eBreast

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Práctica Cáncer de Mama

MANUAL PRÁCTICO PARA LA CONSULTA DE PACIENTES CON CÁNCER DE MAMA

NOVARTIS

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Avales

PARA INFORMACIÓN ADICIONAL, CONSULTAR EL RESTO DE LOS CAPÍTULOS

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PRÓLOGO

eBreast nace como signo de los tiempos.

No es un libro.

No es una app.

Es la respuesta a las nuevas formas de aprender, enseñar y estudiar.

Signo de los tiempos por la importancia y el impacto que tiene el cáncer de mama en nuestra sociedad y en nuestro sistema sanitario.

Signo de los tiempos por la incesante llegada de nuevos profesionales que tienen la gran responsabilidad de cuidar a nuestras pacientes afectas de cáncer de mama y con la necesidad de adquirir un conocimiento riguroso, actualizado y de acceso inmediato, a veces en la propia consulta, para poder ofrecer las mejores opciones que la evidencia científica nos proporciona.

Signo de los tiempos por la forma de enfrentarse a la información. La aparición y expansión de nuevas TIC (Tecnologías de la información y comunicación), algunas de ellas rápidamente absorbidas por las nuevas generaciones, hace preciso adaptarse a ellas.

Signo de los tiempos por el enorme volumen de información que se genera a diario y que hace precisa la intervención de revisores autorizados en cada materia, sobre todo para los clínicos. El fondo de conocimiento médico es inabarcable. Y el conocimiento y el progreso oncológicos son, actualmente, de los más importantes en la medicina moderna: por volumen de publicaciones, recursos que se destinan, impacto social, consecuencias de la enfermedad…

eBreast está dirigido a todos aquellos profesionales que atienden una consulta médica de cáncer de mama, sobre todo a los que se inician en la patología, a los que atienden a estas pacientes de forma más esporádica o simplemente a los que desean mantenerse actualizados. eBreast proporciona una consulta rápida, sencilla y, sobre todo, muy visual e interactiva. Y con este proyecto nos comprometemos a revisar periódicamente los contenidos, actualizando los datos tras los principales acontecimientos científicos del año.

Los coordinadores quisiéramos agradecer el inmenso esfuerzo realizado por todos los autores, así como el apoyo proporcionado por Novartis, y a las sociedades GEICAM, SEOM, SOLTI y a la Universidad CEU Cardenal Herrera por su aval.

No queremos dejar de olvidar el apoyo de nuestras familias y, sobre todo, a LOS/LAS PACIENTES afectos de cáncer de mama, que son el objeto de todos nuestros esfuerzos, estudios y desvelos profesionales y por tanto, los beneficiarios finales de este proyecto, que pretende ser novedoso.

Santiago Olmos Antón **Eduardo Martínez de Dueñas**

ABREVIATURAS

A	Antraciclina
AC	Adriamicina/doxorrubina, ciclofosfamida
ACT	Antraciclina-ciclofosfamida y taxano concurrente
AC-T	Antraciclina-ciclofosfamida y taxano secuencial
AC-D	Adriamicina, ciclofosfamida, docetaxel
AL	Adriamicina Liposomal
ALND	*Axillary lymph node dissection*
AMH	Agente modulador del hueso
ANA	Anastrozol
AO	Ablación ovárica
AP	Adriamicina,paclitaxel
APBI	Radioterapia parcial acelerada
AP-CMF-Q(x)	Adriamicina y paclitaxel-quimioterapia de ciclofosfamida, metotrexato y 5-FU
AP-CMF	Adriamicina y paclitaxel, ciclofosfamida, metotrexato y 5-FU
ASCO	*Sociedad Americana de Clínica Oncología*
AxRT:	*Axillary radiotherapy*
B	Bevacizumab
BAG	Biopsia con aguja gruesa
BAV	Biopsia asistida por vacío
BC	Beneficio clínico
BCS	Supervivencia específica por cáncer de mama
BOADICEA	*Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm*
BSGC	Biopsia selectiva del ganglio centinela
CAF/FAC	Ciclofosfamida, adriamicina y 5-FU
CAFM	Ciclofosfamida, adriamicina, 5-FU y metroxetato
C	Cirugía/Carboplatino
CAP	Capecitabina
CC	Cirugía conservadora
CDDP	Cisplatino
CDI	Carcinoma ductal invasivo

CDIS	Carcinoma ductal *in situ*
CDK	Cinasas dependientes de ciclinas
CEA	Antígeno carcinoembriónico
CEF/FEC	Ciclofosfamida, epirrubicina, 5-FU
CLI	Carcinoma lobulillar infiltrante
CM	Cáncer de mama
CMAJ	*Canadian Medical Association Journal*
CMF	Ciclofosfamida, metotrexato y 5-FU
CMI	Cáncer de mama inflamatorio
CMLA	Cáncer de mama localmente avanzado
CMM	Cáncer de mama metastásico
CMTN	Cáncer de mama triple negativo
cN+	Ganglios linfáticos positivos clínicamente
C-A-CMF	Cirugía-antraciclina-ciclofosfamida, metotrexato y 5-FU
C-AP-CMF	Cirugía-adriamicina, paclitaxel-ciclofosfamida, metotrexato y 5-FU
D	Docetaxel
ddAC	Dosis densas adriamicina y ciclofosfamida
DMO	Densidad mineral ósea
DX	Doxorrubicina
EBCTCG	*Early Breast Cancer Trialists' Collaborative Group*
EC	Epirrubicina, ciclofosfamida
ECG	Electrocardiograma
ECO	Ecografía
ED	Epirrubicina, docetaxel
ESA	Agente estimulador de la eritropoyesis
ESMO	European Society for Medical Oncology
EXE	Exemestano
F	Fulvestrant
FEVI	Fracción de eyección ventricular izquierda
FN	Fiebre neutropénica
GC	Ganglio centinela
GnRH	Hormona liberadora de gonadotropina

G-CSF	Factor estimulante de colonias de granulocitos
TR	Trastuzumab
HD	Altas dosis
HER/EGFR	Receptor de factor de crecimiento epidérmico humano
HNA	Hormonoterapia neoadyuvante
HR	*Hazard ratio*
HT	Hormonoterapia
IA	Inhibidores aromatasa
IAE	Inhibidor no esteroideo de la aromatasa
IANE	Inhibidor de la no esteroideo de la aromatasa
IC	Intervalo de confianza
ICT	Células tumorales aisladas
IHQ	Inmunohistoquímico
ILE	Intervalo libre de enfermedad
IPM	Irradiación parcial de la mama
ISH	Hibridación *in situ*
L	Lapatinib
LA	Linfadenectomía axilar
LET	Letrozol
LHRH	Hormona liberadora de la hormona luteinizante
LR-SLP	Supervivencia libre de progresión locorregional
MMSE	*Mini-Mental State Examination*
MNA	*Mini nutritional assessment*
MRM	Mastectomía radical modificada
MT	Marcadores tumorales
N.A	No aportado
NAB-P	nab-paclitaxel (paclitaxel unido a albúmina)
NCCN	*National Comprehensive Cancer Network*
NCI	*National Cancer Institute*
NCI-CTCAE	*National Cancer Institute Common Terminology Criteria for Adverse Events*
N.S	No significativo
NSABP	*National Surgical Adjuvant Breast and Bowel Project*

OCCR	*Ovarian Cancer Cluster Region*
OR	*Odds Ratio*
ORR	*Objective response rate*
OSNA	*One step nucleic acid amplification*
P	Paclitaxel
PA	Palbociclib
PAAF	Punción aspiración con aguja fina
PE	Progresión de la enfermedad/pertuzumab
PEPI	*Preoperative Endocrine Prognostic Index*
PER	Pertuzumab
PET	Tomografía por emisión de positrones
PF	Preservación de la fertilidad
Post-Op	Postoperatorio
PP	Profilaxis primaria
pRC	Respuesta patológica completa
Pre-Op	Preoperatorio
pRP	Respuesta parcial patológica
pRPmic	Respuesta parcial patológica microscópica
PS	Profilaxis secundaria
QoL	Calidad de vida
QT	Quimioterapia
RANKL	Ligando del receptor activador del factor nuclear k-B
RC	Respuesta completa
RCB	*Residual Cancer Burden* (enfermedad residual posquimioterapia)
RE	Receptor de estrógeno
RFS	Supervivencia libre de recaída
RH	Receptor hormonal
RMN	Resonancia magnética nuclear
ROI	Rastreo óseo isotópico/ gamma o escintigrafía ósea
RP	Receptor de progesterona/Respuesta parcial
RR	Riesgo de recaída
RS	Recurrence score

RT	Radioterapia
Rx	Radiografía
SBRT	Radioterapia estereotáctica de cuerpo
SC	Subcutáneo
SERD	Inhibidor selectivo del RE
SERMS	Modulador selectivo del receptor estrogénico
SG	Supervivencia global
SLE	Supervivencia libre de enfermedad
SLP	Supervivencia libre de progresión
SLR	Supervivencia libre de recaída
SNP	*Single nucleotide polymorphism*
SPPB	Batería corta de rendimiento físico
ST	Tratamiento sistémico
T	Taxano
TA	Tratamiento adyuvante
TAC	Tomografía axial computarizada o Docetaxel, adriamicina, ciclofosfamida
TAM	Tamoxifeno
TBCRC	*Translational Breast Cancer Research Consortium*
TC	Docetaxel y ciclofosfamida
TCH	Docetaxel, carboplatino, trastuzumab
T-DM1	Trastuzumab emtansina
TE	Terapia endocrina
TIL	*Tumor Infiltrating Lymphocites*
THP	Tiempo hasta progresión
TMA	Transplante de células madre autólogo
TN	Triple negativo
TNA	Tratamiento neoadyuvante
TR	Trastuzumab
UCGC	Unidad de consejo genético en cáncer
UI	Unidades Internacionales
V	Vinorelbina

CAPÍTULO 1. SCREENING, DIAGNÓSTICO/ ESTADIFICACIÓN Y CONSEJO GENÉTICO

1

A. CRIBADO

¿Qué beneficios aporta el cribado?

¿Existen perjuicios del cribado? Si es así, ¿cuáles son?

¿Están aceptados por todo el mundo los beneficios de realizar el cribado?

¿En todos los países existen las mismas recomendaciones?

VER RESUMEN
1. Cribado, diagnóstico/ estadificación y consejo genético

¿Qué beneficios aporta el cribado?

BENEFICIOS

Mamografía:

Nueve estudios aleatorizados y cuatro revisiones (canadiense, estadounidense, Cochrane y británica) objetivan una **reducción sobre la mortalidad por cáncer de mama** (1-6):

- ***Mujeres de 50 a 69 años:*** La reducción de la mortalidad por cáncer de mama es del 34 % en este grupo de mujeres, pero la de la mortalidad absoluta es de 50 cada 10.000 mujeres.
- ***Mujeres de 40 a 49 años:*** El beneficio en este grupo está menos claro, aproximadamente de 4 por cada 10.000 mujeres.
- ***Mujeres mayores de 69 años:*** Los datos en mujeres mayores son limitados.

Tabla 1. Revisión canadiense. *Basada en la Guía de práctica clínica CMAJ (2).*

Efecto del cribado con mamografía en el riesgo relativo de muerte por cáncer de mama estratificado por edad e intervalo de cribado						
	Intervalo de cribado < 24 meses			Intervalo de cribado ≥ 24 meses		
Rango edad	N.º ensayos	RR (IC 95 %)	Calidad evidencia	N.º ensayos	RR (IC 95 %)	Calidad evidencia
40-49	5	0,82 (0,72-0,94)	Alta	3	1,04 (0,72-1,50)	Baja
50-69	4	0,86 (0,75-0,98)	Alta	3	0,67 (0,51-0,88)	Moderada
≥ 70	No hay	-	-	2	0,68 (0,45-1,01)	Baja
Todas edades	6	0,83 (0,76-0,92)	Alta	3	0,77 (0,58-1,03)	Baja

RR: riesgo relativo, IC: intervalo de confianza

Frecuencia de realización: No existen datos definitivos. Existe un estudio observacional comparando mamografía anual frente a bianual en mujeres entre 50 y 69 años, sin diferencias en la tasa de detecciones o el pronóstico del estado.

Tipos de exploración: la sensibilidad de la mamografía disminuye enormemente en las mamas densas lo que ha llevado a la aparición de nuevas técnicas:

- Mamografía digital: Una mayor resolución de contraste, ha mejorado los resultados.
- Tomosíntesis: Reconstruye la imagen de la mama con planos paralelos, con lo que se disminuye la superposición de estructuras y mejora la detección de lesiones.

El empleo combinado de la mamografia digital y la tomosíntesis incrementa la sensibilidad diagnóstica y reduce la tasa de rellamadas (7).

Desventajas:

- Incremento en la radiación (pero por debajo de la máxima recomendada)
- Mayores tiempos de lectura/interpretación (8)

Otros métodos:

Resonancia magnética (RM) de mama:

- No existen estudios aleatorizados del efecto del cribado con RMN sobre la mortalidad.
- Una revisión sistemática comparando mamografía y RMN en mujeres de alto riesgo indica (9):
  - Sensibilidad: La sensibilidad de la RMN es mayor que la de la mamografía. Sin embargo, presenta una tasa alta de falsos positivos.

- Especificidad: La especificidad de la RMN es menor que la de la mamografía. Las dos pruebas juntas presentan una sensibilidad alrededor del 95 % y una especificidad aproximada del 76 al 78 %. Ante estos datos, en la **actualidad solo se recomienda realizar ambas pruebas en mujeres de alto riesgo (mutaciones en *BRCA*), las siguientes indicaciones**, aunque no existan datos de reducción de la mortalidad (10):
  - **Portadoras de mutación BRCA**
  - **Portadoras de genes de alta penetrancia (Li Fraumeni, etc...)**
  - **Antecedentes de irradiación torácica entre los 10 a 30 años de edad**
- Pauta: RMN de mama anual desde los 25 años y añadir mamografia desde los 30–40 años.

Autoexploración:

No existen datos de beneficio. **No se recomienda.**

¿Existen perjuicios del cribado? Si es así, ¿cuáles son?

PERJUICIOS DEL CRIBADO (3)

Sobrediagnóstico y tratamiento resultante de cánceres insignificantes: consiste en el diagnóstico de cánceres que nunca hubieran causado síntomas o muerte a lo largo de la vida de una mujer. El problema es que actualmente no hay una forma segura de distinguirlos, por lo que casi siempre se recomienda algún tipo de tratamiento. Se calcula que entre el 20 y el 54 % de los tratamientos obedecen a sobrediagnósticos.

- **Falsos positivos: Conllevan pruebas adicionales y ansiedad.** De media, en cada examen de detección, el 10 % de las mujeres serán llamadas para someterse a más pruebas y solo 5 de cada 100 mujeres que lo hagan presentarán cáncer.
- **Falsos negativos: Producen un falso sentido de seguridad y posible retraso en el diagnóstico de cáncer.** Entre el 6 y el 46 % de las mujeres con cáncer infiltrante tendrán mamografía negativa, sobre todo en mamas densas.
- **Cáncer de mama inducido por radiación:** Extremadamente poco probable por la dosis de radiación (4 mSv/mamografía). La latencia es > 8 años y el aumento de riesgo dura toda la vida.
- **Coste-efectividad en mujeres de 40 a 49 años:** el coste en estas mujeres es cinco veces mayor que en las de > 50 años. Un estudio utilizando el modelo de Markov demuestra ratios de 21.400 $ por año salvado de vida para mujeres entre 50 y 69 años, frente a 105.000 $ en las de 40 a 49.

¿Están aceptados por todo el mundo los beneficios de realizar el cribado?

CONTROVERSIA DEL CRIBADO

Recientemente se han puesto en duda los beneficios del cribado:

Sobre la disminución de la mortalidad:

El metaanálisis de la Cochrane, encuentra que **el beneficio sobre la mortalidad por cáncer de mama que se objetiva en el metaanálisis es poco fiable**, sesgado a favor del cribado, principalmente a causa de una clasificación errónea de la causa de la muerte. Los ensayos con aleatorización adecuada no encuentran un efecto del cribado en la mortalidad del cáncer de mama, después de 10 años (RR 1,02, IC 95 % 0,95 a 1,10), o en la mortalidad por cualquier causa después de 13 años (RR 0,99, IC 95 % 0,95 a 1,03) (3).

Sobre los perjuicios del cribado:

La conclusión de los autores es que si asumimos que el cribado reduce la mortalidad por cáncer de mama en un 15 %, el sobrediagnóstico y sobretratamiento es del 30 %. Esto significa que:

- Por cada 2.000 mujeres, a los 10 años se evita una muerte por cáncer de mama.
- 10 mujeres sanas serán tratadas de forma innecesaria.
- Más de 200 mujeres experimentarán importantes trastornos psicológicos, como ansiedad e incertidumbre, durante años, debido a los resultados falsos positivos.

¿En todos los países existen las mismas recomendaciones?

RECOMENDACIONES DE GRUPOS DE EXPERTOS

Lo que dicen las guías:

- ***Grupos EE. UU.:*** la mayoría recomiendan cribado con mamografía desde los 40 años. Actualmente estas recomendaciones están siendo revisadas.
- ***Canadá:*** recomiendan cribado con mamografía en mujeres desde los 50 años; a las mujeres entre 40 a 49 años, dependiendo del riesgo individual.
- ***Unión Europea:*** cribado con mamografía bianual para mujeres de 50 a 69 años dentro de un plan organizado y con control de calidad; entre los 40 y 49 años, se debe discutir con las pacientes sobre los riesgos y beneficios del cribado y, si se realiza, debe ser con mamografías anuales o cada 18 meses.

CONCLUSIONES (11-13)

- ***Mujeres de 50-69 años:*** cribado con mamografía (Grado 1A) anual o bianual (Grado 2C)
- ***Mujeres de 40-49 años:*** discutir con las pacientes sobre riesgos y beneficios (Grado 2B)
- ***Mujeres > de 69 años:*** solo cribado si la expectativa de vida > o igual a 10 años (Grado 2B)
- ***Mujeres alto riesgo (BRCA o riesgo >20-25 %):*** mamografía y RMN mama anual

Sistema de graduación de evidencias y recomendaciones SIGN (14, 15)

B. DIAGNÓSTICO

¿Cómo se diagnostica el cáncer de mama?

¿En qué me debo centrar en la exploración física?

¿Qué pruebas de imagen se deben solicitar para el diagnóstico?

¿Cuáles son los diferentes tipos de biopsia y cuál es el más aconsejable?

¿Qué determinaciones histológicas se deben realizar y cómo?

¿Cuándo se considera que la muestra es positiva para RH?

¿Cómo se deben considerar los resultados de HER2?

¿Qué valora Ki-67?

¿Existen otros estudios a tener en cuenta?

¿Cómo se debe valorar a la paciente tras el diagnóstico histológico de un carcinoma de mama?

¿Cómo se diagnostica el cáncer de mama?

El proceso diagnóstico ante sospecha de cáncer de mama va a comprender tres aspectos: exploración física, estudio radiológico y estudio histológico.

¿En qué me debo centrar en la exploración física?

EXPLORACIÓN FÍSICA

- **Inspección:** Con paciente sentada y elevación de brazos. Detectar asimetrías, retracciones, etc.
- **Palpación** de la mama y valoración de las zonas ganglionares de drenaje, especialmente axilares, supra e infraclaviculares.

¿Qué pruebas de imagen se deben solicitar para el diagnóstico?

PRUEBAS DE IMAGEN

Se basa fundamentalmente en la mamografía.

- ***Mamografía bilateral:*** **Es la técnica fundamental por su sensibilidad y especificidad**. La estandarización de la terminología en los informes mamográficos se consigue con el sistema BI-RADS.(16)
- ***Ecografía mamaria:*** Es complementaria a la mamografía, a la que no debe sustituir. Útil en mamas densas y mujeres jóvenes, permite además diferenciar entre naturaleza sólida o quística de los nódulos.
- ***RM mama:*** Alta sensibilidad y problemas de especificidad.

  Indicaciones (17):

  - Cribado en pacientes con mutaciones BRCA y otras de alta penetrancia
  - Metástasis axilares de tumor primario desconocido
  - Diferenciar lesiones cicatriciales de recidiva y en prótesis
  - Valorar respuesta a quimioterapia neoadyuvante
  - Mamografías no concluyentes
  - Sospecha de multicentricidad y en tumores lobulillares

VER RESUMEN
1. Cribado, diagnóstico/ estadificación y consejo genético
b) Estudio Histológico

¿Cuáles son los diferentes tipos de biopsia y cuál es el más aconsejable?

DIAGNÓSTICO HISTOLÓGICO

Biopsia diagnóstica

Los procedimientos para el diagnóstico anatomo-patológico de lesiones sospechosas de cáncer de mama que se usan en la actualidad son:

- **PAAF** (punción aspiración con aguja fina): no se aconseja como diagnóstico. Se utiliza para clarificar la naturaleza de ganglios axilares sospechosos.
- **BAG** (biopsia con aguja gruesa): también conocida como *TruCut* o *core*, se realiza guiada por ecografía. **Es la técnica recomendada**, ya que aporta más material tumoral para la realización de los estudios que se recomiendan actualmente: tipo histológico, grado histológico y nuclear, RH, sobreexpresión del receptor-2 del factor de crecimiento epidérmico humano (HER2) y Ki-67.
- ***Biopsia estereotáxica:*** es una biopsia guiada por mamografía que se realiza cuando no es posible realizar BAG, generalmente cuando no es posible detectar la lesión con ecografía, entre otros casos.

- **BAV** (biopsia asistida por vacio): Utiliza una aguja, de mayor grosor que la BAG, que contiene un bisturí rotatorio en su interior. La aguja va conectada a un sistema de aspiración de forma que las muestras se obtienen combinando el efecto del bisturí rotatorio con la aspiración por el vacío. Solo realiza una punción. No solo permite realizar biopsia sino también extirpar de forma completa una lesión específica.
- ***Biopsia escisional*** (o quirúrgica): guiada por arpón, en lesiones en que no es posible obtener una confirmación histológica por BAG.

Actualmente se recomienda **dejar un marcador tanto en la localización de la biopsia como en los ganglios estudiados** (18).

¿Qué determinaciones histológicas se deben realizar y cómo?

Estudio inmunohistoquímico (IHQ)

Se deben determinar en todas las pacientes los RH, la sobreexpresión de HER2 y el Ki-67, ya que nos van a servir para clasificar a las pacientes en diferentes subtipos histológicos (subtipos intrínsecos), establecer el pronóstico y orientarnos en el tratamiento.

¿Cuándo se considera que la muestra es positiva para RH?

a.- Receptores hormonales:

Receptor positivo:

En la actualidad, la tinción de las células tumorales en un ***1 % o más*** **se considera como resultado positivo para el receptor**, sea de estrógenos o progesterona (19, 20) (anteriormente se exigía una positividad de al menos un 10 %). De todas formas, sigue habiendo autores que ponen en duda el comportamiento hormonodependiente de los tumores que expresan receptores en el 1 al 9 %.

Para considerar la muestra como positiva para RH tiene que haber al menos un receptor (estrógenos o progesterona) positivo.

Intensidad del receptor:

A parte del porcentaje de células que expresan los receptores, también debe darse la intensidad de la tinción, que puede indicarse de dos formas:

- **En cruces:** (+) poco intensos, (++) moderada intensidad y (+++) alta intensidad.
- **Puntuación de Allred:** Es un método que combina el porcentaje de células que contienen RH junto a la "intensidad" de la tinción, y se clasifican los resultados en una escala de 0 a 8.

Tabla 2. Puntuación de Allred. Basada en *Qureshi A. et al. (21).*

Puntuación	% tinción	Intensidad	Observación
0	Ninguna	0	Ninguna
1	1 %	1	Débil
2	1-10 %	2	Intermedia
3	10-33 %	3	Fuerte
4	33-66 %		
5	66-100 %		

Suma del porcentaje de la tinción y la intensidad	
Puntuación total	**Interpretación**
0-2	Negativo
3-8	Positivo

¿Cómo se deben considerar los resultados de HER2?

b.- Sobreexpresión de HER2

La determinación se realiza por IHQ y el resultado se da en forma de cruces (de 1 a 3).

- **HER2 NEGATIVO: (0) ó (+):** ninguna expresión (0) o una cruz.
- **HER2 POSITIVO: (+++):** expresión de tres cruces.
- **HER2 EQUÍVOCO: (++):** dos cruces. **En este caso es necesario realizar una prueba de hibridación *in situ* (ISH)** para determinar si existe una amplificación en el gen (22).

Los resultados de la ISH pueden ser:

- ***Amplificado:*** Existe, pues, sobreexpresión de HER2.
- ***No amplificado.***

En algunos centros se confirma el resultado de la IHQ de (+++) realizando una prueba ISH. En caso de discordancia, predomina el resultado de ISH.

¿Qué valora Ki-67?

c.- Ki-67

Es un indicador de proliferación. El problema de esta determinación es que en el momento actual existe una falta de estandarización en la técnica, aunque recientemente se han hecho esfuerzos por conseguirla (23, 24).

Se da en porcentaje:

- Baja proliferación: < 13 %
- Proliferación intermedia: > 13-15 %
- Alta proliferación: 30-35 %

¿Existen otros estudios a tener en cuenta?

d.- Linfocitos Intratumorales (TILs)

- Se han propuesto como biomarcador por su **valor predictivo y predictor de respuesta** a terapia neoadyuvante en los subtipos Triple Negativo y HER2(+)
- Se valoran los del compartimento estromal (linfocitos y células plasmáticas)
- A mayor aumento mejor pronóstico: Por cada 10% de aumento produce un 15-20% de mejoría en supervivencia (25)
- **No está consensuado su uso**. Problemas de reproductibilidad (26)

e.- Mutación germinal de BRCA 1/2

Debe ofrecerse a pacientes con carcinoma de mama de grupos alto riesgo (27):

- Criterios de remisión a consejo genético (ver más adelante)
- Carcinoma triple negativo antes de los 60 años
- Cáncer de mama en el varón

¿Cómo se debe valorar a la paciente tras el diagnóstico histológico de un carcinoma de mama?

Una vez diagnosticada histológicamente o ante problemas diagnósticos en la sospecha de tumoración maligna, **la paciente debe ser valorada por un *comité multidisciplinar de tumores mamarios***, compuesto al menos por: un cirujano experto en cirugía de mama, un radiólogo experto en mamografía, un patólogo, un oncólogo médico y un radioterapeuta, donde se toma la decisión terapéutica y se diseña y coordina cómo completar el diagnóstico, si es necesario, y las diversas acciones terapéuticas y su secuencia.

C. ESTADIFICACIÓN

¿Existen variaciones entre el estudio de anatomía patológica en la pieza quirúrgica y la biopsia? ¿Cómo nos enfrentamos al informe de anatomía patológica?

¿Cómo valoramos el riesgo de recaída de la paciente?

¿Cómo determinamos el subtipo intrínseco?

¿Cuáles son y cómo valoramos los factores pronósticos clásicos?

¿Qué es y cuándo utilizar una firma genética para determinar el riesgo?

Ya lo tengo todo; ¿cómo estadifico la enfermedad?

¿Hay que hacer estudio de extensión a todas las mujeres?

¿Qué pruebas se solicitan para el estudio de extensión?

¿Existen variaciones entre el estudio de anatomía patológica en la pieza quirúrgica y la biopsia? ¿Cómo nos enfrentamos al informe de anatomía patológica?

ESTUDIO DE LA PIEZA QUIRÚRGICA

El informe histopatológico debe realizarse de una forma protocolizada y debe recoger una descripción macroscópica y microscópica. **Básicamente, se estudian los mismos aspectos ya presentados en la biopsia, además del tamaño tumoral, estado de bordes e infiltraciones y estudio ganglionar:**

- Tipo histológico, tamaño, existencia de componente *in situ* y uni o multicentricidad
- Estado de bordes (libres o infiltrados) y distancia del tumor al borde en mm
- Afectación de piel o músculo e infiltración vascular o linfática
- Grado histológico y nuclear
- Estudio ganglionar: n.º de ganglios extirpados y n.º de ganglios afectos; rotura capsular o no
- RH
- Sobreexpresión de HER2
- Ki-67

No es necesario repetir las determinaciones de RH y HER2 si se han realizado en la biopsia; en cambio, sí se recomienda repetir el Ki-67, ya que se detectan cambios con frecuencia (mayor en la pieza).

¿Cómo valoramos el riesgo de recaída de la paciente?

VALORACIÓN DEL RIESGO

Se seguirán los siguientes pasos para la valoración del riesgo:

1. *Clasificar por subtipo intrínseco: generalmente se valora la IHQ*
2. *Valoración de los factores pronósticos clásicos*
3. *Determinar si la paciente precisa aplicar una firma genética para determinación de riesgo*

¿Cómo determinamos el subtipo intrínseco?

Clasificar por subtipo intrínseco

Estos subtipos surgen del análisis de miles de genes y se agrupan según la similitud de la expresión. Es lo que se conoce como ***análisis no supervisados***.

En el cáncer de mama se detectaron cinco grupos de pacientes con evoluciones diferentes: luminal A, luminal B, Basal, HER2 y normal (28). Existen plataformas comerciales para determinarlos (PROSIGNA, etc.), pero son costosas, por lo que en la clínica diaria se utiliza una aproximación fenotípica mediante técnicas de IHQ. En 2008, se presentaron dos subestudios (del BCIRG 001 y PACS 01) (29) que indicaban que existe cierta concordancia entre estos subtipos intrínsecos y los determinados por IHQ.

Tabla 3. Resumen de subtipos intrínsecos de cáncer de mama por IHQ. ***Adaptado de guías SEOM (30) y ESMO (20)***

Subtipo intrínseco	Características	Tipos	Características	Pronóstico	Tratamiento principal
LUMINAL	RH(+)/ HER2(-)	**A**	RE(+) >60 % y RP(+) y Ki-67 < 13-15 %	El de MEJOR PRONÓSTICO	***HT***
		B	RE(+) <60 % ó RP(-) ó Ki-67 > 15 %	PRONÓSTICO VARIABLE	QT seguido ***HT***
HER2(+)	HER2(+++) o ISH amplificado	RH(-)		BUEN PRONÓSTICO (si se trata)	QT + ***antiHER2***
		RH(+)	**Luminal B HER2**		QT + ***antiHER2*** + ***HT***
TRIPLE(-)	RE(-)/RP(-)/HER2(-)			El de PEOR PRONÓSTICO	***QT***

HT: hormonoterapia; QT: quimioterapia; RE: receptor de estrógeno; RP: receptor de progesterona.

Subtipo luminal A:

- Baja proliferación, considerada como Ki-67 ≤ 13 %.
- Alta expresión de RH (RH(+++)).
- Escasa sensibilidad a la quimioterapia.
- El de mejor pronóstico.

Subtipo luminal B:

- Proliferación considerada como Ki-67 > 14 %.
- RH(+) pero de menor expresión (RP(-), RE < 50 %, etc.).
- Más sensible a quimioterapia y peor pronóstico que el luminal A.

Subtipo HER2:

- 10-15 % de los tumores.
- **Dos poblaciones diferentes** y cuyo comportamiento también es muy diferente:
  - ***HER2(+)/RH(-)*:** muy sensibles al tratamiento de quimioterapia asociado a tratamiento antiHER2 (trastuzumab, trastuzumab/pertuzumab y lapatinib, T-DM1), obteniéndose largas supervivientes en la enfermedad metastásica, incluso con metástasis cerebrales.
  - ***HER2(+)/RH(+)*** (enfermedad triple positiva): estas pacientes deberían ser estudiadas aparte de las que no expresan RH, ya que tienen un comportamiento diferente:
    - Responden menos a la quimioterapia con tratamiento antiHER2, como han demostrado todos los estudios de neoadyuvancia (31), donde sus tasas de pRC son inferiores de forma estadísticamente significativa cuando se las compara con las de las pacientes HER2(+)/RH(-).
    - Responden menos al tratamiento hormonal solo, lo que hace pensar que las dos vías (HER2 y RH) deberían ser bloqueadas a la vez, hipótesis que comienza a ser estudiada.

A pesar de lo comentado, en enfermedad metastásica, la supervivencia es mayor en las pacientes triple (+) (32).

Subtipo Triple Negativo (TN):

- 10 a 15 % de los tumores.
- Definido como RE(-), RP(-) y HER2(-). Solo en el 75 % de los casos son *Basal Like* (un 25 % de los TN son del resto de subtipos).

- En realidad **es un cajón de sastre** donde existen varios subtipos más que están en estudio: BRCA, *Clauding-Low*, receptores de andrógenos (+), etc.
- Engloba subtipos clínicos que se caracterizan por una gran agresividad, una alta proliferación (>Ki-67, G3…) y un mal pronóstico en general. A pesar de que presenta una alta sensibilidad a la quimioterapia, **es el grupo de peor pronóstico**.

¿Cuáles son y cómo valoramos los factores pronósticos clásicos?

Valoración de los factores pronósticos clásicos

Tras clasificar el tumor en subtipo intrínseco, hay que valorar los factores clásicos para intentar afinar más en el riesgo. Es importante sobre todo en los luminales, ya que las recomendaciones de tratamiento que hemos visto en la tabla pueden cambiar; por ejemplo que un luminal A precise quimioterapia o que un luminal B no la precise.

1. **Afectación ganglionar:** **es el factor más importante**. A mayor afectación peor pronóstico (33, 34).
   - Ganglios (-): bajo riesgo; SG a los 10 años aproximadamente del 83 %
   - Ganglios (+): Riesgo alto: N1: 1-3 ganglios SG aproximadamente del 73%
     N2: 4-9 ganglios SG aproximadamente del 46%
     N3: > 10 ganglios SG aproximadamente del 28 %
2. **Tamaño tumoral: el segundo en importancia**: a mayor tamaño peor pronóstico.
   - **Bajo riesgo**: Tumores < 2 cm: Riesgo recaída (RR) a 20 años entre 10 % (T1) y 25 % (T2).
   - **Alto riesgo:** Tumores > 2 cm: RR (20 a) 50 % (T2)
3. **Grado de diferenciación**: a menor diferenciación peor pronóstico.
4. **Edad**: < 30 años riesgo alto.
5. **Tipo histológico**: existen subtipos de mejor pronóstico que son:
   - Papilar puro, tubular y mucinoso.
   - Cáncer medular: tiene mejor pronóstico que el carcinoma ductual invasivo (CDI) pero no tanto como los anteriores.
6. **Receptores hormonales (RH)**: es **un factor pronóstico y predictivo de respuesta**.
   - La positividad se asocia a menor agresividad (factor pronóstico), aunque tiene recaídas más tardías (> 10 años) y predice probabilidad de respuesta al tratamiento hormonal (factor predictivo).
   - Los tumores RH (-) tienen peor supervivencia, mayor tasa de recaídas y son más precoces, junto a más afectación visceral.

¿Qué es y cuándo utilizar una firma genética para determinar el riesgo?

Determinar si la paciente precisa aplicar una plataforma genética

Las firmas genéticas surgen de los análisis de expresión génica, que se denominan también **análisis supervisados**.

La mayoría se han desarrollado analizando ***pacientes de edad inferior a 55 años, RH(+), sin afectación ganglionar*** o hasta tres ganglios afectos y *naive* al tratamiento. El objetivo de estas firmas, independientemente de cómo estiman el pronóstico, es definir qué pacientes se benefician de recibir quimioterapia adyuvante.

Tabla 4. Plataformas genéticas de valoración de riesgo. Creada por el autor.

	Oncotype DX®	***Prosigna®***	***Mammaprint®***	***EndoPredict®***
Validación	Prospectiva	Retrospectiva	Prospectiva	Retrospectiva
Ganglios (-) **ganglios (+)**	sí no (en estudio)	sí sí	sí sí	sí no
Indice valoración	RS < 25 bajo riesgo de recaída	ROR	ALTO/BAJO RIESGO DE RECAÍDA	
Predicción	Riesgo de recaída con HT Beneficio de QT	Riesgo de recaída con HT	Riesgo de recaída con HT	Riesgo de recaída con HT

HT= hormonoterapia; QT= quimioterapia; ROR= *risk of recurrence*; RS= *recurrence score;

Todas estas plataformas también permiten una reclasificación de las pacientes, de tal forma que pacientes que considerábamos de buen pronóstico por las características clínicas, etc. pueden ser de mal pronóstico y viceversa.

Las más desarrolladas son MammaPrint® y Oncotype DX®.

En la actualidad está aceptada por parte de diferentes consejerías de sanidad la utilización de dichas firmas para **tomar la decisión del tipo de tratamiento adyuvante** en aquellas pacientes luminales (RH(+)/HER(-)) con perfil dudoso después de haber realizado las dos valoraciones anteriores: tumores de hasta 5 cm, N0 o bien N1 con micrometástasis y algún factor de riesgo (30):

- Ki-67 intermedio (15 a 30 %)
- Poca expresión de RE (<60 %)
- Receptor de progesterona negativo (RP(-))

Tras la publicación de las actualizaciones de los resultados de los ensayos Taylor X (35) y MINDACT (36) sobre la utilidad clínica de las plataformas, solo NCCN y ASCO han actualizado sus recomendaciones, (37) para las pacientes RH(+)/HER2(-) que se resumen en las tablas siguientes.

Tabla 5. Utilización de plataformas. GUIAS ASCO 2022 (38)

ASCO 2022	Subtipo	Ganglios	Oncotype	MammaPrint	EndoPredict	BCI
Mujeres posmenopausicas o Mujer > 50 años	HER2(-)/ RH(+)	N0	si	si	si	si
		N1(1-3)	si	si	si	si
		N2(4-9)	No evidencia para su utilización			
Premenopáusicas		N0	si	si		
		N1	Los datos actuales indican beneficio de la QT independientemente del resultado del test genético			
	HER2(-)/RH(-)	NO INDICADO				
	HER2(+)/ RH(+)	NO INDICADO				

BCI: Breast Cancer Index

Se puede ofrecer BCI a pacientes con 0-3 ganglios positivos que recibieron 5 años de terapia endocrina sin evidencia de recurrencia para guiar las decisiones sobre la terapia endocrina extendida.

Tabla 6. Utilización de plataformas. GUIAS ASCO 2022 (38)

ONCOTYPE	Subtipo	Ganglios	RS	Mujer ≤ 50 años	Mujer > 50 años
	HER2(-)/RH(+)	N0	< 16	Solo HT*	Solo HT*
			16-25	QT seguido de HT	
			> 25		QT seguido de HT
		N(+)	Valorar QT		
	HER2(-)/RH(-)	NO INDICADO			
	HER2(+)/RH(+)	NO INDICADO			

QT: quimioterapia; HT: hormonoterapia
*La QT ofrece poco o ningún beneficio

Ya lo tengo todo; ¿cómo estadifico la enfermedad?

CLASIFICACIÓN TNM

Una vez tenemos todos los datos, tenemos que clasificar por el TNM del cáncer de mama.

¿Hay que hacer estudio de extensión a todas las mujeres?

ESTUDIO DE EXTENSIÓN

El cáncer de mama se considera una enfermedad sistémica con gran capacidad para producir metástasis. Por este motivo, en el momento del diagnóstico inicial se pueden realizar una serie de pruebas complementarias para descartar la existencia de metástasis a distancia, lo que nos permite conocer el pronóstico con exactitud y programar la secuencia terapéutica más adecuada. Pero no todas las mujeres tienen el mismo riesgo de presentar metástasis, por lo que las pruebas deben ser en cierta forma individualizadas:

- Las pacientes con tumores de bajo riesgo definidos como ganglios negativos o RH(+) y baja proliferación tienen un riesgo de tener metástasis inferior al 5 %, por lo que no se aconseja realizarlo si no hay signos o síntomas de alerta (síntomas, alteraciones analíticas, etc.)(20, 39).

¿Qué pruebas se solicitan para el estudio de extensión?

Pruebas

- Analítica: con hemograma y bioquímica hepática.
- Marcadores tumorales:
  - Es un tema controvertido, ya que se pueden elevar por otros tumores y también en procesos benignos de mama, afecciones inflamatorias de órganos epiteliales y tabaquismo (antígeno carcinoembrinoario (CEA)).
  - A pesar de su utilización en la práctica clínica, las guías clínicas no recomiendan su utilización en el cribado, diagnóstico, estadificación o seguimiento en pacientes libres de enfermedad (donde habitualmente sí se utilizan en la práctica).
  - Se recomienda su uso en pacientes metastásicas para valorar la efectividad del tratamiento.
  - Marcadores utilizados: Ca 15.3 y CEA.
- Radiografía (Rx) tórax, ecografía abdominal o tomografía axial computarizada (TAC) toracoabdominal.
- ROI (rastreo óseo isotópico/gamma o escintigrafía ósea): recomendado solo en pacientes con alto riesgo (G(+), tumores grandes…). En estadios iniciales sin clínica ósea y sin elevación de fosfatasa alcalina puede evitarse realizarla.
- Estudio cardiológico: hay que realizar electrocardiograma (ECG). El control de fracción de eyección se realiza solo si se van a utilizar fármacos cardiotóxicos y/o hay factores de riesgo de cardiotoxicidad.
- PET (tomografía por emisión de positrones)/TAC: su utilidad está en estudio en la actualidad, siendo su única indicación la elevación de marcadores séricos sin evidencia de enfermedad tumoral en las pruebas radiológicas convencionales.

D. CONSEJO GENÉTICO

¿Es frecuente el cáncer de mama familiar?

¿Qué genes intervienen?

¿Cuándo hay que solicitar un estudio genético?

¿A quién hay que realizarle el estudio genético?

¿Si existe la mutación, qué medidas se pueden tomar?

INTRODUCCIÓN

¿Es frecuente el cáncer de mama familiar?

Solo **el 5-10 % de los cánceres de mama se consideran hereditarios** y, por tanto, debido a una mutación heredada de uno de los padres (línea germinal), siendo las mutaciones más frecuentes las de BRCA 1/2 seguidas de PALB2. En **el 15-20 % existen casos de agregación familiar sin presentar un patrón de herencia conocido**.

La mayoría de los síndromes hereditarios de cáncer obedecen a un patrón de herencia autosómica dominante (50 % de probabilidad de heredar la mutación).

La penetrancia de estas mutaciones es con frecuencia incompleta y una proporción variable de individuos, a pesar de ser portadores de la mutación, no padecerán cáncer (la penetrancia se define como la probabilidad de que el portador desarrolle un cáncer a lo largo de su vida y suele expresarse como riesgo acumulado a los 70 años).

¿Qué genes intervienen?

Tabla 7 Genes implicados en cáncer de mama y ovario familiar. ***Creada por el autor*****.**

Gen	Síndrome	Herencia	Penetrancia	Cánceres	Alt clínicas
P53	Li-Fraumeni			Sarcomas, osteosarcomas tumores SNC, mama, leucemias	
PTEN	Cowden	Autosómica dominante	~100 %	Tiroides, mama, endometrio	Lesiones mucocutáneas, Hamartomas
STK11	Peutz-Jeghers	Autosómica dominante	~100 %	Gastrointestinales, mama, ovario (no epitelial)	Pigmentación mucocutánea Poliposis hamartomatosa
BRCA	Hereditario mama y ovario	Autosómica dominante	Alta penetrancia	Mama, ovario (epitelial), próstata, páncreas, colon	

BRCA1, BRCA2

- Son genes encargados de la reparación del ADN.
- Sus mutaciones son las más importantes por su frecuencia y las que más frecuentemente se asocian al cáncer de mama/ovario hereditarios.
- Mutaciones en línea germinal de alta penetrancia y herencia autosómica dominante.
- Las mutaciones más frecuentes de los genes *BRCA* son pequeñas mutaciones, que en población española tienen una prevalencia alrededor del 24 %(40). Por otra parte, existen los grandes reordenamientos con mucha menor prevalencia (*por debajo del 2 %*)(40).
- Si se considera realizar tests múltiples, algunas guías recomiendan incluir TP53, ATM, PALB2, BRIP1, RAD51C y RAD51D(41). Actualmente, las mutaciones en ATM y PALB2 deben considerarse de alto riesgo, recomendándose considerar el control con RMN mama(42).

Tabla 8. Gen mutado (36).

GEN MUTADO		
	BRCA 1	BRCA2
CÁNCER DE MAMA	55 %	47 %
CÁNCER DE OVARIO	39 %	17 %

Riesgo acumulado de cáncer de mama y ovario a los 70 años (40)

Las personas con mutación *BRCA* presentan también riesgo de presentar otros tumores:

1.- ***Mutaciones en BRCA1, presentan además un riesgo elevado de (40)***:

- Cáncer de colon y de próstata
- Cáncer de páncreas (RR=2.26)
- Carcinoma de endometrio (RR=2.65) y cérvix (RR=3.72)

2.-***Mutaciones en BRCA2 (40)***:

- Menos relacionadas con el cáncer de ovario (aunque existe un dominio denominado OCCR [*Ovarian Cancer Cluster Region*], donde las mutaciones parece que tienen un riesgo más elevado de padecerlo)
- Cáncer de próstata y carcinoma laríngeo
- Cáncer de estómago (RR=2,59), páncreas (RR=3,51) y vías biliares (RR=4,97)
- Melanoma maligno (RR=2,58)

¿Cuándo hay que solicitar un estudio genético?

CRITERIOS PARA REMITIR A UNA UNIDAD DE CONSEJO GENÉTICO DEL CÁNCER (UCGC)

Tabla 9. Criterios para remitir a una unidad de consejo genético del cáncer (UCGC). Adaptado de la guía SEOM (30)

1 caso de cáncer en la familia	Cáncer de mama y cáncer de ovario **sincrónico** o **metacrónico** en la misma persona Cáncer de mama diagnosticado a**ntes de los 40 años** Cáncer de mama **bilateral**, cuando el **1.º** fue diagnosticado **antes de los 50 años** Cáncer de mama **triple negativo** (CMTN) diagnosticado **antes de los 60 años** **Carcinoma de ovario seroso-papilar de alto grado** **Cáncer de mama metastásico HER2(-) elegible para tratamiento con inhibidores PARP** **Mutación somática BRCA con frecuencia alélica > 30%**
2 casos de cáncer en la familia	Cáncer de mama bilateral + cáncer de mama diagnosticado antes de los 50 años 1 cáncer de mama en el **varón** 2 cánceres de mama diagnosticados antes de los 50 años Cáncer de mama + cáncer de ovario Cáncer de mama antes de los 50 años y cáncer próstata o páncreas < 60 años
≥3 casos de cáncer en la familia	≥3 casos de cáncer de mama y/o cáncer de ovario y/o cáncer páncreas o próstata (Gleason ≥ 7)

¿A quién hay que realizarle el estudio genético?

SELECCIÓN DE LA CANDIDATA AL ESTUDIO GENÉTICO

En caso de haber varios miembros afectos vivos se dará preferencia al caso índice familiar, que tiene más probabilidad de tener la mutación, por los siguientes criterios:

- La mujer diagnosticada de cáncer de ovario
- La mujer diagnosticada a edad más precoz
- La mujer diagnosticada de cáncer de mama bilateral
- El hombre diagnosticado de cáncer de mama

Hay que añadir que, a pesar de cumplir los criterios, aproximadamente en más del 70 % de los casos índice no se encuentran mutaciones patogénicas, lo que se denomina como ***casos no informativos***; o la presencia de variantes de efecto desconocido. En estos casos se puede aproximar el riesgo mediante herramientas informáticas como *Breast and OvarianAnalysis of DiseaseIncidence and CarrierEstimationAlgorithm* (BOADICEA).

¿Si existe la mutación, qué medidas se pueden tomar?

VER RESUMEN
1. Cribado, diagnóstico/ estadificación y consejo genético
d) Medidas de Reducción de Riesgo

MEDIDAS DE REDUCCIÓN DEL RIESGO TRAS LA DETECCIÓN DE MUTACIÓN EN BRCA

I/ Prevención: Dieta y estilo de vida

Aunque no existe un nivel de evidencia alto, parece razonable recomendar a las mujeres con alto riesgo de cáncer de mama reducir la ingesta calórica total, moderar el consumo de alcohol, evitar la obesidad y realizar ejercicio físico con regularidad (43).

II/ Seguimiento

- **Es la recomendación directiva**

  Dado que la mamografía y ecografía son relativamente poco sensibles en este grupo de mujeres, debido a la alta densidad mamaria y las rápidas tasas de crecimiento tumoral, ***se recomienda la realización de una RMN mamaria junto a la mamografía*** (44).

Tabla 10. Seguimiento en portadoras de mutaciones. Guía SEOM 2019.

Gen	Breast cancer screening	Ovarian cancer screening	Other cancer screening
BRCA1/BRCA2	Women Annual breast MRI with contrast from the age of 30–70 years **(II,A)**[a,b] Annual mammography from the age of 30 to 75 years **(II,A)**[c,d] Men No evidence of clinical benefit of breast screening **(III, C)**. Consider mammography in the case of gynecomastia	6-monthly, transvaginal ultrasound and Ca.125 may be considered from the age of 30 until the age of RRSO or for those who have not elected RRSO **(III,C)**	Annual screening with PSA for prostate cancer from the age of 40 years, Recommended in BRCA2, and offer in BRCA1 **(II,B)** Consider pancreatic cancer surveillance with EUS and MRI in carriers with a first-degree-relative with pancreatic cancer from the age of 50 or 10 years before the youngest diagnosis in the family **(II,C)** Consider skin and eye examination for melanoma screening according personal/familiar risk factors **(III,C)**
PALB2	Annual breast MRI with contrast from the age of 25 years **(III,A)**[c] Annual mammography from the age of 35 years **(III,A)**[c]	Moderate evidence of increased OC risk. Insufficient evidence for recommend RRSO or screening **(III,C)**	Discuss pancreatic cancer surveillance with EUS and MRI in carriers with a first-degree-relative with pancreatic cancer from the age of 50 or 10 years before the youngest diagnosis in the family **(II,C)**
ATM	Consider annual breast MRI with contrast from the age of 40 years according personal/familiar risk factors **(III,A)**[c] Annual mammography from the age of 40 years **(III,A)**[c]	Potential increase in OC risk. Insufficient evidence for recommend RRSO or screening **(III,C)**	Consider offer pancreatic cancer surveillance with EUS and MRI in carriers with a first-degree-relative with pancreatic cancer from the age of 50 or 10 years before the youngest diagnosis in the family **(II,C)**
CHEK2	Consider annual breast MRI with contrast from the age of 40 years **(III,A)**[c] Annual mammography from the age of 40 years **(III,A)**[c]	No evidence of increased risk	Consider colonoscopy from the age of 40 years, and repeat every 5 years **(II,B)**
RAD51C	Unknown o insufficient evidence for BC risk Recommend BC screening based only on family history	No evidence of clinical benefit. Consider offer annual transvaginal ultrasound and Ca.125 from the age of 40 until the age of RRSO or for those who have not elected RRSO **(III,C)**	
RAD51D	Unknown o insufficient evidence for BC risk Recommend BC screening based only on family history	No evidence of clinical benefit. Consider offer annual transvaginal ultrasound and Ca.125 from the age of 40 until the age of RRSO or for those who have not elected RRSO **(III,C)**	
BRIP1	No increased BC risk Recommend BC screening based only on family history	No evidence of clinical benefit. Consider offer annual transvaginal ultrasound and Ca.125 from the age of 40 until the age of RRSO or for those who have not elected RRSO **(III,C)**	

(II, A): (Evidence Level II, Recommendation Grade A)

BC breast cancer, *OV* ovarian cancer, *RRSO* bilateral risk reduction salpingo-oophorectomy, *EUS* endoscopic ultrasound, *MRI* magnetic resonance imaging

[a]Or early if family history of breast cancer before 30 years

[b]When MRI is unavailable, we recommend screening with mammography and breast ultrasound (II,B)

[c]Discuss delaying until 40 years for BRCA1 if annual MRI screening

[d]Even beyond, according to comorbidity

[e]Individualised if family history

III/ Quimioprevención en portadoras de mutación BRCA

A.- Quimioprevención del cáncer de mama

- **No existe una información sólida.** No hay beneficio claro demostrado para las pacientes con mutación BRCA. La evidencia en prevención primaria es IIC y en prevención secundaria IIA.
- Se podría considerar ofrecer ***tamoxifeno*** a algunas mujeres seleccionadas con mutación en ***BRCA2***, ya que presentan más tumores hormonosensibles (45, 46).

B.- Quimioprevención del cáncer de ovario

- Es aún más controvertida.
- El uso previo de anticonceptivos orales ha demostrado ser protector frente al cáncer de ovario en portadoras de mutación en BRCA (47), pero pueden causar un ligero aumento en el riesgo de cáncer de mama (48).

IV/ Cirugía reductora de riesgo en portadoras de mutación BRCA

Es la estrategia más efectiva de que disponemos en la actualidad para disminuir el riesgo de cáncer de mama y ovario, al lograr una reducción de riesgo superior al 90 % (45), pero es una medida difícil de aceptar para muchas mujeres, ya que es una intervención agresiva y mutilante, por lo **que se considera una opción preventiva y no una recomendación directiva**.

A.- Cirugía reductora de riesgo de cáncer de mama

Es la ***mastectomía bilateral*** reductora de riesgo con reconstrucción inmediata o diferida, que se ofrece a la mujer como una opción preventiva, no como una recomendación directiva.

1. ***Mastectomía simple y mastectomía ahorradora de piel***
   - Elimina todo el tejido mamario: extirpación de la mama y del complejo areola/ pezón.
   - Una variante es la ***mastectomía ahorradora de piel***, en la que se reduce la cantidad de piel extirpada y que permite, con más facilidad, la reconstrucción inmediata (aunque con un mayor riesgo de necrosis cutánea).
2. ***Mastectomía subcutánea preservando el complejo areola/pezón***
   - Extirpa únicamente la glándula mamaria, preservando la totalidad de la piel, incluido el complejo areola/ pezón, pero ***dejando un pequeño porcentaje de parénquima mamario***, teóricamente susceptible de cancerización.
   - Mejores resultados estéticos.
   - Esta técnica no ha sido comparada con las previas en ensayos fase III pero **hoy en día se considera efectiva y segura.**

B.- Cirugía reductora del riesgo de cáncer de ovario

Salpingo-oforectomía bilateral laparoscópica:

- Se incluye la exéresis de las trompas, debido al riesgo de desarrollar cánceres tubáricos de las portadoras de mutación en *BRCA*.
- Constituye la alternativa más eficaz para las mujeres de > 35 años que han completado sus deseos reproductivos.
- **Reduce el riesgo de cáncer de ovario en más de un 80 %** (persiste un riesgo de un 5 % de aparición de un ***cáncer peritoneal primario***) (49, 50) y el de mama en un 50 % si se realiza antes de los 50 años (no parece haber una reducción significativa del riesgo de cáncer de mama después de los 50 años, lo que sugiere que el beneficio se debe a la deprivación hormonal) (50).

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