | vol. 111 | no. 39 | 14205–14210

CrossMark click for updates

Population-based screening for breast and ovarian cancer risk due to *BRCA1* and *BRCA2*

Efrat Gabai-Kapara[a,b,1], Amnon Lahad[b,c,1], Bella Kaufman[d], Eitan Friedman[e,f], Shlomo Segev[g], Paul Renbaum[a], Rachel Beeri[a], Moran Gal[a], Julia Grinshpun-Cohen[a], Karen Djemal[h], Jessica B. Mandell[i], Ming K. Lee[i], Uziel Beller[j], Raphael Catane[d], Mary-Claire King[i,2], and Ephrat Levy-Lahad[a,b,2]

Population-wide screening will require significant efforts to educate the public and to develop new counseling strategies, but this investment will both save women's lives and provide a model for other public health programs in genomic medicine. Women do not benefit by practices that "protect" them from information regarding their own health. They should have the choice to learn if they carry an actionable mutation in *BRCA1* or *BRCA2*.

¿Debemos añadir como criterio de estudio genético independientemente de la Hª familiar **sólo** el cáncer de ovario "seroso de alto grado"?

http://dragonflytraining.files.wordpress.com/2013/10/man-with-question-01.png