FAUT IL MODIFIER LES BORNES DU DEPISTAGE EN FRANCE?

Suzette Delaloge

Gustave roussy

INTER CEPTION
GUSTAVE ROUSSY
Le programme de prévention personnalisée des cancers

DISCLOSURES

* Not personal - to my institution

	Consulting	Conferences	Clinical trials	Congress	Stock options
Astra Zeneca	X *	X*	X*	x	
Healthcare needs	X*				
BMS	X*		X*		
Daichi			X*		
Exact Sciences		X*	X*		
Lilly	X*		X*		
MSD		X*	X*		
Novartis	X*	X*	X*	x	
Pfizer	X*	X*	X*	x	
Puma	X*	X*	X*		
Roche	X*	X*	X*		
Sanofi	X*		X*		
Seagen		X*			
Taiho			X*		

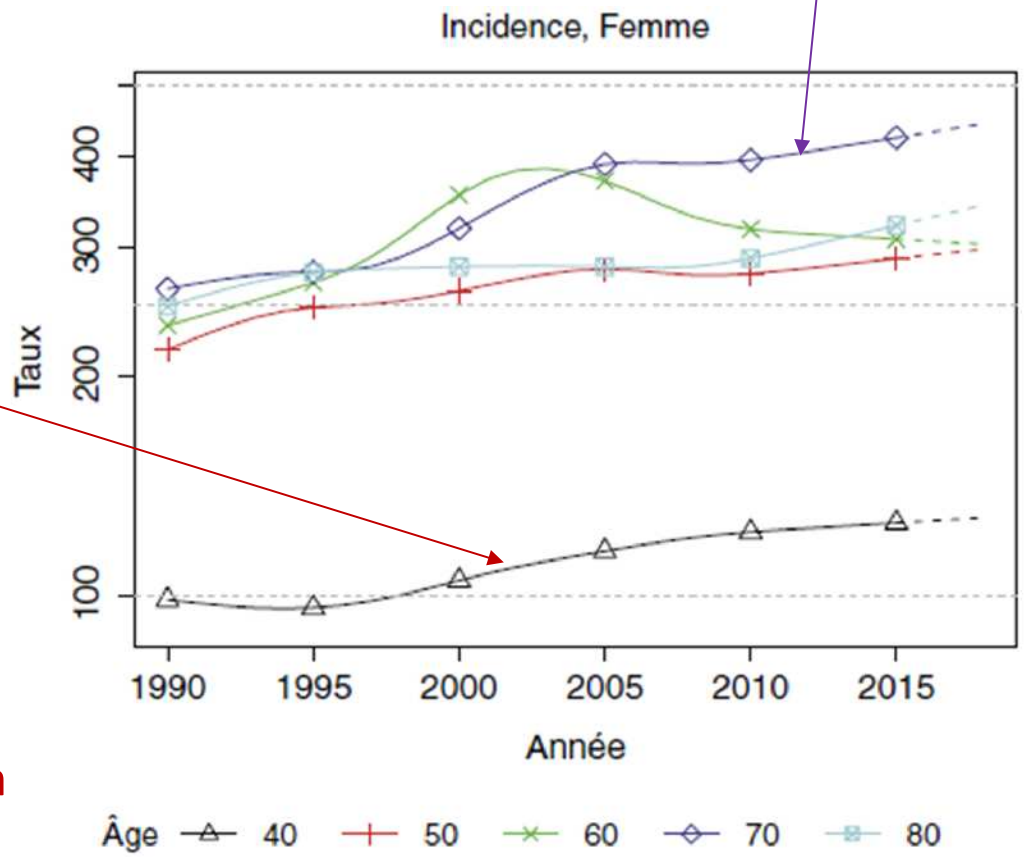
Faut il modifier les bornes du dépistage en France

- Arguments et données
- Recommandations
- Perspectives

Incidence de cancer du sein selon l'âge

70-79 ans
30% des K sein
Incidence en hausse

Age	US SEER 2018	France 2018 Inca	Italie 2010	UK, 2014-2016
40-44	122.5	**164.6**	143.1	123.9
45-49	188.6	**259.9**	226.1	217.1
50-54	224	285.1	233.1	282.0
55-59	266.4	273.1	239.7	278.9
60-64	346.7	324.5	293.9	344.6
65-69	420.2	401.7	342.7	419.2
70-74	433.8	**420.9**	324.7	370.9



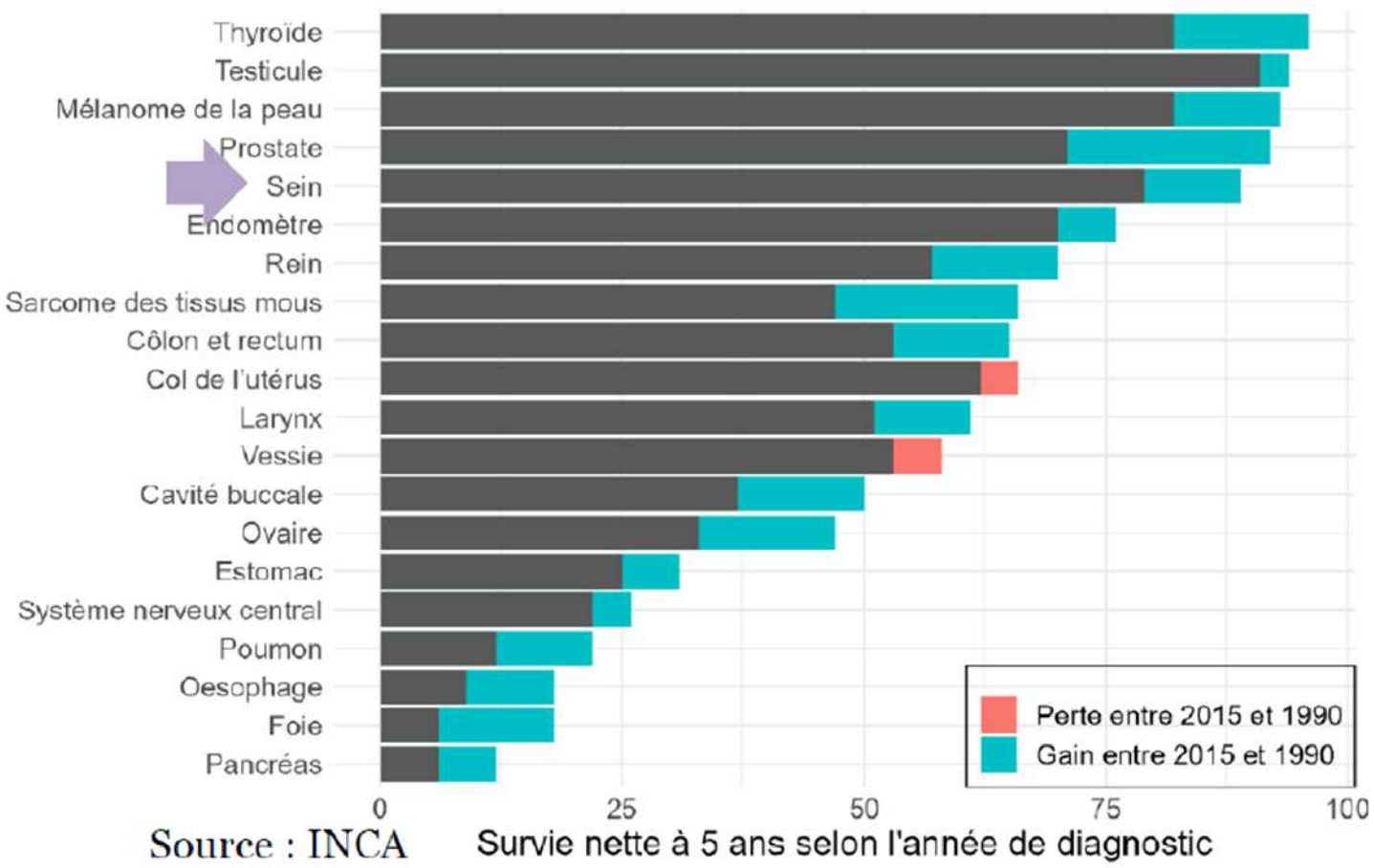
< 50 ans
22% des cancers du sein
40% de stade 2+
Incidence en hausse

Inca 2019

La survie nette après cancer du sein s'améliore

Survie nette à 5 ans : 2015 vs 1990

- Survie nette standardisée à 5 ans, par localisation cancéreuse
- Comparaison des survies de cancers
  - Diagnostiqués en 2015
  - Diagnostiqués en 1990
- Tous âges et tous sexes confondus

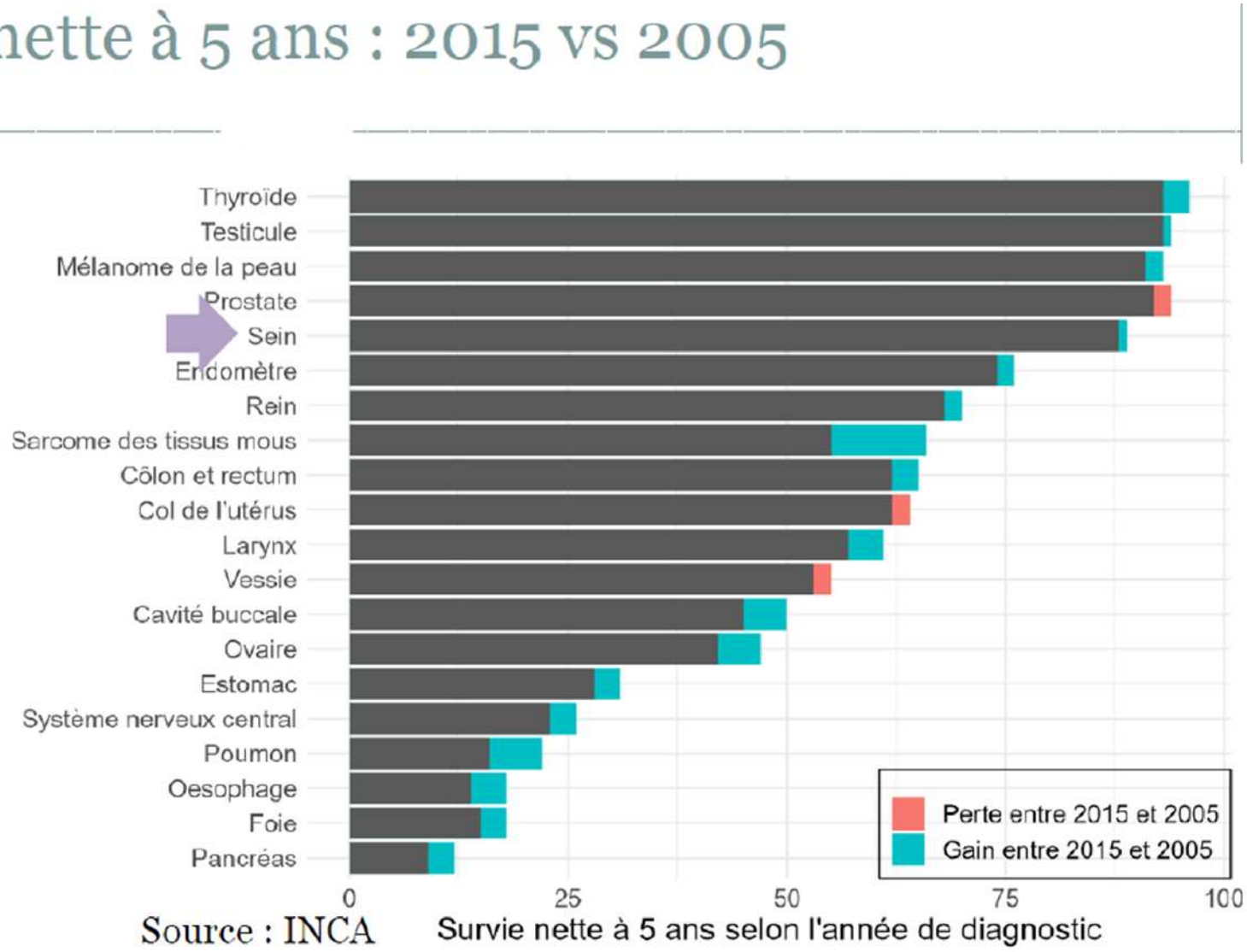


Source : INCA

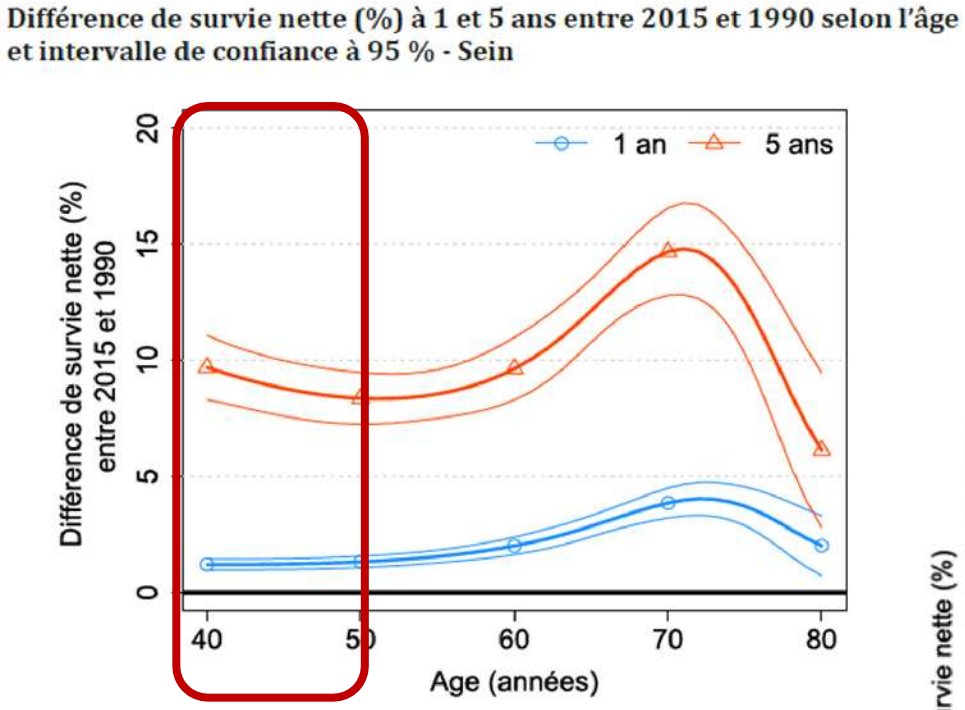
La survie nette après cancer du sein s'améliore…

mais très peu actuellement malgré des fardeaux thérapeutiques majeurs dans les stades 2+

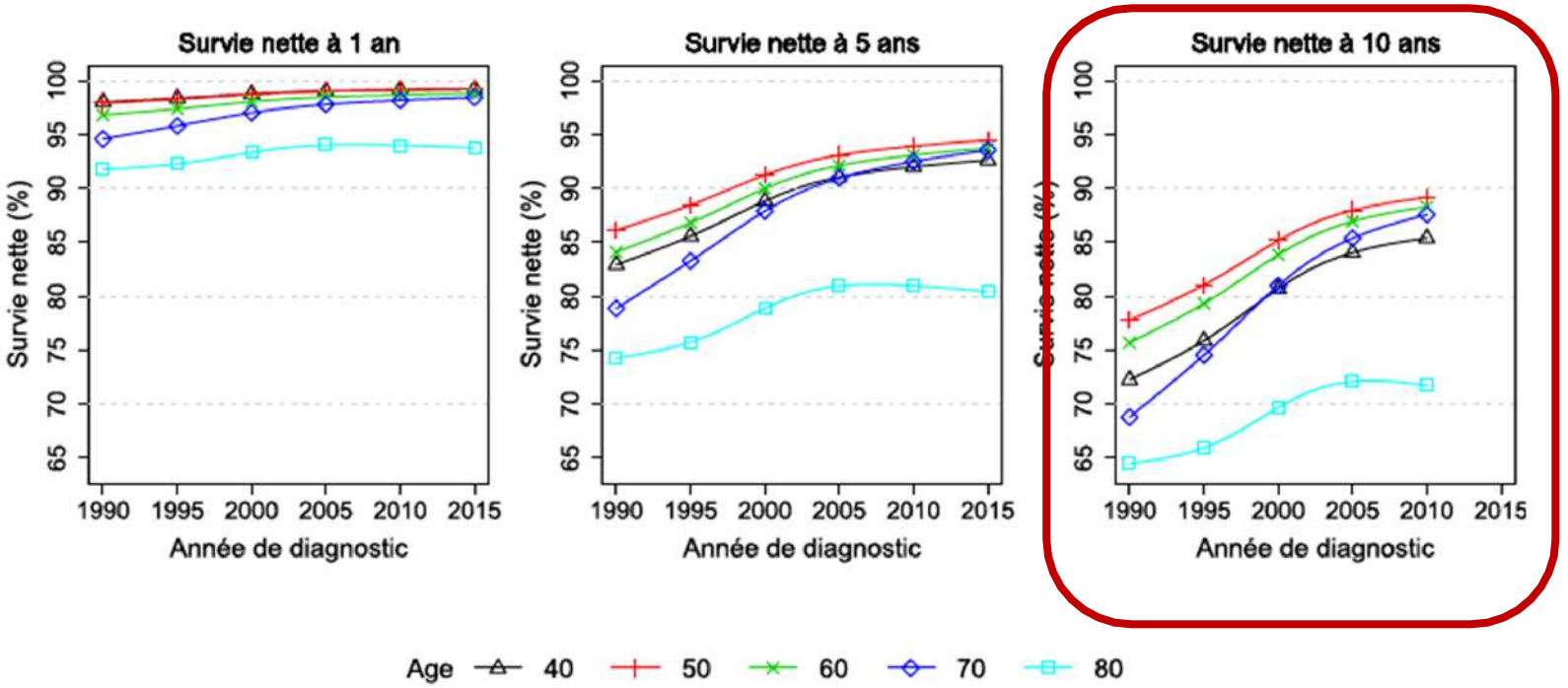
- Survie nette standardisée à 5 ans, par localisation cancéreuse
- Comparaison des survies de cancers
  - Diagnostiqués en 2015
  - Diagnostiqués en 2005
- Tous âges et tous sexes confondus



La différence de survie nette en rapport avec le cancer du sein est plus élevée aux âges extrêmes

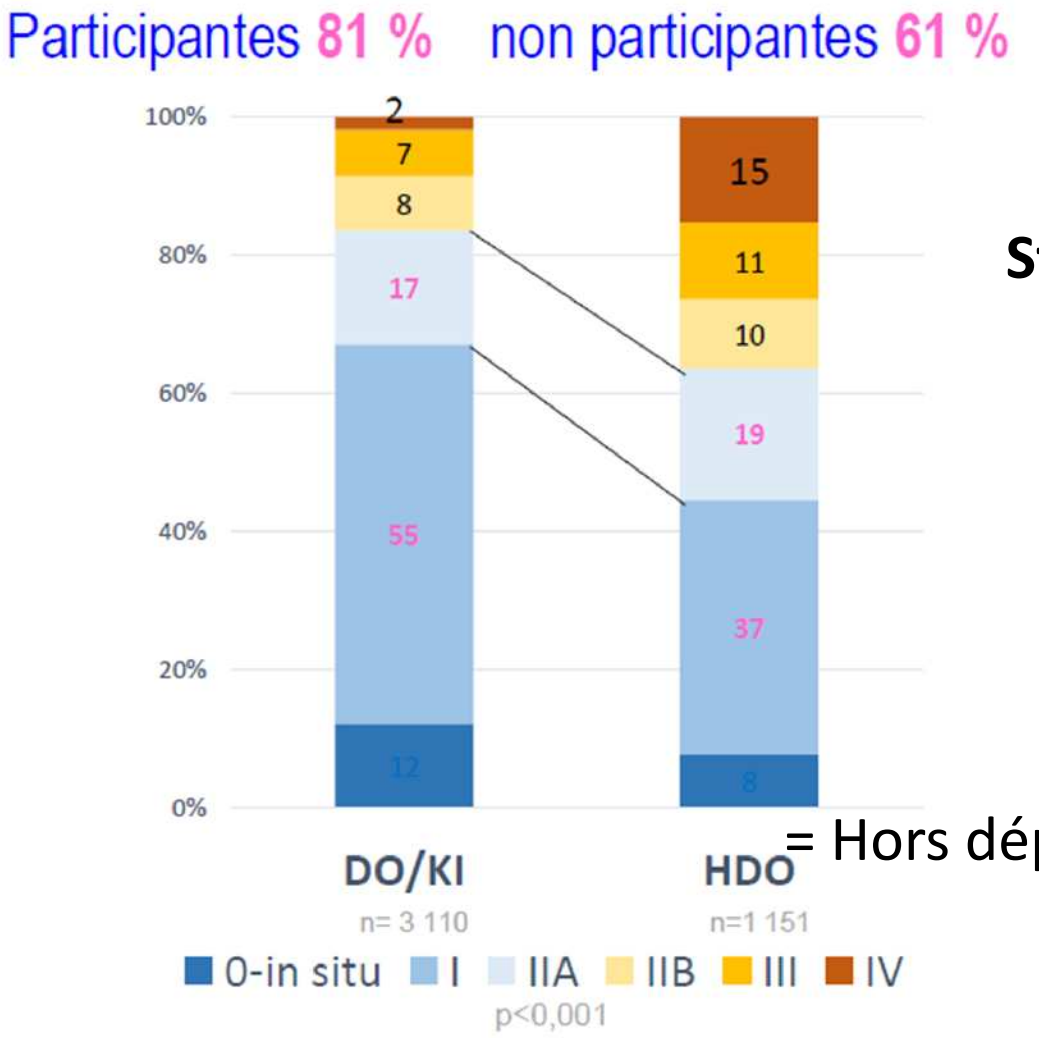


La survie nette est la survie qui serait observée si la seule cause de décès possible était le cancer étudié (ex survie relative)



Molinie et al, FRANCIM HCL INCa 2020

La participation au DO diminue les stades au diagnostic



Stades au diagnostic

= Hors dépistage organisé

Registres 2007-2015 – F Molinie et al Journées Françaises de radiologie 2022

L'indication de dépistage est une affaire de rapport bénéfice-risque à l'échelle d'une population

Risque de surdiagnostic: augmente avec l'âge mais…. plus on débute tard le dépistage et moins on a de recul, plus élevé le taux de surdiagnostic

Estimates of the mean and 95%CI of the number of overdiagnosed breast cancers per 100,000 women screened once at different follow-up times after screening stops for women with different screening start age.

Screen start age	2 years	3 years	4 years	5 years	10 years	15 years
50	98.5 (75.8–121.3)	44.6 (34.1–55.1)	21.6 (10.8–32.4)	12.9 (4.6–21.1)	12.3 (5.3–23.0)	13.4 (4.9–21.9)
52	107.9 (94.1–121.6)	47.6 (36.3–59.0)	20.3 (12.5–28.1)	12.1 (6.5–17.8)	12.1 (5.3–19.0)	12.4 (5.5–19.2)
54	121.1 (104.4–137.8)	53.6 (39.8–67.3)	24.9 (16.5–33.5)	15.5 (7.4–23.7)	12.3 (7.5–17.1)	13.4 (6.6–20.3)
56	138.2 (113.4–162.9)	60.8 (49.1–72.5)	28.4 (16.3–40.5)	16.8 (5.2–28.3)	13.2 (5.5–20.9)	16.4 (3.2–29.6)
58	139.0 (112.8–165.1)	58.8 (42.2–75.3)	27.6 (15.2–39.9)	16.1 (6.6–25.6)	12.3 (5.3–19.4)	14.0 (6.1–22.0s)
60	148.8 (131.3–166.4)	70.1 (54.1–86.1)	37.4 (23.3–51.6)	24.2 (13.1–35.2)	17.1 (9.3–25.0)	16.6 (9.8–23.5)
62	167.6 (144.0–191.3)	82.3 (64.2–100.5)	47.4 (34.8–59.9)	32.9 (18.8–47.0)	21.8 (12.4–31.2)	22.5 (14.5–30.5)
64	186.3 (157.0–215.7)	95.4 (73.0–117.8)	62.9 (48.4–77.3)	51.0 (36.4–65.6)	22.8 (9.1–36.4)	21.8 (11.8–31.8)
66	239.1 (196.0–282.2)	155.9 (126.2–185.6)	119.2 (98.7–139.8)	76.0 (56.2–95.9)	31.9 (16.8–47.0)	29.0 (19.1–38.9)
68	297.0 (264.5–329.4)	176.7 (144.0–209.3)	110.2 (80.9–139.6)	74.2 (50.9–97.5)	36.7 (20.6–52.9)	34.2 (17.5–50.8)

Ding, Eur J cancer 2022

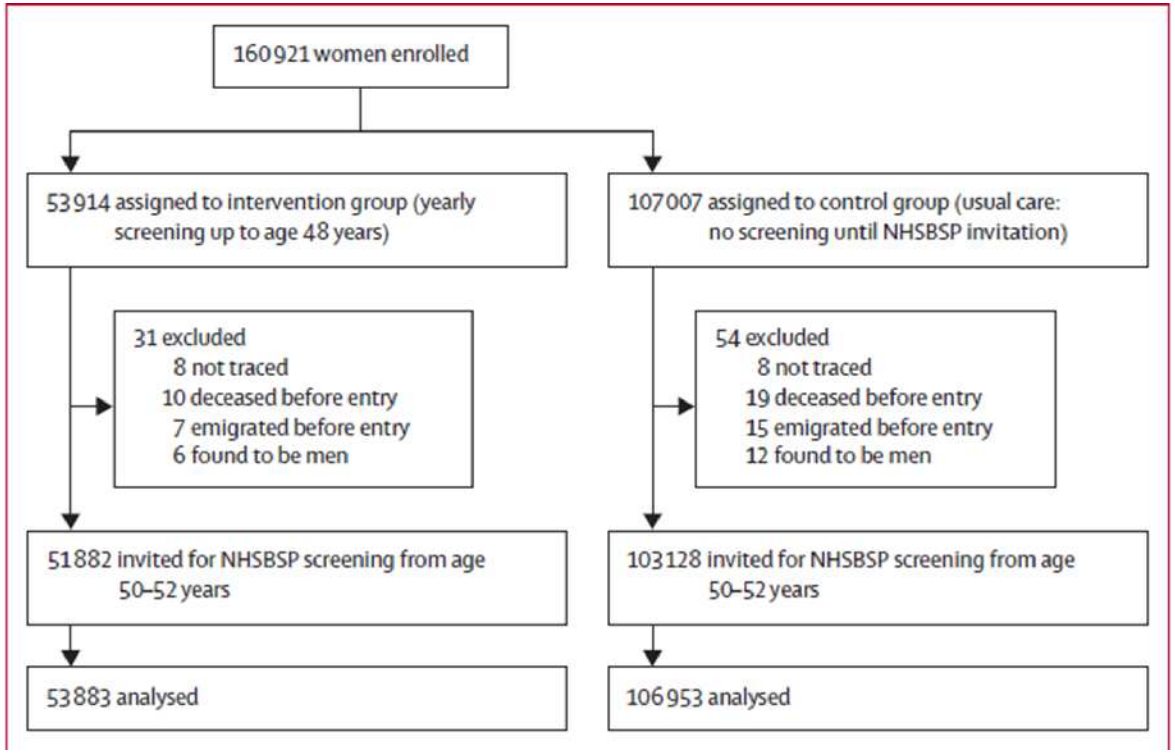
Données 40-50 ans: UK age trial

Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial

Stephen W Duffy*, Daniel Vulkan*, Howard Cuckle, Dharmishta Parmar, Shama Sheikh, Robert A Smith, Andrew Evans, Oleg Blyuss, Louise Johns, Ian O Ellis, Jonathan Myles, Peter D Sasieni*, Sue M Moss*

Duffy, Lancet Aug 2020
22 years results of the Age trial

90% power to detect a 20% reduction in breast cancer mortality in the intervention group at 14 years of follow-up, assuming 30% non-compliance, a control group mortality rate of 0·317 per 1000 person-years of follow-up, and one-sided testing



	Intervention group		Control group		RR (95% CI)
	Deaths, n	Follow-up, person-years	Deaths, n	Follow-up, person-years	
Cancers diagnosed in the intervention period, up to immediately before first NHSBSP screen (primary analysis)					
Total	209	1 201 010	474	2 385 006	0·88 (0·74–1·03)
Observation period					
<10 years	83	532 729	219	1 058 236	0·75 (0·58–0·97)
≥10 years	126	668 281	255	1 326 770	0·98 (0·79–1·22)
Cancers diagnosed in the period up to and including the first NHSBSP screen (post-hoc analysis)					
Total	216	1 201 010	498	2 385 006	0·86 (0·73–1·01)
Observation period					
<10 years	83	532 729	219	1 058 236	0·75 (0·58–0·97)
≥10 years	133	668 281	279	1 326 770	0·95 (0·77–1·17)

RR=relative rate. NHSBSP=National Health Service Breast Screening Programme.

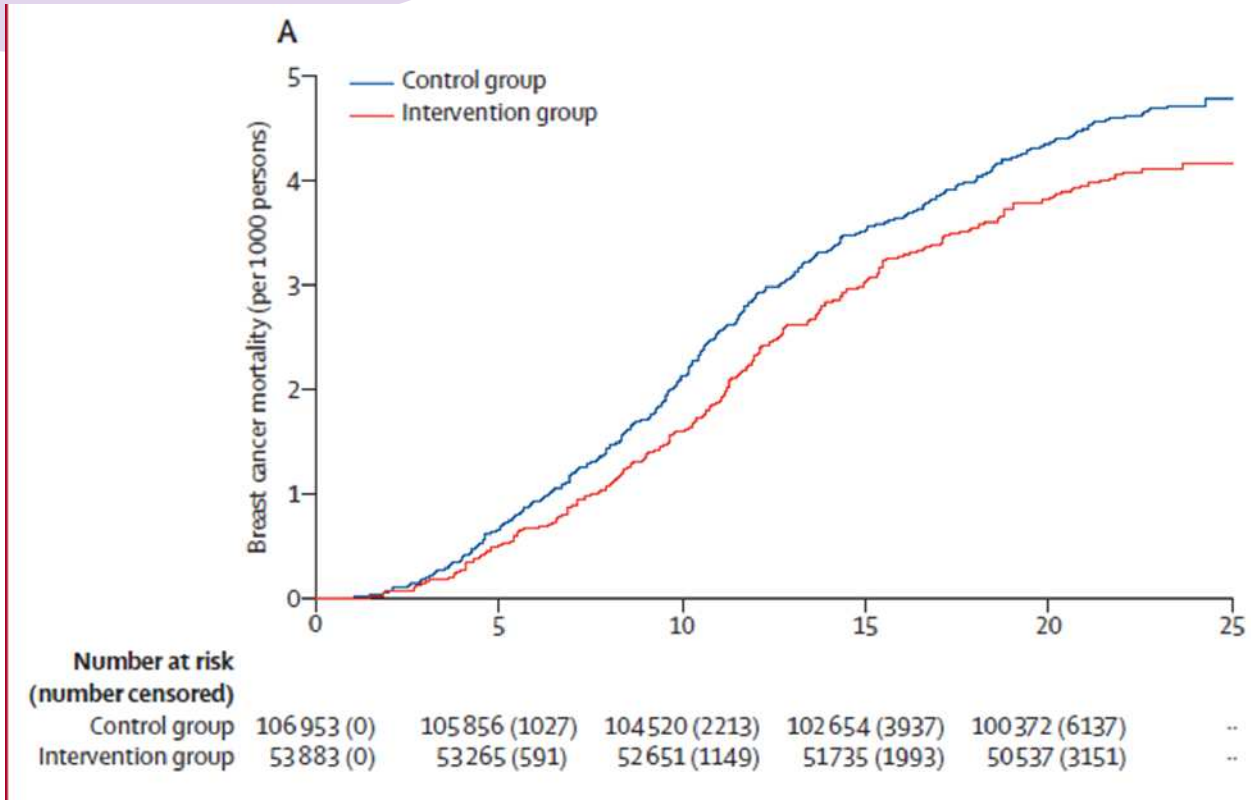
Table 1: **Mortality from breast cancers by period of cancer diagnosis and follow-up period**

Per protocol = same results

Données 40-50 ans: UK age trial

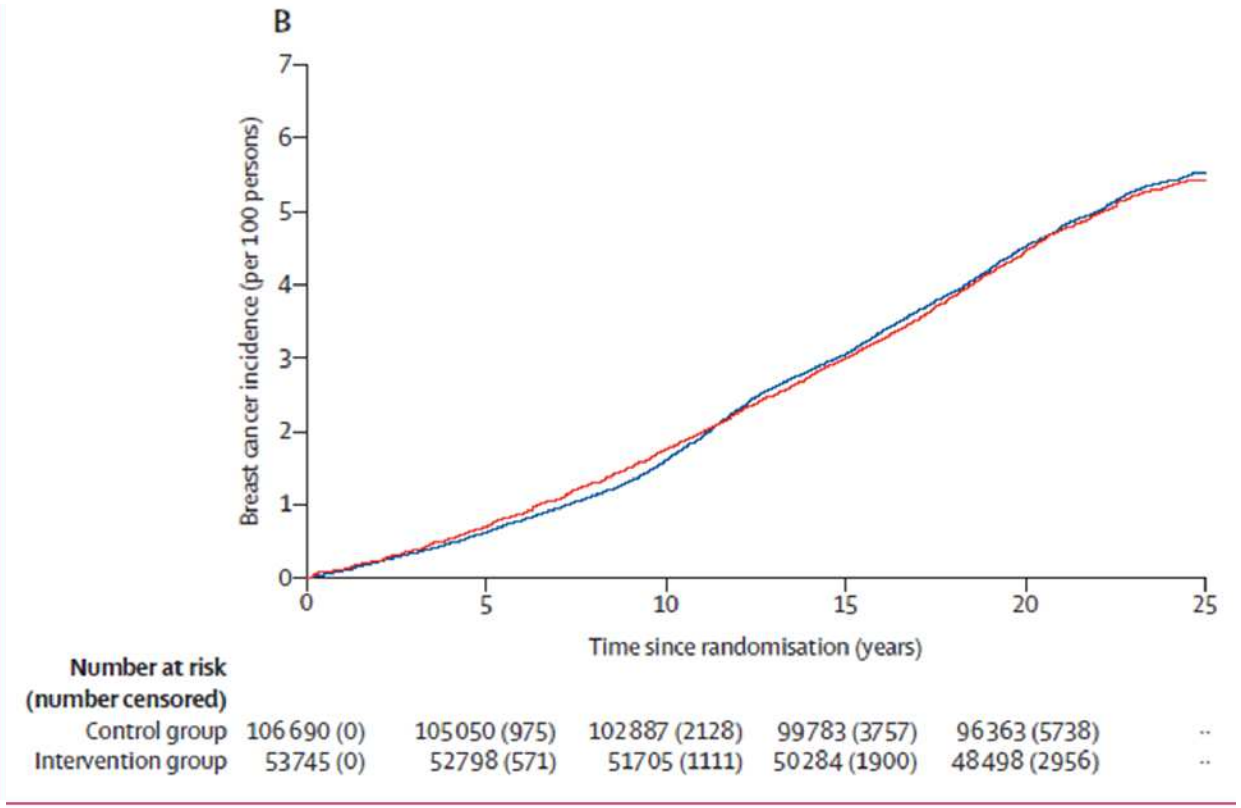
Duffy, Lancet Aug 2020
22 years results of the Age trial

BC mortality



Number at risk (number censored)						
Control group	106 953 (0)	105 856 (1027)	104 520 (2213)	102 654 (3937)	100 372 (6137)	..
Intervention group	53 883 (0)	53 265 (591)	52 651 (1149)	51 735 (1993)	50 537 (3151)	..

BC incidence



Number at risk (number censored)						
Control group	106 690 (0)	105 050 (975)	102 887 (2128)	99 783 (3757)	96 363 (5738)	..
Intervention group	53 745 (0)	52 798 (571)	51 705 (1111)	50 284 (1900)	48 498 (2956)	..

Figure 2: **Breast cancer mortality and incidence**
(A) Cumulative breast cancer mortality from randomisation to end of follow-up, from cancers diagnosed during the intervention period of the trial. (B) Cumulative incidence of breast cancer of any type, from randomisation to end of follow-up. Initial numbers are smaller than the totals analysed for mortality because women with breast cancer before randomisation have been excluded from the analysis of breast cancer incidence.

NNT (avoid 1 BC death) 1150

UK age trial surdiagnostics

	Intervention group		Control group		Intervention group vs control group, RR (95% CI)
	Breast cancers, n	Follow-up, person-years	Breast cancers, n	Follow-up, person-years	
Invasive cancers only					
Intervention period	835	569 632	1628	1129 985	1·02 (0·94–1·11)
Up to and including first NHSBSP screen	970	569 632	2021	1129 985	0·95 (0·88–1·04)
By the end of follow-up	2288	1177 990	4640	2 339 852	0·98 (0·93–1·03)
In-situ cancers only					
Intervention period	118	573 221	103	1137 432	2·27 (1·75–2·95)
Up to and including first NHSBSP screen	155	573 221	226	1137 432	1·36 (1·11–1·67)
By the end of follow-up	329	1195 224	620	2 375 349	1·05 (0·92–1·20)
All cancers					
Intervention period	953	569 016	1731	1129 491	1·09 (1·00–1·19)
Up to and including first NHSBSP screen	1125	569 016	2247	1129 491	0·99 (0·93–1·07)
By the end of follow-up	2617	1174 649	5260	2 334 516	0·99 (0·94–1·04)

Intervention period was defined as the period from randomisation up to immediately before first NHSBSP screen. RRs and 95% CIs are for incidence of breast cancer in intervention group compared with control group. RR=relative rate. NHSBSP=National Health Service Breast Screening Programme.

Table 2: **Cumulative incidence of breast cancer by trial group, cancer type, and follow-up period**

Pas d'effet sur la mortalité des grades 3

Breast cancer mortality by grade at 20 years follow-up, in intervention and control groups

Grade	Intervention group		Control group		RR (95% CI)
	Deaths	Rate per 1000 women	Deaths	Rate per 1000 women	
1 and 2	43	0.0008	112	0.0010	0.76 (0.45-1.08)
3	99	0.0018	190	0.0018	1.03 (0.81-1.32)

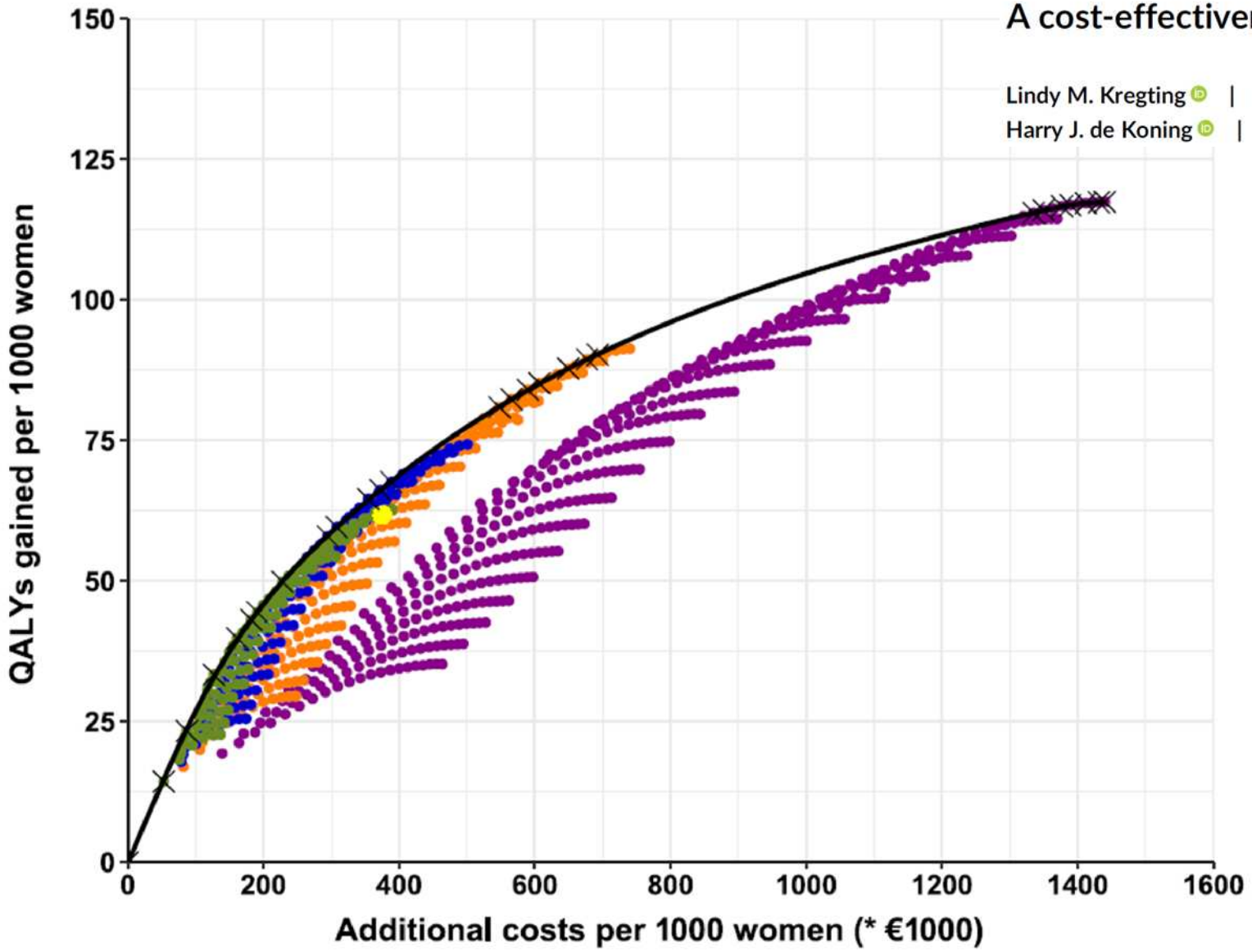
Modéliser la stratégie optimale

Finding the optimal mammography screening strategy:
A cost-effectiveness analysis of 920 modelled strategies

Lindy M. Kregting | Valérie D. V. Sankatsing | Eveline A. M. Heijnsdijk |
Harry J. de Koning | Nicolien T. van Ravesteyn

IJC INTERNATIONAL JOURNAL of CANCER

2022



Recommandation UE 2022
45-74 ans

Penser aussi les modalités

Supplemental MRI Screening for Women with Extremely Dense Breast Tissue

M.F. Bakker, S.V. de Lange, R.M. Pijnappel, R.M. Mann, P.H.M. Peeters, E.M. Monninkhof, M.J. Emaus, C.E. Loo, R.H.C. Bisschops, M.B.I. Lobbes, M.D.F. de Jong, K.M. Duvivier, J. Veltman, N. Karssemeijer, H.J. de Koning, P.J. van Diest, W.P.T.M. Mali, M.A.A.J. van den Bosch, W.B. Veldhuis, and C.H. van Gils, for the DENSE Trial Study Group*

Table 2. Interval-Cancer Rates and Rate Difference between Trial Groups, According to Two Analysis Methods.*

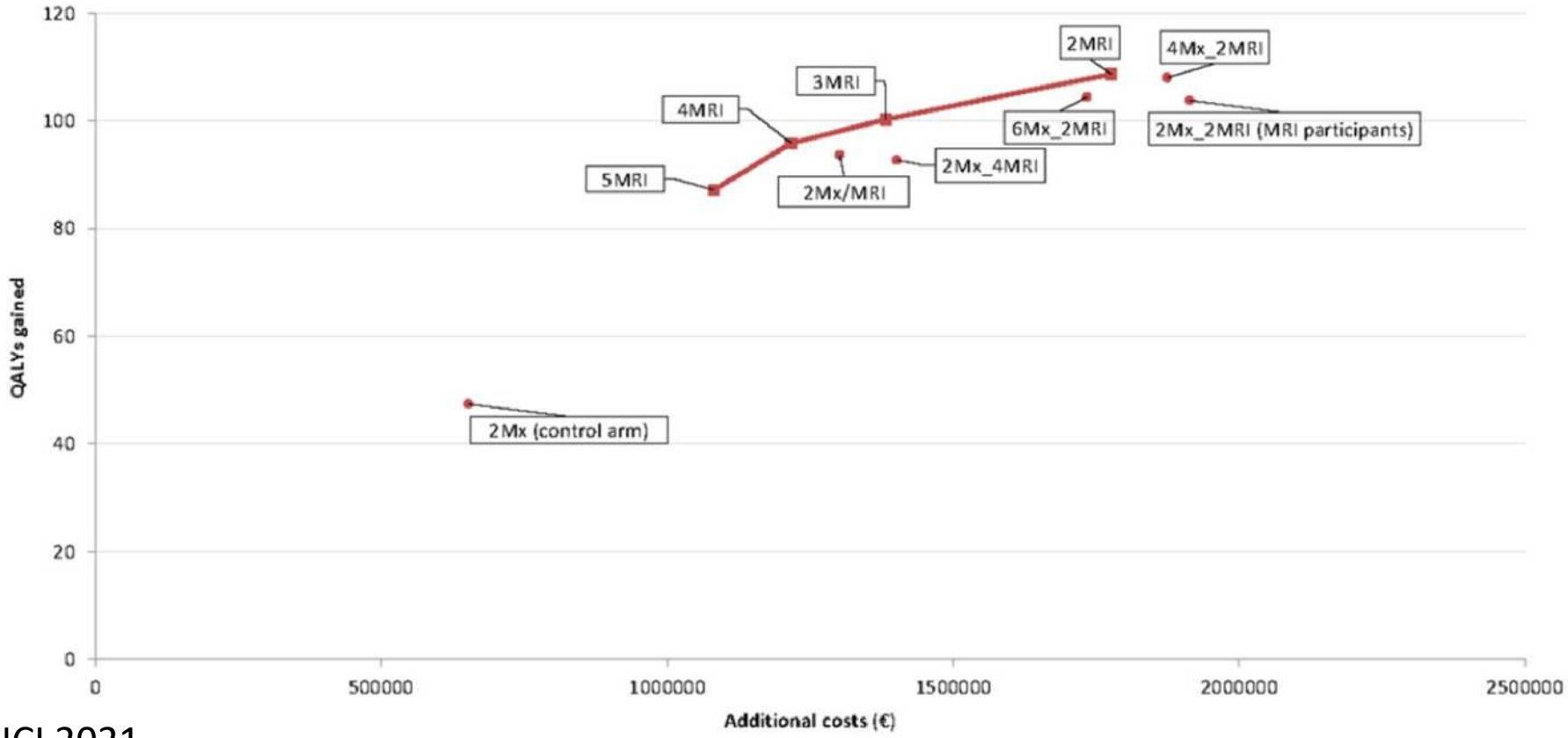
Type of Analysis	MRI-Invitation Group	Mammography-Only Group	Rate Difference (95% CI)
Intention-to-screen analysis			
Women with interval cancer — no./total no.	20/8061	161/32,312	
Interval-cancer rate (95% CI)			
No. per 1000 screenings	2.5 (1.6–3.8)	5.0 (4.3–5.8)	2.5 (1.0–3.7)
No. per 1000 person-yr	1.3 (0.7–1.8)	2.5 (2.1–2.9)	1.3 (0.6–1.9)

Bakker et al NEJM 2020

Cost-Effectiveness of Magnetic Resonance Imaging Screening for Women With Extremely Dense Breast Tissue

H. Amarens Geuzinge, MSc,[1,*] Marije F. Bakker, PhD,[2] Eveline A.M. Heijnsdijk, PhD,[1] Nicolien T. van Ravesteyn, PhD,[1] Wouter B. Veldhuis, MD,[3] Ruud M. Pijnappel, MD,[3] Stéphanie V. de Lange, MD,[2,3] Marleen J. Emaus, PhD,[3] Ritse M. Mann, MD,[4,5] Evelyn M. Monninkhof, PhD,[2] Petra K. de Koekkoek-Doll, MD,[5] Carla H. van Gils, PhD,[2] Harry J. de Koning, MD,[1] on behalf of the DENSE trial study group

Mis en place NL
Recommandation EUSOBI 2022
Recommandation UE 2022



Geuzinge JNCI 2021

Faut il modifier les bornes du dépistage en France

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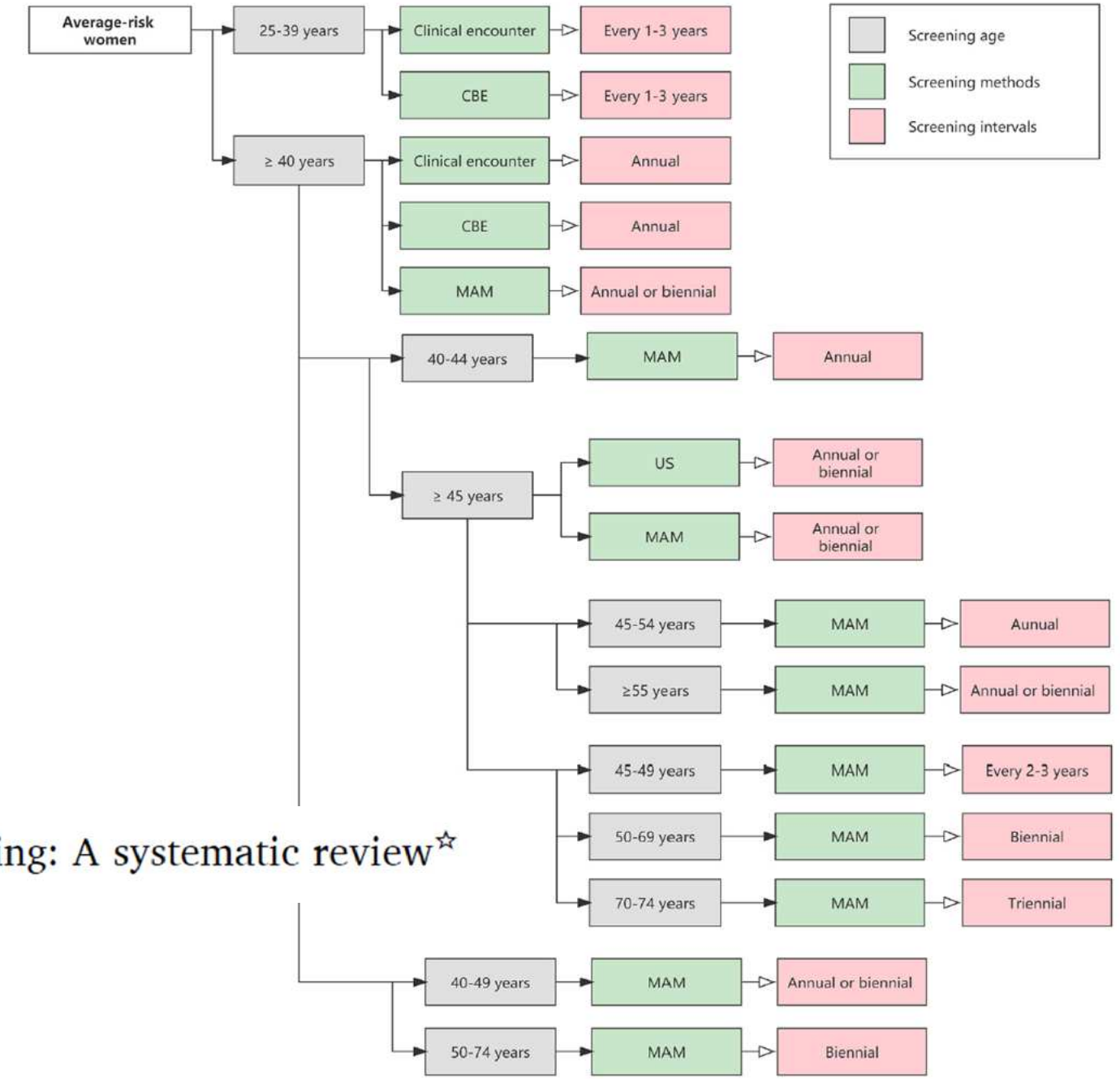
Les recommandations existantes sont assez variables



Global guidelines for breast cancer screening: A systematic review☆

Ren, The Breast 2022

UE- circulaire 2022

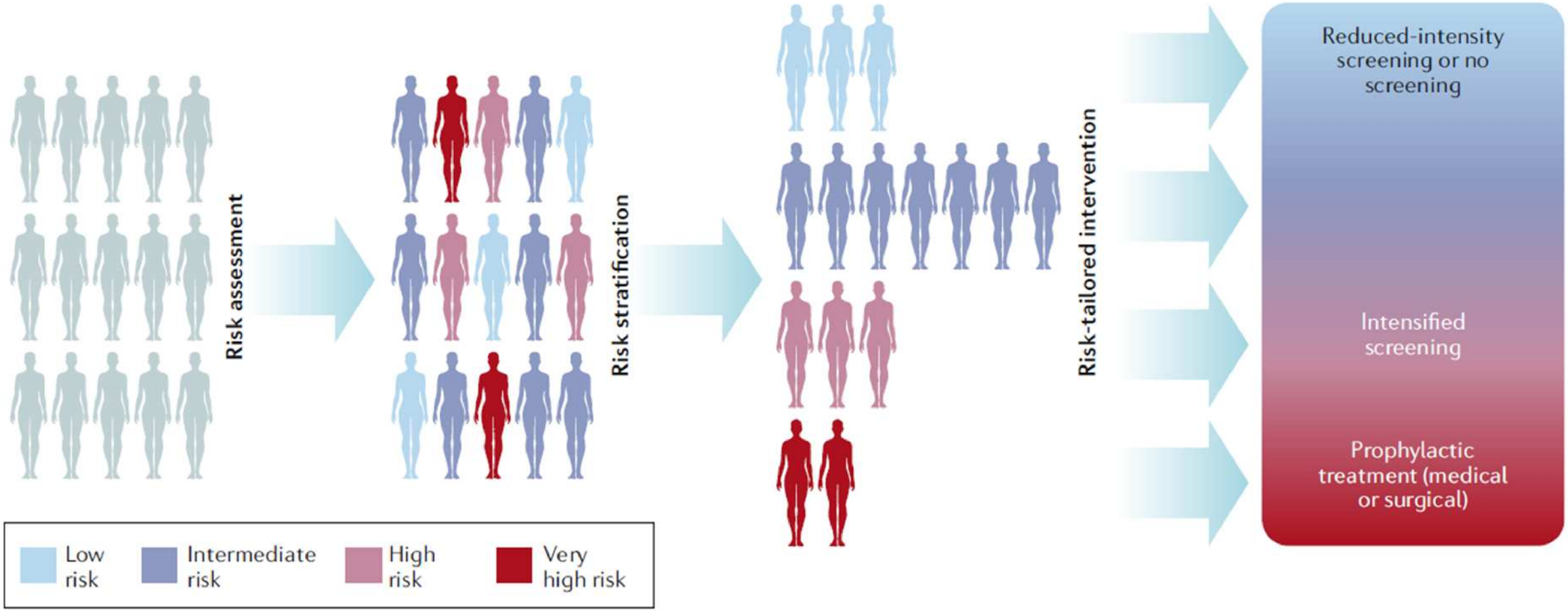
This proposal for a new Council Recommendation replacing Recommendation 2003/878/EC has the following objectives:

- Supporting cancer screening through the whole pathway of cancer care as part of a new Union approach to cancer prevention under Europe's Beating Cancer Plan.
- Supporting the development of the new EU-supported Cancer Screening Scheme to ensure that 90% of the EU population who qualify for breast, cervical and colorectal cancer screenings are offered screening by 2025;
- Regular systematic monitoring of screening programmes including disparities via the European cancer information system and the Cancer Inequalities Registry;
- Sharing data on cancer screening, including through the planned European Health Data Space[4];
- Updating the breast, cervical and colorectal cancer screening recommendations;
- Extending breast cancer screening from women aged 50 to 69 to include women between 45 and 74 years of age and to consider specific diagnostic measures for women with particularly dense breasts;

Faut il modifier les bornes du dépistage en France

- Arguments et données
- Recommandations
- Perspectives

Dépistage stratifié?



Pashayan et al Nature Rev Clin Oncol 2020

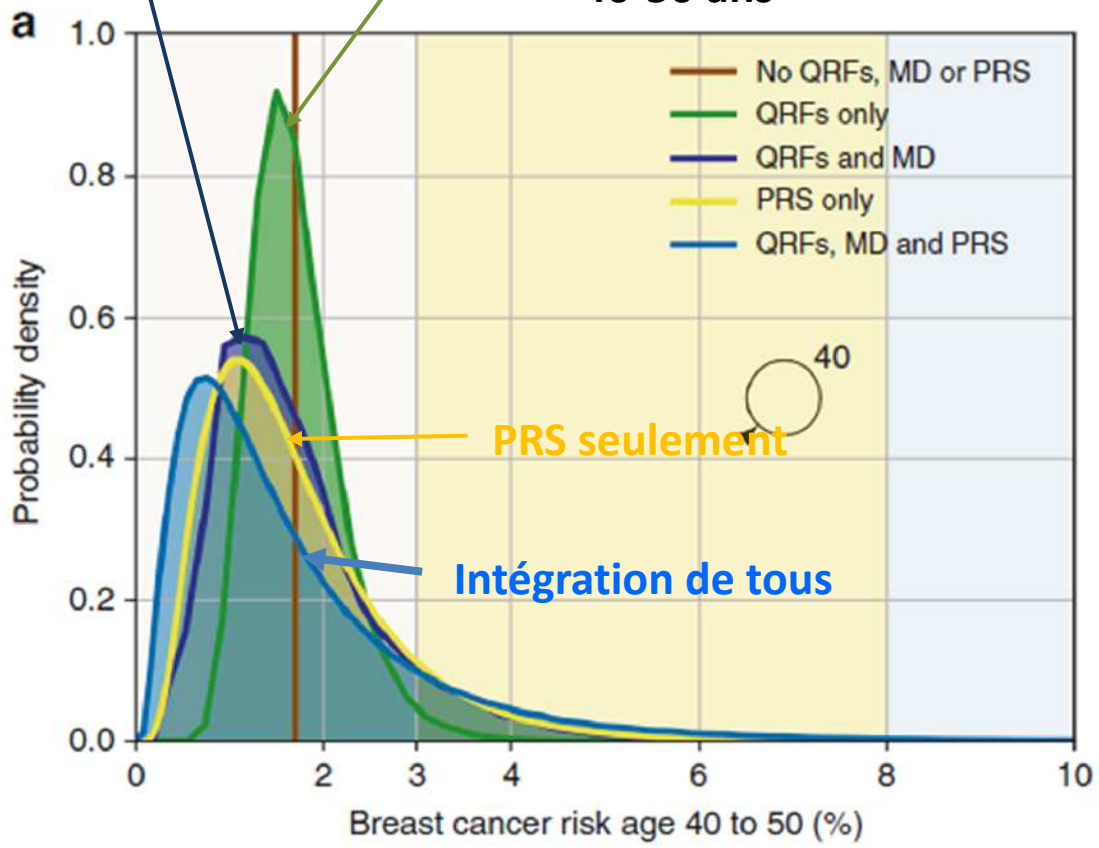
Scores de risque incluant un PRS

Les SNPS améliorent la discrimination des scores de risque ds tous les modèles de risque

Densité mammographique seulement

Questionnaires seulement

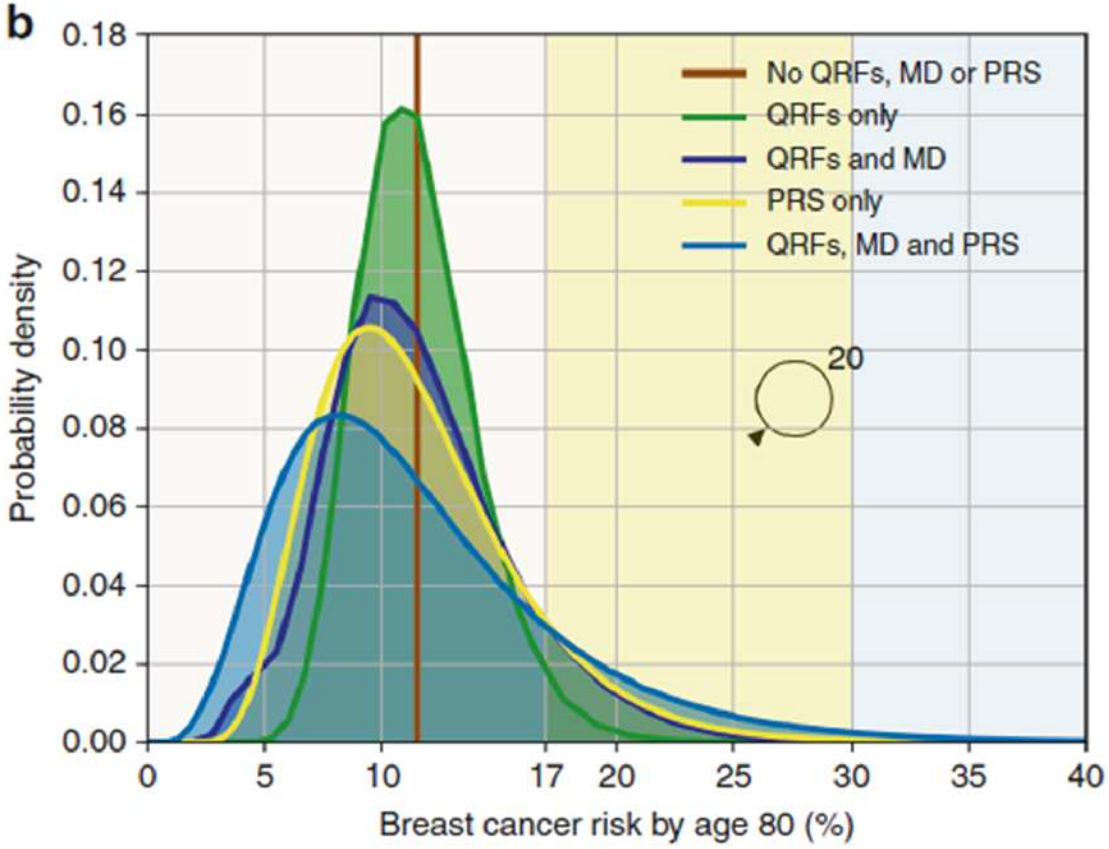
40-50 ans



PRS seulement

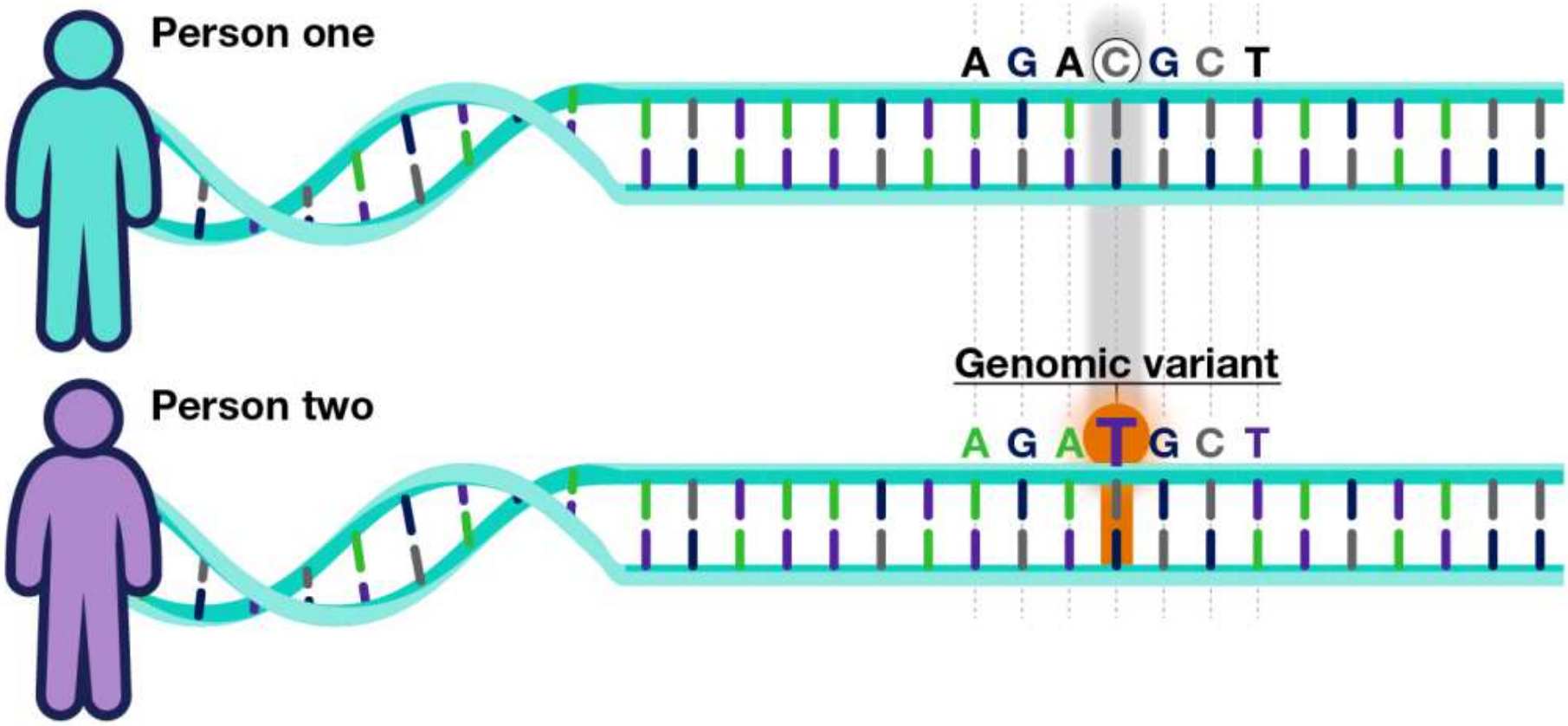
Intégration de tous

lifetime



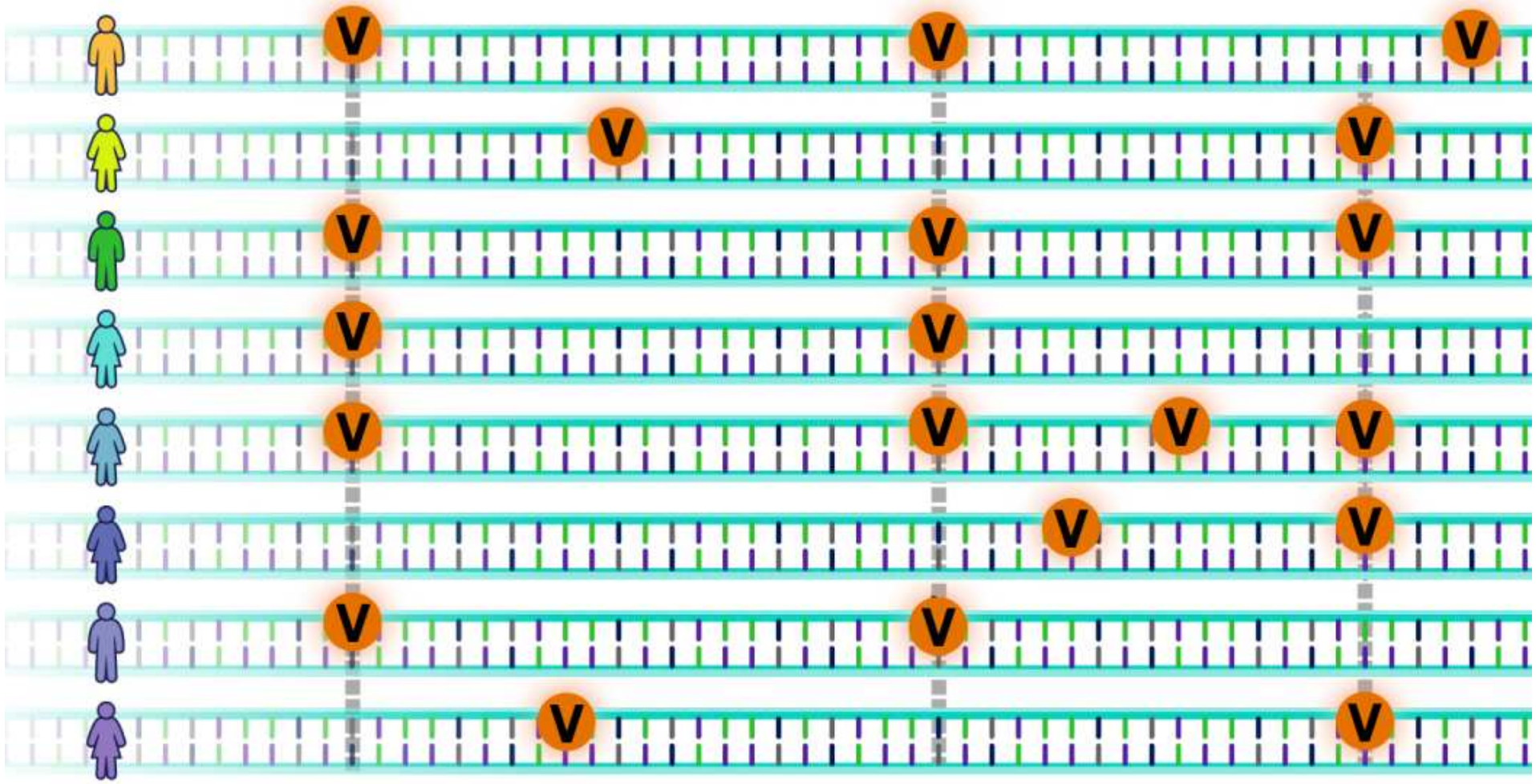
Lee et al Genet Med 2019

Un SNP (Single Nucleotide Polymorphism) est une variation (polymorphisme) d'une seule paire de bases de l'ADN du génome, par rapport aux autres individus d'une même espèce.



Source NIH, National Human genome Research Institute

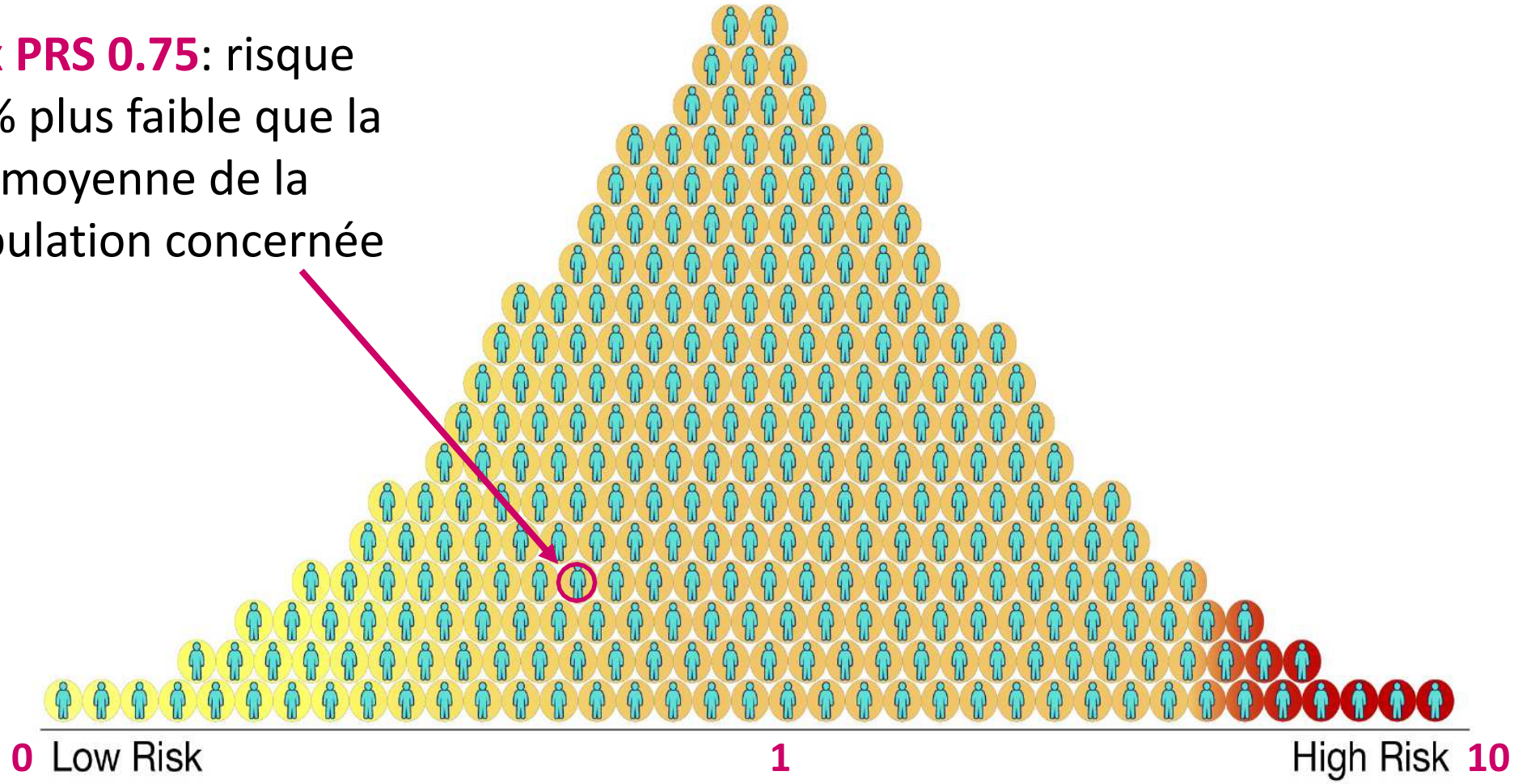
Ces variations sont très fréquentes (environ une paire de bases sur mille dans le génome humain, soit 4-5 millions de variations!)



Source NIH, National Human genome Research Institute

Un score de polymorphismes (PRS) donne un risque relatif pour une maladie donnée

Ex PRS 0.75: risque 25% plus faible que la moyenne de la population concernée



Source NIH, National Human genome Research Institute

Preuve de concept PRS/risk-based screening: MyPeBS Trial

56,000 women, 5 countries
2.5 years inclusion
4 year-follow-u

40000 inclusions à ce jour

40-70 years-old women
Invitation from organized screening centres or volunteering

Dedicated visit

Exclusion criteria:
Women with prior breast cancer or already identified very high risk

ELIGIBILITY

Randomisation

Arm 1 - Standard

Standard screening according to ongoing recommendations

Arm 2 - Risk-stratified

Risk evaluation (including salivary test)

Risk-based screening according to 5-year risk

Low risk
=> Next mammogram at 4 years

Average risk
=>2-yearly mammogram

High risk
=> yearly mammogram

Very high risk
=> Annual mammogram and MRI

Primary endpoint: Incidence of stage 2 or higher breast cancer in each group at 4 years

AT 10 AND 15 YEARS :

LONG TERM FOLLOW-UP INCLUDING BREAST CANCER MORTALITY

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Choice of multi-gene testing
  - The introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to hereditary cancer testing of at-risk patients and their families. Based on next-generation sequencing (NGS) technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.
  - An individual's personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history through a multi-gene panel test may be more efficient and cost-effective and increase the yield of detecting a pathogenic/likely pathogenic variant in a gene that will impact medical management for the individual or thier at-risk family members.
  - There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
  - Some individuals may carry pathogenic/likely pathogenic germline variants in more than one cancer susceptibility gene; thus, consideration of a multi-gene panel for individuals already known to carry a single pathogenic/likely pathogenic germline variant from phenotype-directed testing may be considered on a case-by-case basis, based on the degree of suspicion for there being additional variants.
  - Because commercially available tests differ in the specific genes analyzed, variant classification, and other factors (eg, methods of DNA/RNA analysis or option to reflex from a narrow to a larger panel; provision of financial assistance for cascade testing of relatives), it is important to consider the indication for testing and expertise of the laboratory when choosing the specific laboratory and test panel.
  - Multi-gene testing can include "intermediate" penetrant (moderate-risk) genes.[b] For many of these genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene tests are necessarily clinically actionable.
  - It may be possible to refine risks associated with both moderate and high penetrance genes, taking into account the influence of gene/gene or gene/environment interactions. In addition, certain pathogenic/likely pathogenic variants in a gene may pose higher or lower risk than other pathogenic/likely pathogenic variants in that same gene. This information should be taken into consideration when assigning risks and management recommendations for individuals and their at-risk relatives.
  - In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.
  - Pathogenic/likely pathogenic variants in many breast, ovarian, pancreatic, and prostate cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions, thus posing risks to offspring if the partner is also a carrier.
  - As more genes are tested, there is an increased likelihood of finding VUS, mosaicism, and clonal hematopoiesis of indeterminate potential (CHIP).
  - Multi-gene panel testing increases the likelihood of finding pathogenic/likely pathogenic variants without clear clinical significance.
  - Germline confirmatory testing should be done when a pathogenic variant is found on tumor genomic testing that has clinical implications if also identified in the germline.
  - There are significant limitations in interpretation of polygenic risk scores (PRSs). PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial. See Discussion.

Le risque en images??!

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

A risk model for digital breast tomosynthesis to predict breast cancer and guide clinical care

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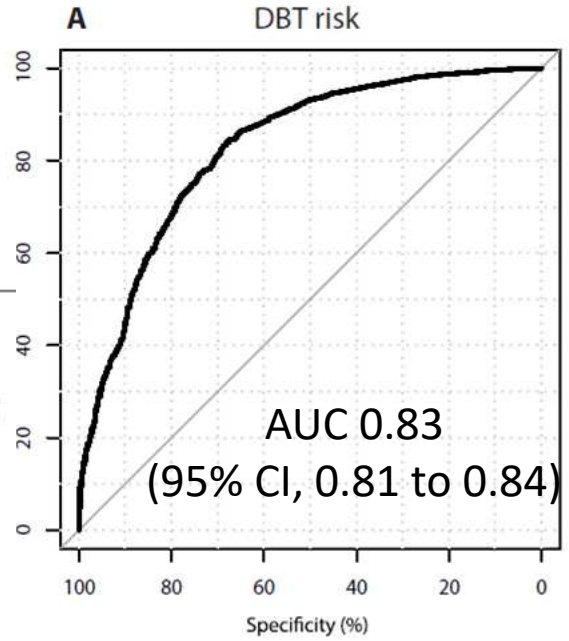
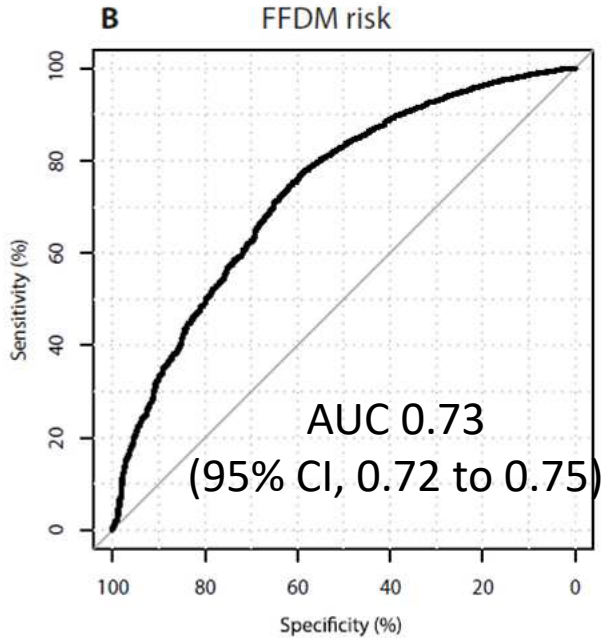
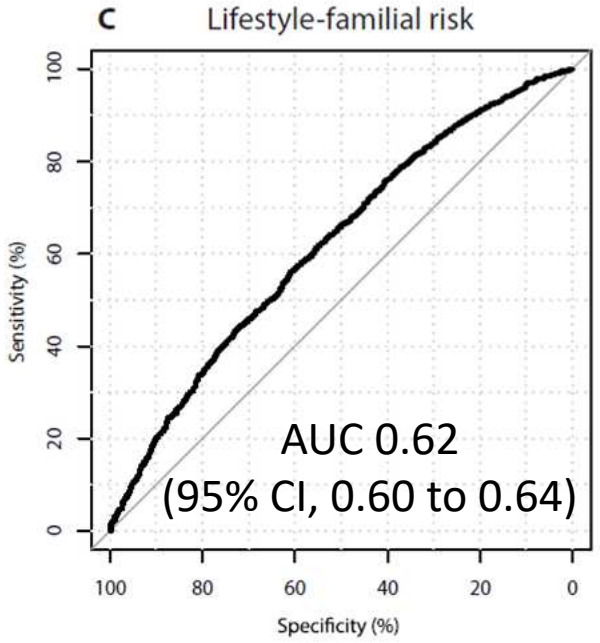
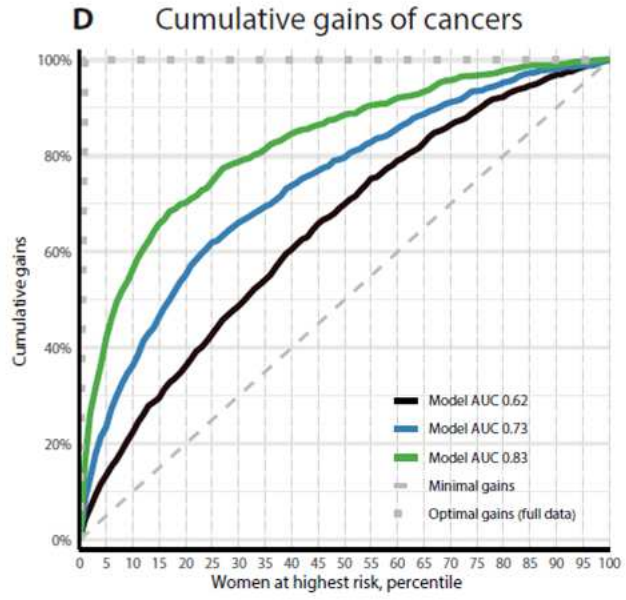
Short term (2 year) breast cancer risk model based on images
First developed on 2D mammograms

New development on 3D (tomosynthesis) and validation in 2 US caase-control cohorts



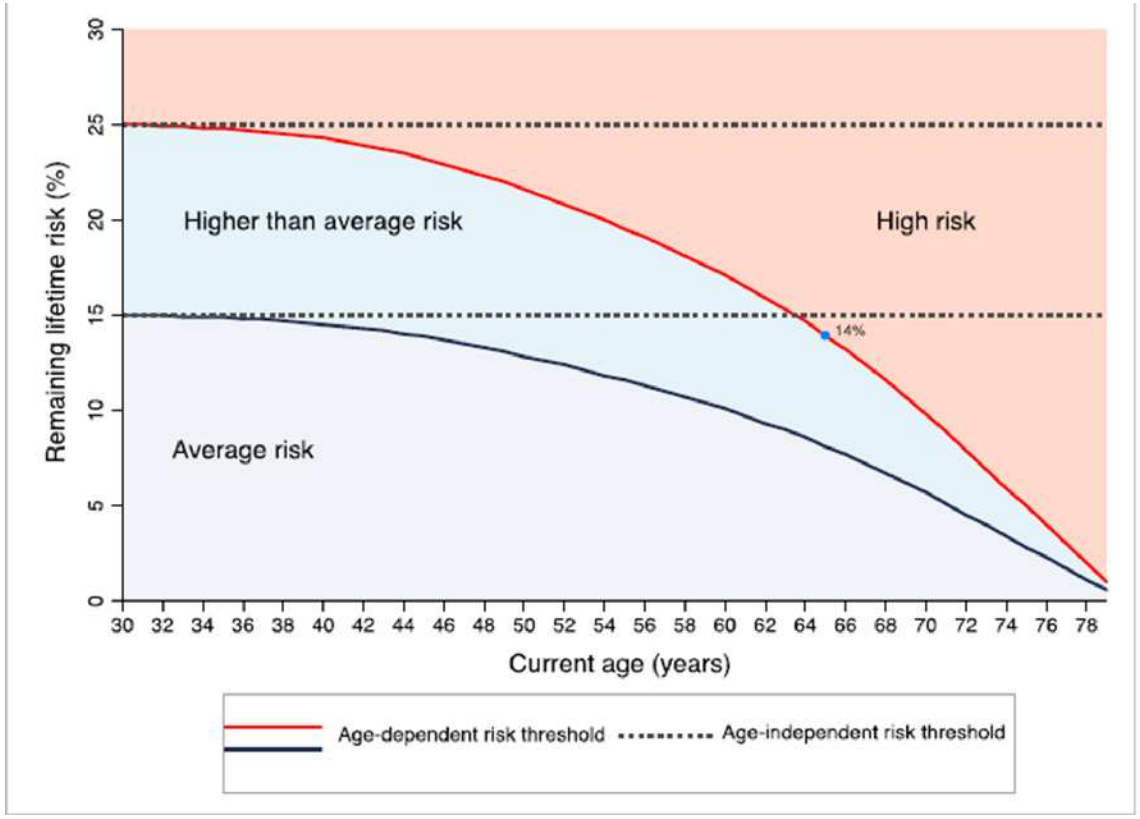




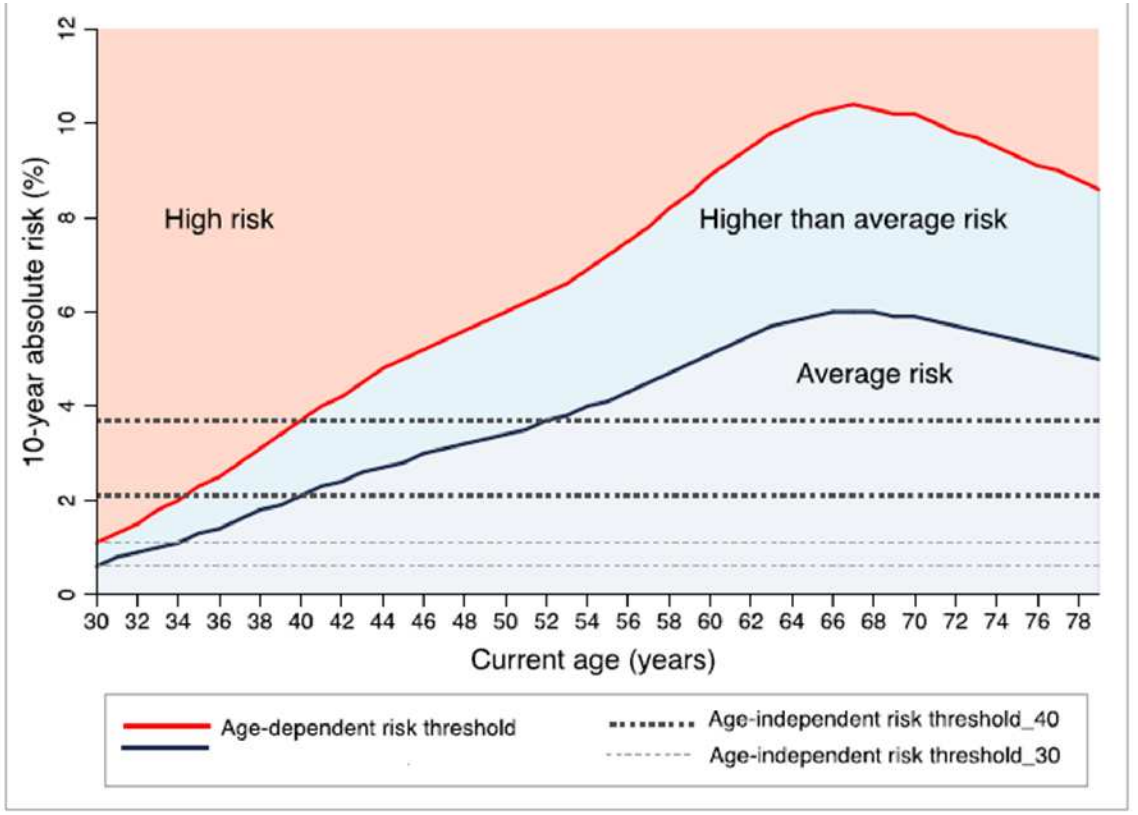


Cut-off de risque dépendant de l'âge?

Risque restant au cours de la vie



Risque absolu dans les 10 ans à venir



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Conclusions: mon opinion!

- Le cancer du sein demeure un problème de santé publique majeur
- Malgré des investissements massifs et leur lourdeur, les progrès des traitements peinent maintenant à améliorer mortalité
- Élargir le dépistage aux 45-50 est une recommandation de l'UE
- Sa mise en œuvre pourrait comporter une modalité d'aide décisionnelle individuelle sur le rapport bénéfice-risque
- Le dépistage individuel après 74 ans génère actuellement des inégalités de santé et n'est pas délivré scientifiquement
- Un dépistage stratifié selon le risque individuel pourrait, si démontré formellement, être une modalité majeure dans le futur

Merci!!!!