La prédisposition génétique au cancer: quand le drame devient familial

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Le génome humain

- Maladies monogéniques

  Ex: C. Huntington

  découverte rapide

  dépistage et pronostic précis

- Maladies polygéniques:

  Ex: diabète, dépression, cancer

  recherches complexes

  dépistage et pronostic imprécis

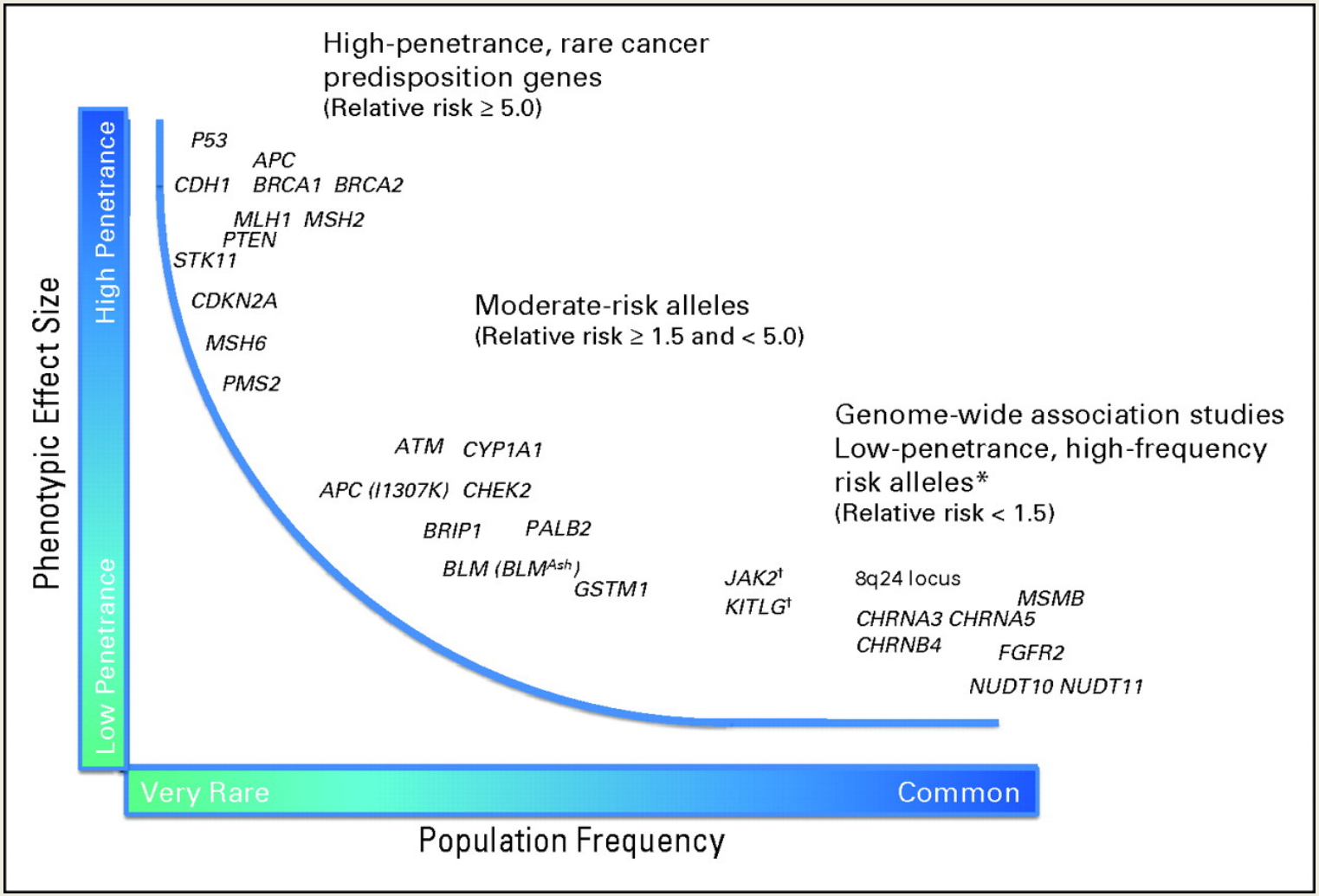
  facteurs environnementaux

Syndromes de cancer héréditaire

(sélection)

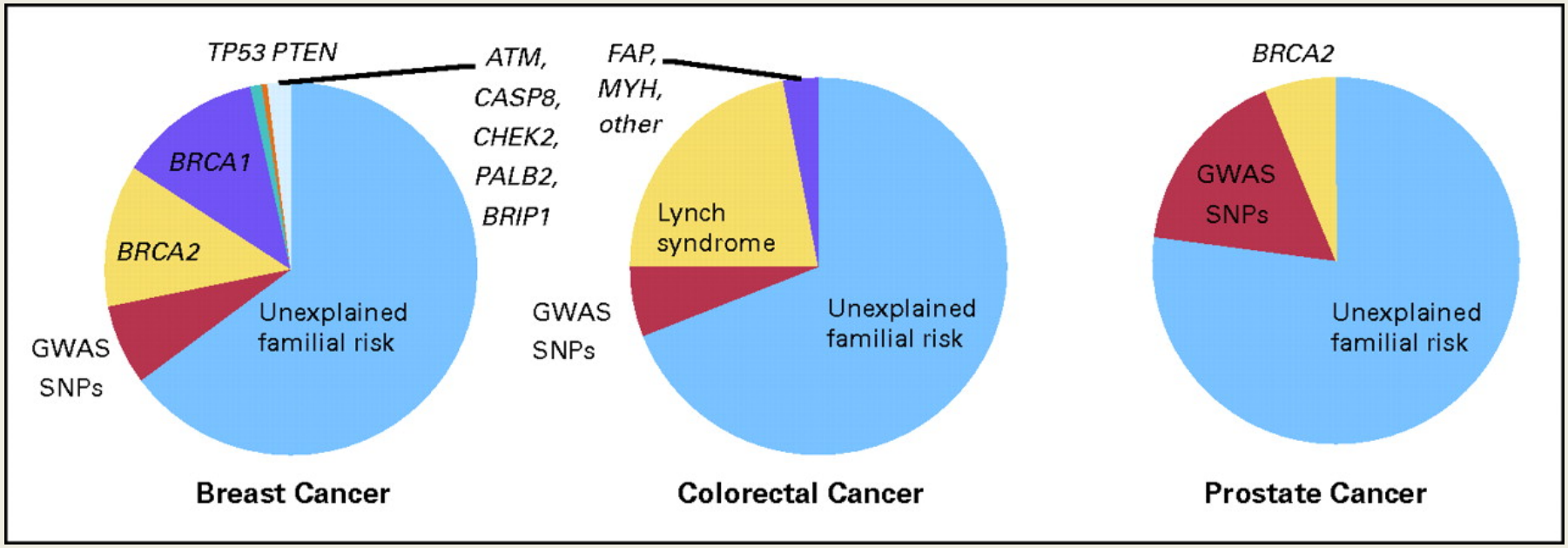
SYNDROME	GÈNES	Organes cibles
Cancer du sein et ovaire héréditaire	BRCA 1-2	Sein, ovaire, (prostate, pancréas, mélanome)
Li-Fraumeni	TP53	Sein, sarcome, leucémie, cerveau, surrénale, etc
Cowden	PTEN	Sein, thyroïde, endomètre
Lynch(HNPCC)	MSH2 , MLH1, MSH6 PMS2 ,EPCAM	Colon, endomètre, G.I., sein, foie, cerveau, bassinet, etc
Polypose familiale adm.	APC	Colon, intestin, peau, os, cerveau, etc
MEN 1-2	MEN(1), RET(2)	1-Pancréas endoc., parath., hypophyse 2- medul. thyroïde, phéo.
Von Hippel-Lindau	VHL	Rein, phéo., cerveau

Phenotypic effect size and frequency of occurrence.



Stadler Z K et al. JCO 2010;28:4255-4267

Familial risk of common cancers.



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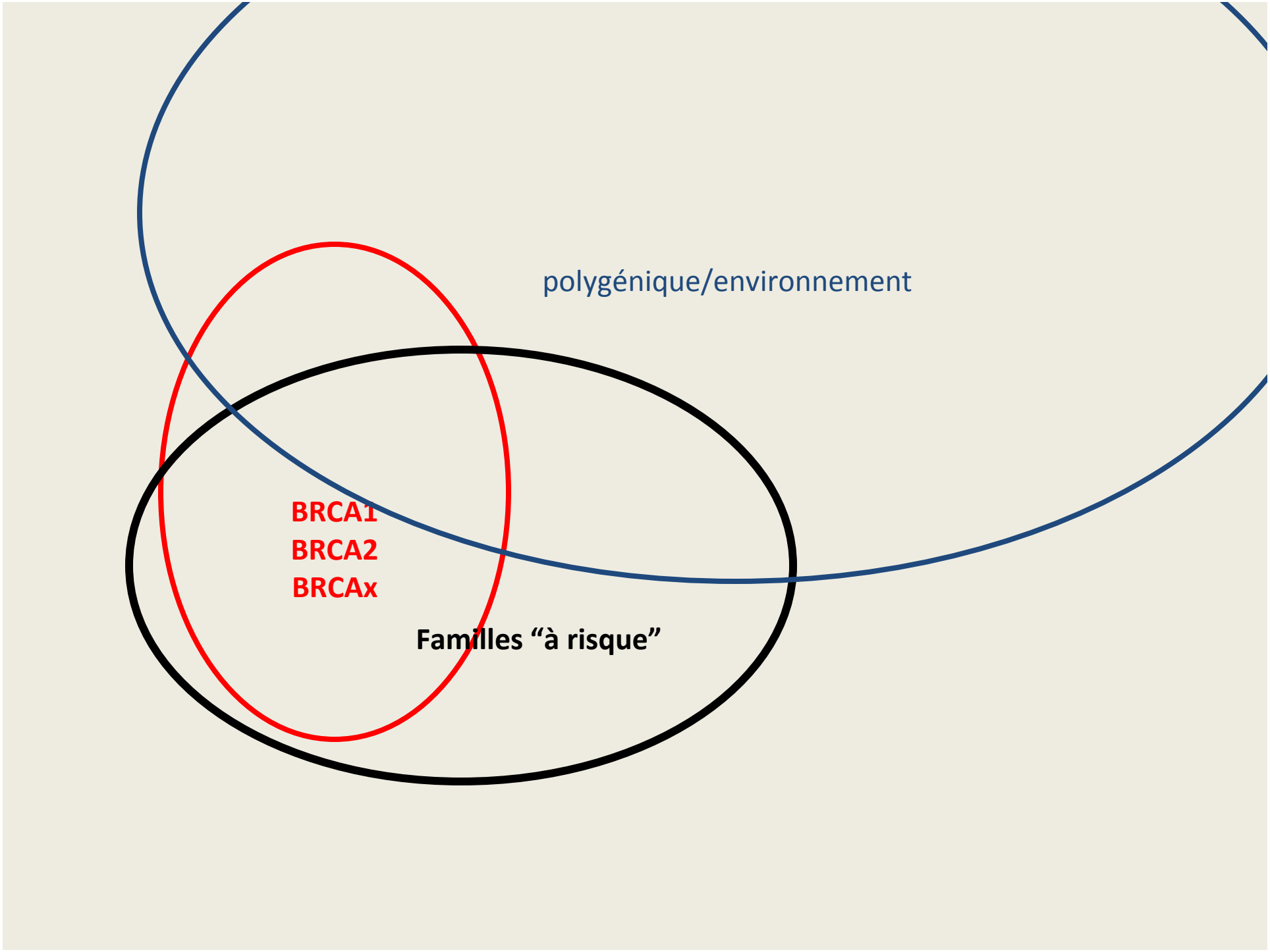

polygénique/environnement
BRCA1
BRCA2
BRCAx
Familles “à risque”

Mutations **BRCA-1** et **BRCA-2**

- Impliqués dans la réparation du DNA
- Plusieurs mutations identifiés
- Transmission autosome dominante
- Mutations secondaires (instabilité génétique)
- Pénétrance élevée
- Prédispositions spécifiques à certains organes
- Facteurs héréditaires et environnementaux

- Cancer du sein
  - Histoire familiale: 15-30%
  - Profil héréditaire: 5-10%
    - BRCA-1: 45%, BRCA-2: 35%, Autres: 1-5%, Inconnu: 10-15%
- Cancer de l'ovaire
  - 15% BRCA 1-2
  - Hx familiale, 50% BRCA 1-2

Mutations **BRCA-1** et **BRCA-2**

risques de cancer

- Sein
  - **BRCA-1**
    - 40 ans: 20% 50 ans: 51% 70 ans: 87%
    - Âge précoce, haut grade, triple neg. basaloïde
  - **BRCA-2**
    - 50 ans: 28% 70 ans: 84%
    - Hommes: 6%
    - Profil sporadique, ER+
  - **second cancer du sein**
    - 5 ans: 25% 70 ans: 65%

Prognostic: similaire aux cancers sporadiques

Mutations **BRCA-1** et **BRCA-2**

risques de cancer

- Ovaires
  - BRCA-1 70 ans:45%
  - BRCA-2 70 ans: 27%
  - Pronostic meilleur (chimiosensibilité?)
- Autres (BRCA-2)
  - Prostate, pancréas, mélanome

Table 1. Genes Known to Be Associated with a Hereditary Predisposition to Breast Cancer.*

Gene	Syndrome	Relative Risk of Breast Cancer	Breast-Cancer Risk by Age of 70 Years	Major Associated Cancers
		relative risk (age range)	%	
High penetrance				
BRCA1	HBOC	17 (20–29 yr); 32 (40–49 yr); 14 (60–69 yr)	39–87	Ovarian and pancreatic cancers
BRCA2	HBOC	19 (20–29 yr); 10 (40–49 yr); 11 (60–69 yr)	26–91	Ovarian, prostate, and pancreatic cancers†
p53	Li–Fraumeni syndrome	1.46 overall; 5.96 (15–29 yr)	56 at age 45 yr; >90 at age 70 yr	Soft-tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma, leukemia, colon cancer
PTEN	Cowden's disease; Bannayan–Riley–Ruvalcaba syndrome; Proteus syndrome; Proteus-like syndrome	2–4	25–50	Thyroid, endometrial, and genitourinary cancers
STK11/LKB1	Peutz–Jeghers syndrome	15	45–54	Small-intestine, colorectal, uterine, testicular, and ovarian sex cord cancers; other tumors
CDH1	Hereditary diffuse gastric carcinoma	3.25	39	Lobular breast and diffuse gastric cancer; other tumors
Low-to-moderate penetrance				
ATM (heterozygote)	Ataxia–telangiectasia	3–4	NA	Undefined in heterozygotes
CHEK2	Li–Fraumeni variant	2 for women; 10 for men	NA	Undefined
BRIP1	Fanconi's anemia	2	NA	Undefined in heterozygotes
PALB2	None known	2.3	NA	Undefined in heterozygotes

* High-penetrance mutations are associated with a prominent family history of breast cancer and a high risk of breast cancer. Mutations with a low-to-moderate penetrance are associated with a smaller increase in the risk of breast cancer and a less prominent family history of breast cancer. References for genes in the table are listed in the Supplementary Appendix, which is available with the full text of this article at www.nejm.org. HBOC denotes hereditary breast and ovarian cancer syndrome, and NA not available.

† Prostate cancer does not occur at an earlier age than in the general population.

Robson M, Offit K. N Engl J Med 2007;357:154-162.

Qui dépister?

- Ca. du sein précoce
- Ca. du sein bilatéral/multifocal
- Ca. ovaire
- Ca. sein homme
- Profil familial
- Groupe à risques (Ashkenazi,…)
- Famille connue BRCA 1-2

Dépistage BRCA1-2 (critères NCCN)

- Sujet atteint cancer du sein
  - >45 ans
  - >50 ans famille restreinte
  - > 60 ans triple négatif
  - Tout âge
    - +1 parent 1-2-3 deg ca. sein/ov >50ans
    - +2 parent 1-2-3 deg ca. sein/ov tout âge
    - +2 parent 1-2-3 deg ca. pancréas/prostate haut grade
    - +2 parent 1-2-3 deg ca. sein homme
  - Ethnicité à risque

Dépistage BRCA1-2 (critères NCCN)
suite

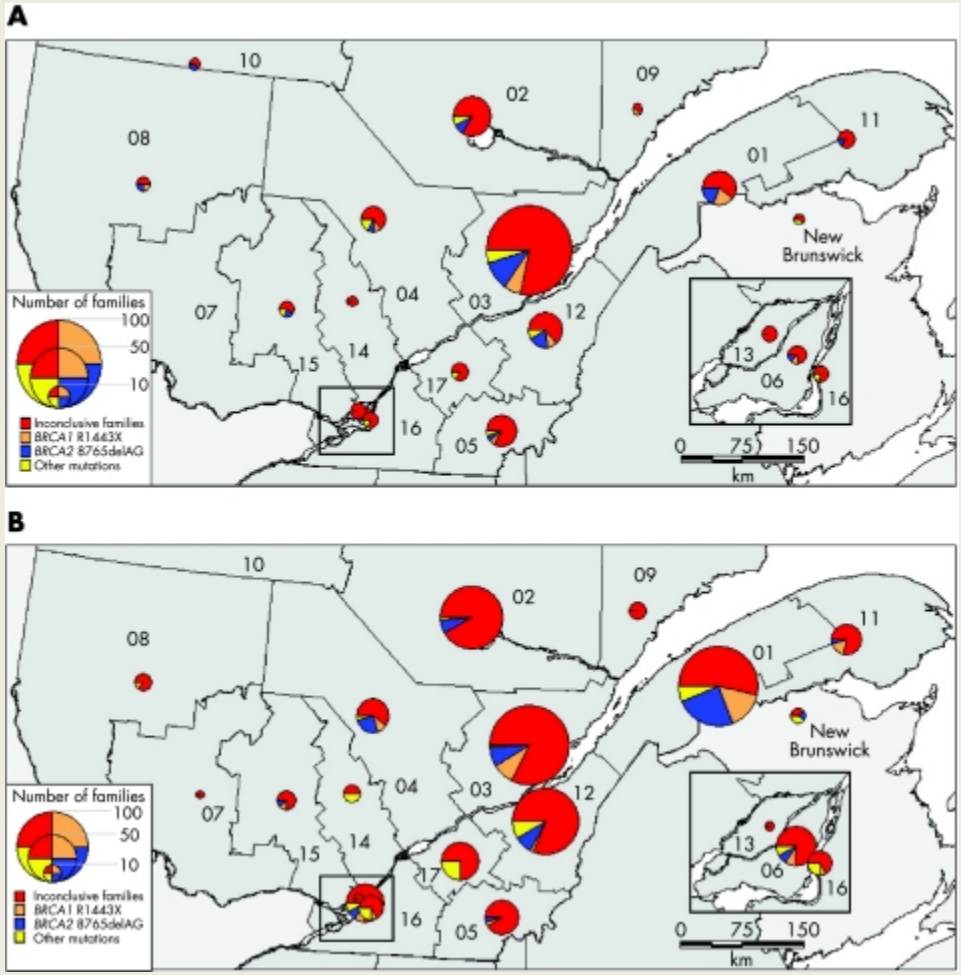
- Sujet atteint cancer ovaire/trompe/péritoine
- Sujet atteint cancer pancréas, prostate (haut grade)
  - +2 parents deg 1-2-3 ca. sein/ov/pancréas/prostate h. gr.
- Sujet non atteint
  - +1 parent 1-2 deg avec critères de sujet natteint
  - +2 parent 3 deg avec ca. sein(< 50 ans)/ovaire

Table 2. Models Commonly Used to Predict the Risk of Breast Cancer and the Probability of Detecting a *BRCA* Mutation.*

Model, Description, and Access	Measures	Limitations
Risk of breast cancer for unaffected women		
Gail et al.[2] provide risk of breast cancer by a given age†‡	Age, family history of breast cancer (FDR), reproductive factors, number of breast biopsies, personal history of atypia§	Does not include breast cancer in non-FDR or family history of ovarian cancer; derived from a population undergoing screening
Claus et al.[3] provide 5-year and lifetime probability of breast cancer‡	Age, family history of breast cancer (FDR, SDR)	Does not include risk factors other than family history or family history of ovarian cancer; incomplete validation in nonwhite populations
Tyrer–Cuzick (Tyrer et al.[4]) provides 10-year and lifetime probability of breast cancer¶	Age, family history of breast and ovarian cancer; Ashkenazi ethnic background, reproductive factors, morphometric factors (height, weight), personal history of atypia, lobular carcinoma in situ	Incomplete validation, especially in nonwhite populations
BRCAPRO (Berry et al.[5]) provides age-specific probability of breast cancer‡‖	Age, family history of breast and ovarian cancer, Ashkenazi ethnic background	Does not include risk factors other than family history; incomplete validation in nonwhite populations
Probability of detecting *BRCA* mutation (affected and unaffected women)		
Tyrer–Cuzick[4] (see listing above)	Personal or family history of breast and ovarian cancer, Ashkenazi ethnic background	Incomplete validation, especially in nonwhite populations
BRCAPRO[5] (see listing above)	Personal or family history of breast and ovarian cancer, Ashkenazi ethnic background	Incomplete validation in nonwhite populations; requires information on all unaffected FDRs and SDRs
Frank et al.[6] provide empirical experience of one laboratory based on 65,000 observations**	Personal or family history of breast and ovarian cancer, Ashkenazi ethnic background	Empirical model with incomplete validation; does not include unaffected family members
Manchester (Evans et al.[7]) provides a scoring system not available as a computer program but presented in the article	Personal or family history of breast and ovarian cancer	Uncertain applicability to nonwhite populations; does not account for ethnic background (especially Ashkenazi)

* FDR denotes first-degree relative, and SDR second-degree relative.
† The model is available as an interactive tool at www.cancer.gov/bcrisktool.
‡ The model is available for download at www4.utsouthwestern.edu/breasthealth/cagene/default.asp and at www.tucows.com/preview/221909.
§ Reproductive risk factors include the age at menarche, menopause, and first childbirth and the number of live births.
¶ The model is available on request; send e-mail to ibis@cancer.org.uk.
‖ The model is available for download at astor.som.jhmi.edu/BayesMendel/brcapro.html.
** The model is available for download at www.myriadtests.com/provider/brca-mutation-prevalence.htm.

Robson M, Offit K. N Engl J Med 2007;357:154-162.

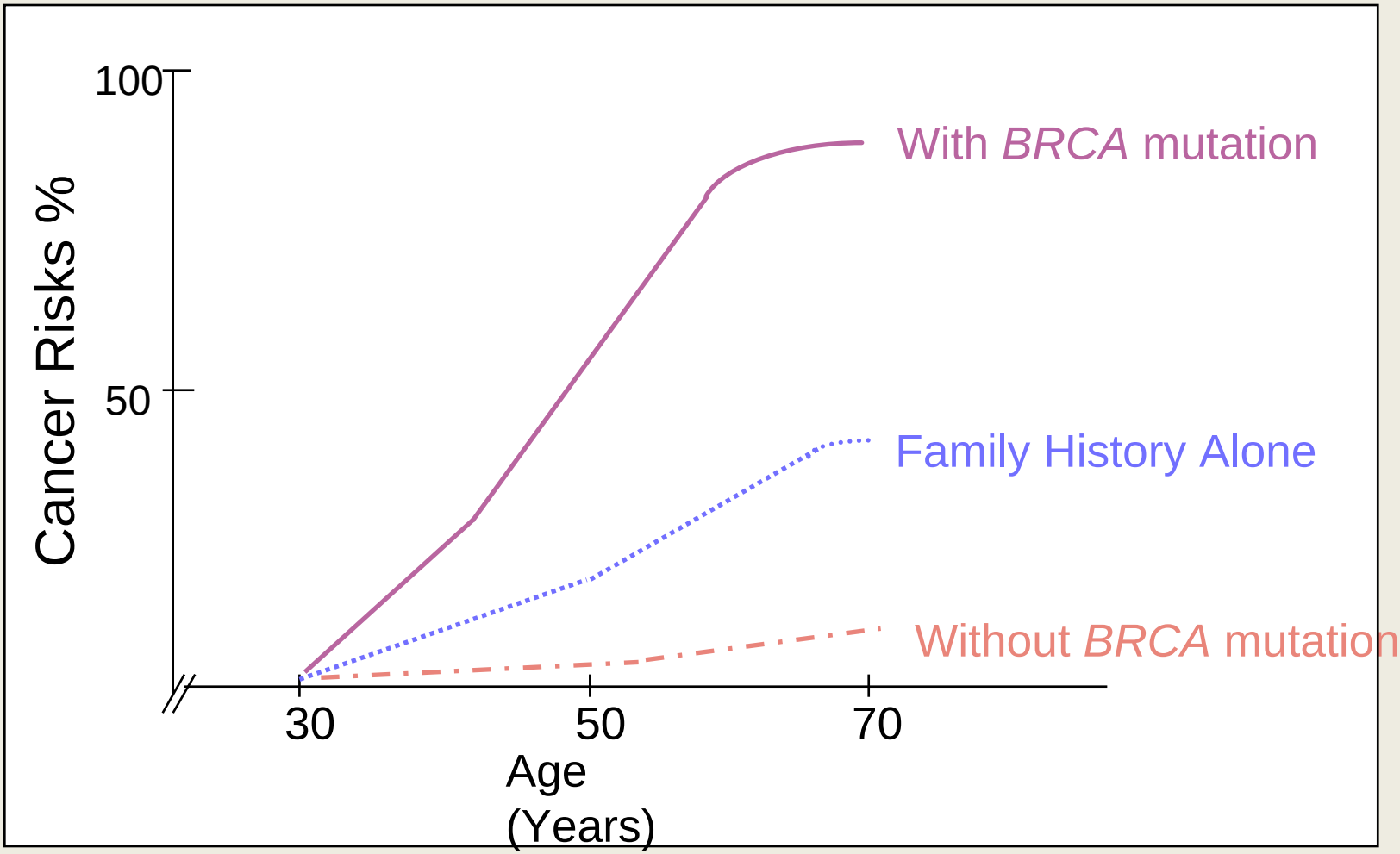


Simard J. Et al: J Med Genet. 2007 Feb;44(2):107-21

Désignation	BRCA1				BRCA2		
Variant de séquence[a]	Effet	Mutation récurrente[b]	Distribution[c](%)	Variant de séquence[a]	Effet	Mutation récurrente[b]	Distribution[c](%)
Mutations pathogéniques	185delAG	39Ter			2558insA	778Ter	
360C>T	Gln81Te		0,6	**2816insA**	880Ter	Oui	0,6
1081G>A	Trp321Ter		0,6	3034delAAAC	958Ter		0,6
1623delTTAAA	505Ter		< 0,5	**3398delAAAAG**	1064Ter	Oui	2,0
2072insG	699Ter		< 0,5	3773delTT	1182Ter		0,6
2953delGTAinsC	950Ter	Oui	4,0	**6085G>T**	Glu1953Ter	Oui	6,0
3768insA	1218Ter		< 0,5	**6503delTT**	2099Ter	Oui	1,0
3875delGTCT	1262Ter	Oui	1,0	7235G>A	Arg2336His		0,6
4160delAG	1354Ter		< 0,5	**8765delAG**	2867Ter	Oui	10,0
4184delTCAA	1364Ter		< 0,5	8904delA	2908Ter		
4446C>T	Arg1443Ter	Oui	15,0				
5221delTG	1714Ter		0,6				
Signification inconnue	1224G>A	Asp369Asn					
1606G>A	Arg496His			4486G>T	Asp1420Tyr		
2341C>T	Ser741Phe			5540G>A	Gly1771Asp		
2598C>A	Thr826Lys		< 0,5 [d]	6328C>T	Arg2034Cys		
3419C>T	Pro1099Leu			8801A>G	Gln2858Arg		
3759G>A	Glu1214Lys			8410G>A	Val2728Ile		
3827T>G	Asn1236Lys			10204A>T	Lys3326Ter		
4158A>G	Arg1347Pro						
VS21-8C>T				VS14+6G>A			

Tonin P, Bull Cancer. 2006 Sep;93(9):841-6.

Family History is Not Enough



Consultation en génétique

- Introduction
  - Motivations, connaissances
- Histoire personnelle
  - néoplasies
- Histoire familiale
  - Pedigree
  - néoplasies
- Documentation
  - néoplasies
- Contexte familial et psychosocial

Consultation en génétique

- Interpréter l'histoire médicale
- Expliquer les principes de génétique et d'hérédité
- Estimer les chances de mutation

  (versus cancer sporadique)
- Discuter des risques et inconvénients du dépistage
  - Inconvénients personnels
  - Dynamique familiale
  - Risques de bris de confidentialité
  - Discrimination (employeur, assurances)

Consultation en génétique

- Expliquer la signification des résultats en génétique
  - Résultats positifs, négatifs, ambigües
  - Fiabilité des tests
- Discuter des conséquences de ces résurtats
  - Personnelles, familiales
- Établir une stratégie de dépistage
- Se familiariser avec le consentement éclairé
- Expliquer le mode de divulgation prévu

Interventions

- Style de vie
- Surveillance et dépistage
- Chimio-prévention
- Chirurgies prophylactiques

Surveillance et dépistage

- Auto-examen des seins :
  - Recommandée, aucune preuve
  - Aux 4-6 mois à partir de 18 ans?
  - Aux 6 mois à 25 ans
- Examen clinique
  - Aux 6 mois à 25 ans ?
- Mammographie:
  - faible sensibilité chez <50ans
  - Annuel
  - Début 25-30 ans (10 ans avant le plus jeune sujet atteint)
  - Durée?
- IRM
  - Annuel (en alternance Q 6 mois avec mammographie)
- Écho trans-vaginal
  - Annuel
  - Efficacité?
- Ca-125
  - Aux 6 mois
- Autres organes
  - Recommandations standards (habituellement)
  - Dépistage cancer prostate 40 ans

Chirurgies prophylactiques

- Mastectomie
  - Réduction ca. sein: 90%
  - Âge?, reconstruction?
- Salpingo-oophorectomie
  - Réduction ca. sein: 50% (<50 ans)
  - Réduction ca. ovaire: 90%
  - Âge? 35-40 ans
  - hystérectomie?, hormonothérapie?

The New York Times

The Opinion Pages

WORLD U.S. N.Y. / REGION BUSINESS TECHNOLOGY SCIENCE HEALTH

OP-ED CONTRIBUTOR

My Medical Choice

By ANGELINA JOLIE
Published: May 14, 2013 | 1712 Comments

LOS ANGELES

Enlarge This Image

n Capelli

MY MOTHER fought cancer for almost a decade and died at 56. She held out long enough to meet the first of her grandchildren and to hold them in her arms. But my other children wi never have the chance to know her an experience how loving and gracious she was.

We often speak of "Mommy's mommy," and I find myself trying to explain the illness that took her away from us. They have asked if the same could happen to me. I have always tol but the truth is I carry a "faulty" gene, sharply increases my risk of developir ovarian cancer.

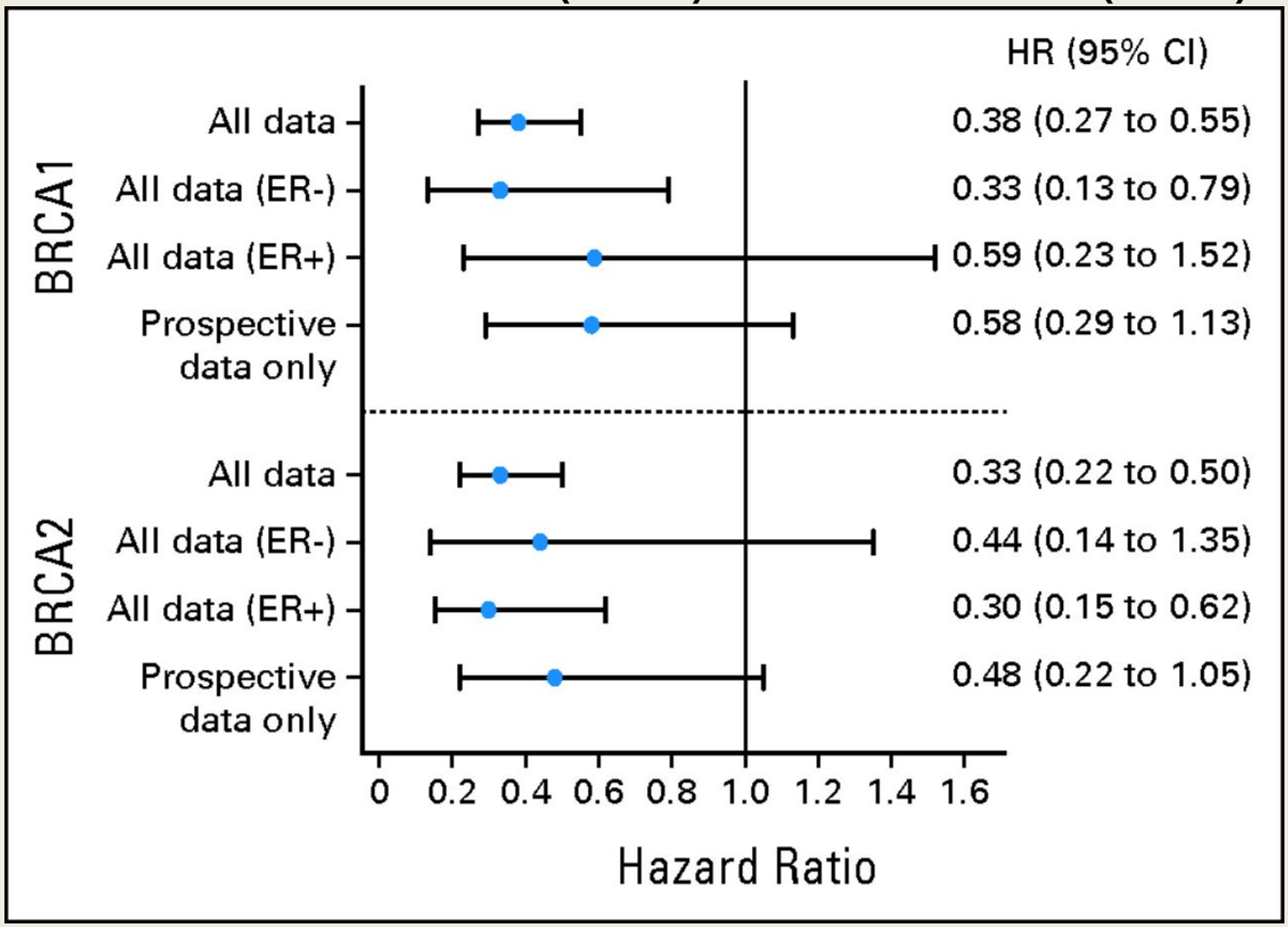
Chimio-prévention

- Tamoxifène
  - Études restreintes
  - Efficacité semble moindre que pour les cancer sporadiques

    BRCA-1: 13%? BRCA-2: 27%? étude P1: 49%
  - Prévention second cancer du sein?

- Anovulants
  - Plusieurs données négatives
  - Effets sein versus ovaire imprévisibles

Hazard ratio (HR) estimates (represented by circles) and corresponding 95% CIs (represented by horizontal lines) for risk of contralateral breast cancer associated with tamoxifen use by women with BRCA1 mutations (BRCA1) and BRCA2 mutations (BRCA2).



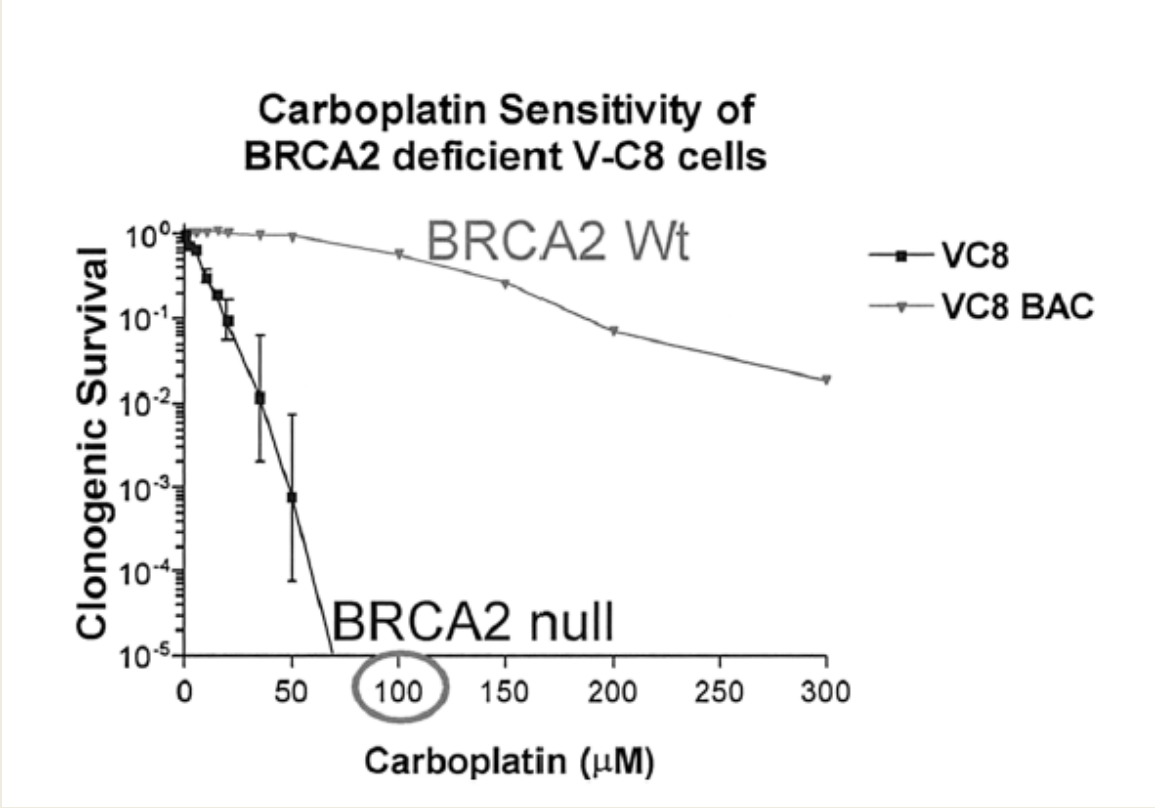
Phillips K et al. JCO 2013;31:3091-3099

Options de reproduction

- Pré-ovariectomie…
- Diagnostic pré-implantation
- Diagnostic in utéro

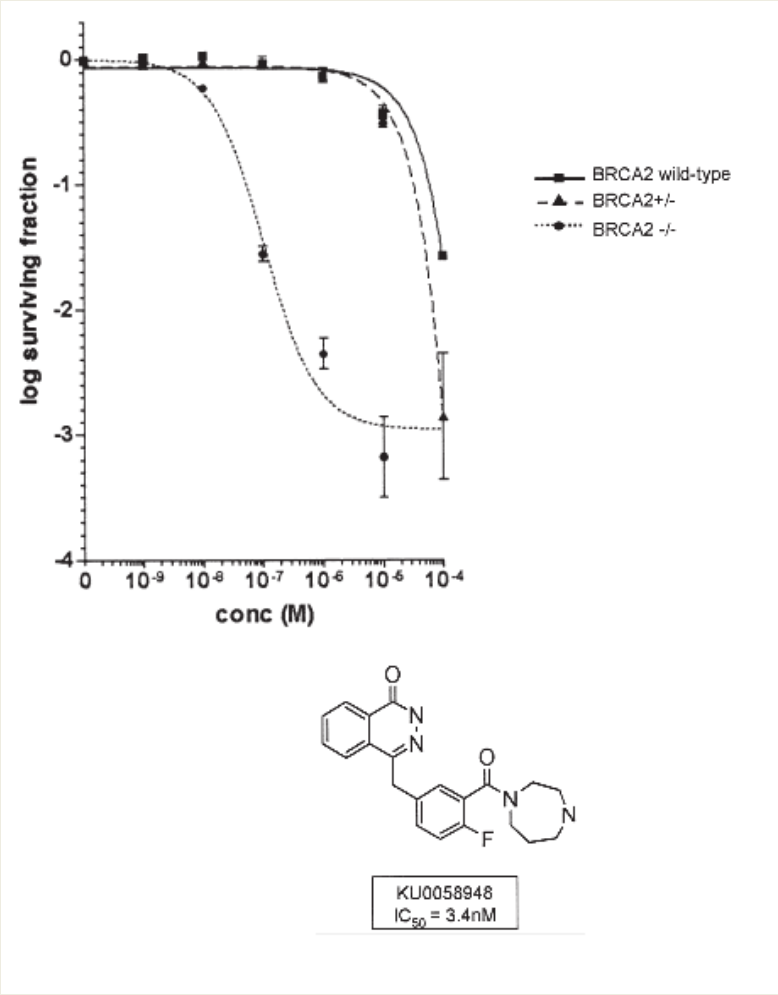
Traitements systémiques

- Spéculatif, aucune recommandation
- Chimiosensibilité: cisplatine, mitomicine C
- Chimiorésistance: Taxanes
- Traitements ciblées?
  - ✓ PARP



A.N.T. Tutt: Cold Spring Harbour Symposia Quant Biol, 2005; vol LXX: 139

PARP inhibition



A.N.T. Tutt: Cold Spring Harbour Symposia Quant Biol, 2005; vol LXX: 139

Hereditary Breast and Ovarian Cancer Foundation (HBOC)
tel. :514-482-8174
info@hboc.ca

Hereditary Breast + Ovarian Cancer Foundation
Fondation du cancer héréditaire du sein + des ovaires

Centre des maladies du sein Deschênes-Fabia
CHU de Québec-Hôpital du Saint-Sacrement
1050 chemin Ste-Foy, Québec, G1S 4L8.
Courriel : centre-rose@uresp.ulaval.ca
Tel : 418-682-7511, poste 4621

Syndrome de Lynch (« HNPCC »)

- Autosome dominant
- Cancer du colon précoce (45 ans, pas 63)
- Surtout colon droit
- Carcinogénèse accélérée
- 25-30% 2^{ième} ca colon/10 ans (sans colectomie totale)
- Autres néoplasies:
  - Endomètre (40-60%), ovaire (15%), gastro-intestinal, pancréato-biliaire, urothélial, cerveau.
  - Lésions cutanées bénignes/malignes
- Bon pronostic, résistance au 5-FU, pathologie typique
- Plusieurs mutations connues
  - MSH2 , MLH1, MSH6, PMS2 ,EPCAM
  - Instabilité des microsatellites (« MSI »)
- Critères diagnostiques (Amsterdam, Bethasda)


MERCI