Genetic predisposition to breast cancer in Asian women

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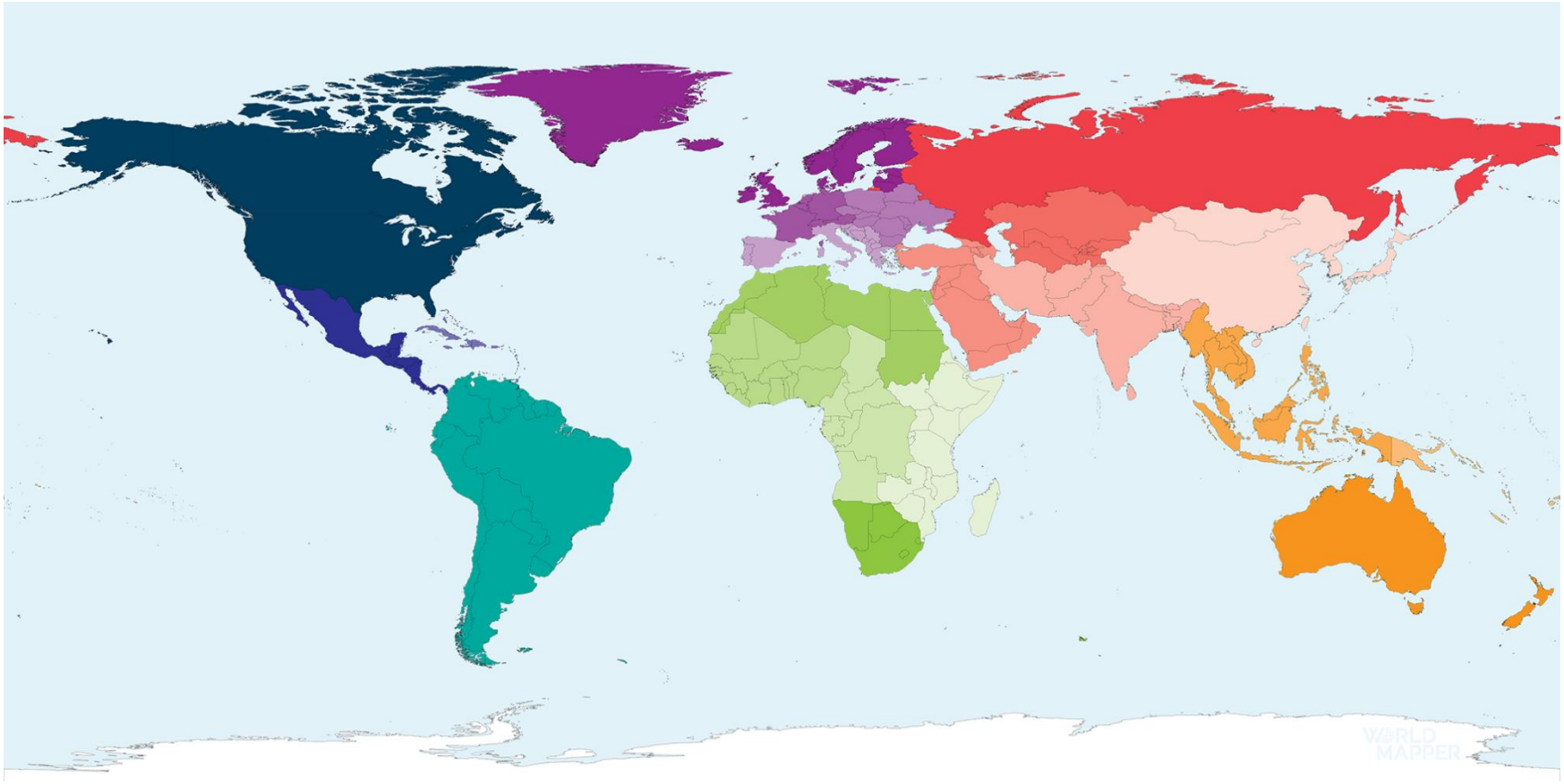
Cancer Research Malaysia

Disclosures

- None

The world as we know it…



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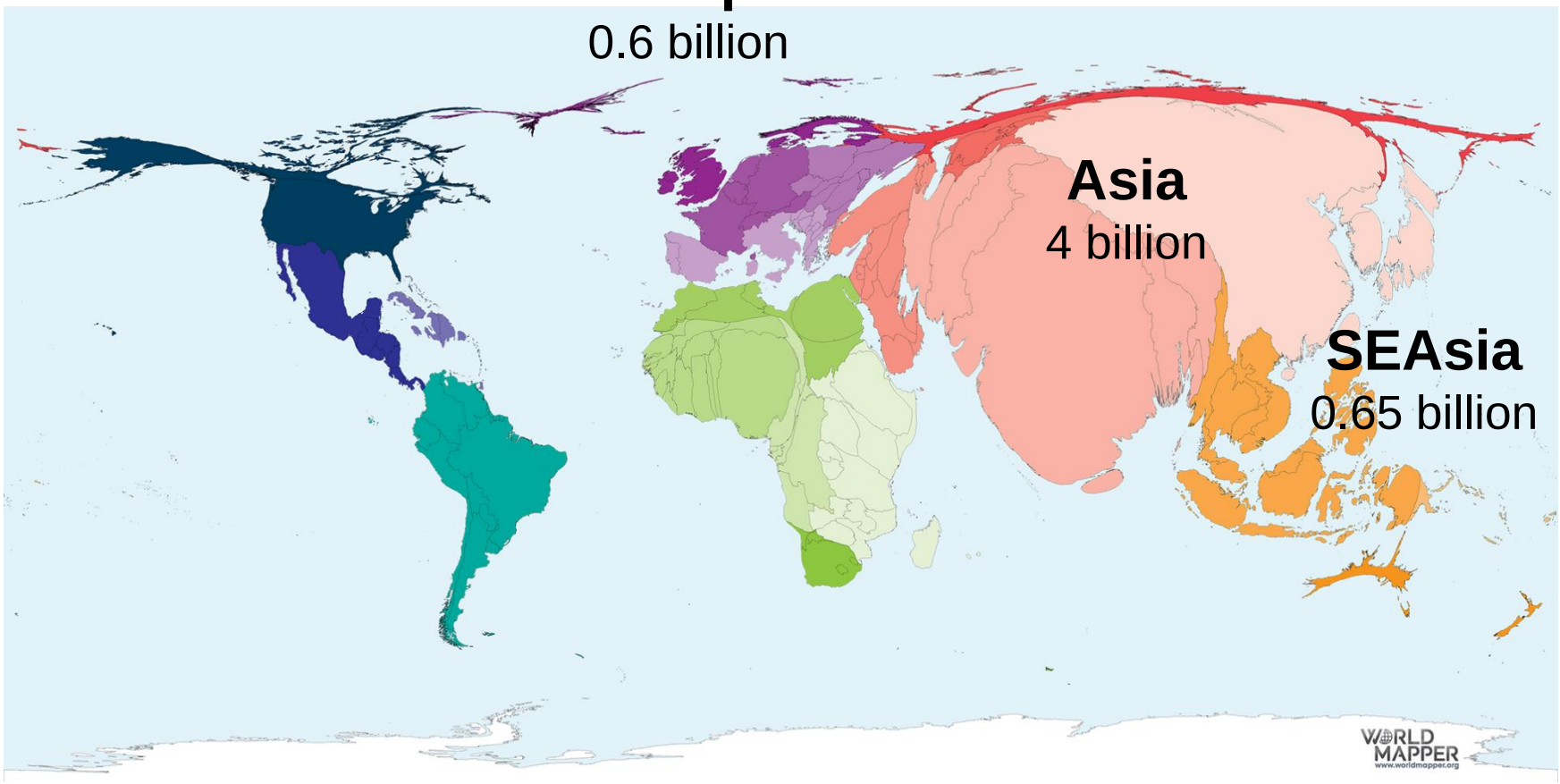
The world by population size



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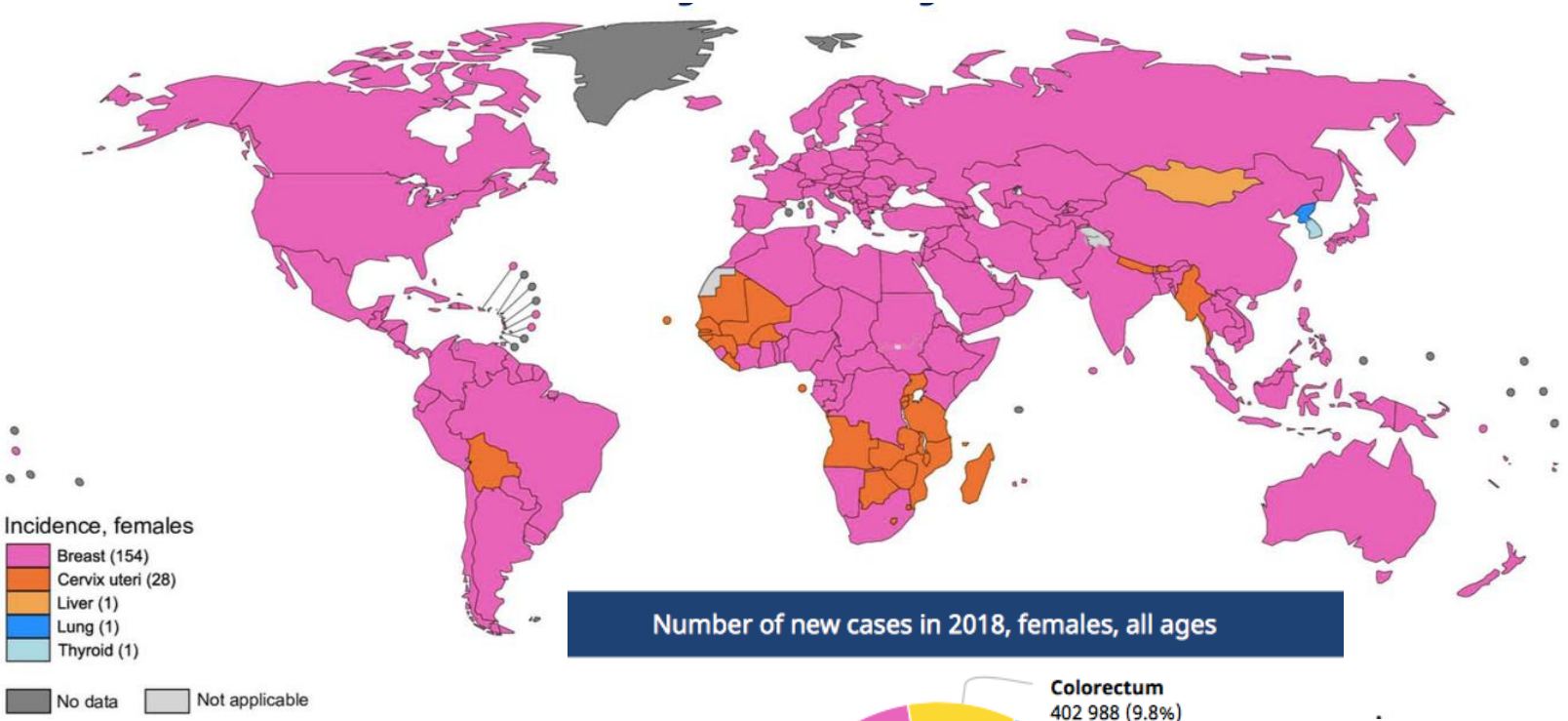
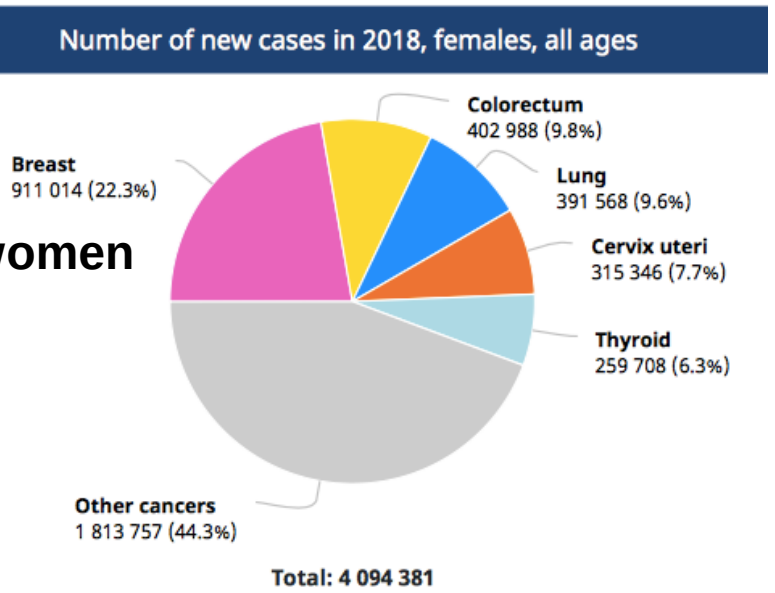
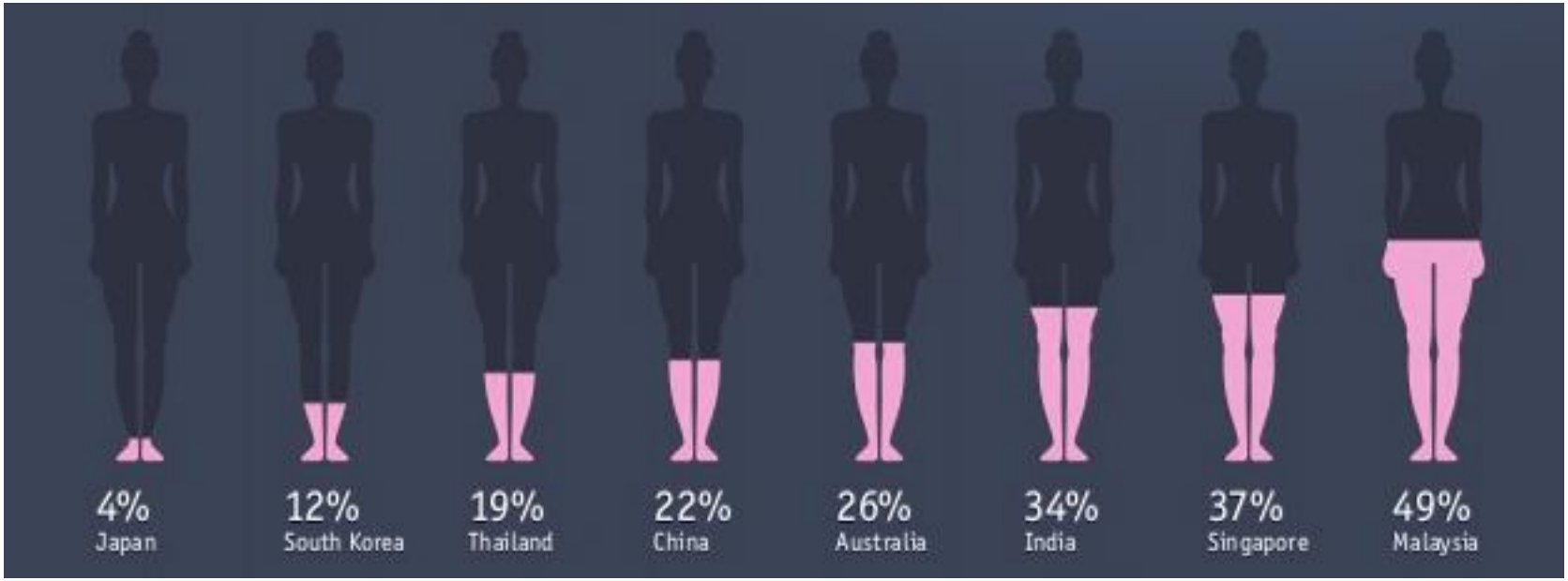
Most common cancer in women

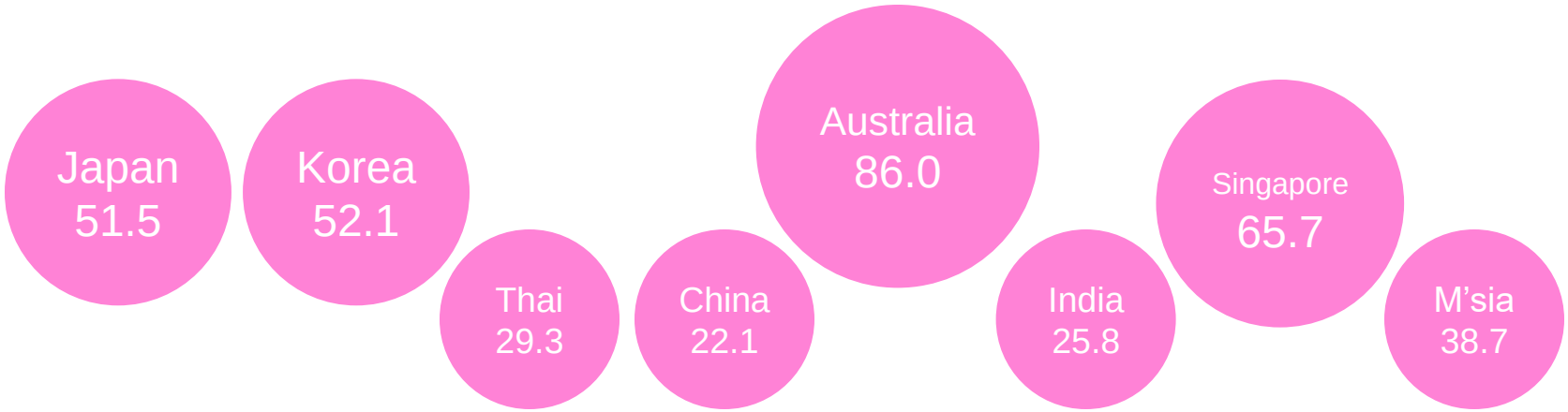


1 in 5 cancers in Asian women



Breast cancer in Asia in increasing





Survival in Asia in lags other regions

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In the face of significant challenges in cancer control,

(especially lack of man-power and funding, and competing priorities)

is there a role for genetics and genomics?

No population-based screening programmes:

Could risk stratified approaches identify individuals who might benefit from screening?
[Doug Easton, Antonis Antoniou]

Insufficient funding for targetted therapy

Could genomics identify individuals who benefit the most?
[Carlos Caldas, Chin Suet Feung]

Are Asians the same?

Rare variants

- 60,466 cases, 53,461 controls
  - European studies: 52,230 cases, 45,579 controls
  - Asian studies: 8,236 cases, 7,882 controls

- Panel sequencing with 34 genes
  - Fluidgm Juno, Illumina
  - Vardict caller

Dorling et al., submitted

Similar prevalence (except CHEK2)

	European studies [52,230 cases, 45,479 controls]				Asian studies [8,236 cases, 7,882 controls]				
Gene	Cases	Prevalence	Controls	Prevalence	Cases	Prevalence	Controls	Prevalence	**p-diff**
BRCA1	425	**0.8**	55	0.1	65	**0.8**	3		**NS**
BRCA2	607	**1.2**	118	0.2	136	**1.6**	17		**NS**
PALB2	235	**0.4**	48	0.1	35	**0.4**	7		**NS**
TP53	7	**0.01**	2	<0.01	0	**0**	0		**-**
CHEK2	693	**1.3**	307	0.7	11	**0.1**	8		
ATM	266	**0.5**	138	0.3	26	**0.3**	11		**NS**
PTEN	11	**0.02**	5	<0.01	3	**<0.01**	1		**NS**
BARD1	51	**0.1**	28	0.06	11	**0.1**	4		**NS**
RAD51C	39	**0.07**	19	0.04	15	**0.2**	7		**NS**
RAD51D	37	**0.07**	19	0.04	14	**0.2**	6		**NS**
MSH6	34	**0.07**	23	0.05	3	**<0.01**	0		**NS**
NF1	23	**0.04**	16	0.04	8	**<0.01**	1		**NS**

Absence of 1100delC

Dorling et al., submitted

Similar association in risk

	European studies [52,230 cases, 45,479 controls]					Asian studies [8,236 cases, 7,882 controls]					
Gene	Cases	Controls	OR	95% CI	p.value	Cases	Controls	OR	95% CI	p-value	**p-diff**
BRCA1	425	55	9.33	(7.00-12.43)	1.75E-52	65	3	22.07	(6.91-70.48)	1.8E-07	**0.16**
BRCA2	607	118	5.38	(4.38-6.59)	7.63E-59	136	17	8.16	(4.90-13.57)	6.2E-16	**0.14**
PALB2	235	48	4.99	(3.62-6.86)	5.71E-23	35	7	4.52	(2.00-10.22)	2.9E-04	**0.83**
TP53	7	2	3.06	(0.63-14.92)	0.17	0	0	-	--		**-**
CHEK2	693	307	2.57	(2.23-2.95)	2.51E-39	11	8	1.51	(0.60-3.82)	0.39	**0.27**
ATM	266	138	2.07	(1.68-2.57)	2.0E-11	26	11	2.34	(1.15-4.76)	0.019	**0.75**
PTEN	11	5	2.14	(0.72-6.34)	0.17	3	1	2.81	(0.29-27.37)	0.38	**0.83**
BARD1	51	28	2.02	(1.26-3.24)	0.0038	11	4	2.54	(0.81-8.00)	0.11	**0.72**
RAD51C	39	19	1.89	(1.08-3.31)	0.027	15	7	2.04	(0.83-5.02)	0.12	**0.89**
RAD51D	37	19	1.65	(0.94-2.91)	0.082	14	6	2.27	(0.87-5.92)	0.09	**0.58**
MSH6	34	23	1.66	(0.96-2.86)	6.760E-02	3	0	0.00	(0-Inf)	0.91	**0.92**
NF1	23	16	1.36	(0.71-2.62)	0.36	8	1	7.84	(0.98-62.74)	0.052	**0.12**

Dorling et al., submitted

Clinical characteristics of carriers

cancer research malaysia

Variable	Category	Model A (Unselected cohort)										
		BRCA1/2 n=5,391 (205 BRCA1/2 Carriers)				BRCA1 n=5,258 (72 BRCA1 Carriers)				BRCA2 n=5,319 (133 BRCA2 Carriers)			
		OR	95% CI		P-value	OR	95% CI		P-value	OR	95% CI		P-value
Baseline		0.06	0.02	0.16	<0.001	0.02	0.00	0.09	<0.001	0.03	0.01	0.09	<0.001
Age of Diagnosis		**0.95**	**0.93**	**0.96**	**<0.001**	**0.93**	**0.91**	**0.96**	**<0.001**	**0.95**	**0.94**	**0.97**	**<0.001**
Ethnicity	Chinese	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
	Malay	**1.62**	**1.12**	**2.34**	**0.010**	1.71	0.90	3.26	0.104	**1.60**	**1.02**	**2.45**	**0.039**
	Indian	**2.06**	**1.36**	**3.14**	**0.001**	**2.97**	**1.57**	**5.64**	**0.001**	1.61	0.93	2.80	0.091
	Other	1.85	0.56	6.17	0.314	2.17	0.28	17.01	0.460	1.73	0.41	7.33	0.458
Bilateral Breast Cancer	Unilateral	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
	Contralateral	**2.37**	**1.46**	**3.86**	**0.001**	**2.99**	**1.41**	**6.38**	**0.004**	**1.96**	**1.05**	**3.65**	**0.035**
	Ipsilateral	0.81	0.25	2.67	0.734	0.74	0.09	5.83	0.774	0.86	0.21	3.59	0.835
ER Status	ER+	1.00	-	-	-	1.00	-	-	-	-	-	-	-
	ER-	**1.57**	**1.15**	**2.14**	**0.004**	**6.62**	**3.70**	**11.86**	**<0.001**	-	-	-	-
HER2 Status	HER2+	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
	HER2-	**2.55**	**1.75**	**3.71**	**<0.001**	**4.22**	**2.05**	**8.70**	**<0.001**	**2.04**	**1.32**	**3.14**	**0.001**
Grade	One	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
	Two	**2.28**	**1.20**	**4.35**	**0.012**	0.92	0.35	2.41	0.861	3.79	**1.51**	**9.52**	**0.005**
	Three	**3.41**	**1.79**	**6.50**	**<0.001**	1.43	0.56	3.62	0.454	5.20	**2.08**	**13.01**	**<0.001**
First Degree Family History of Breast Cancer	No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
	Yes	**2.85**	**2.06**	**3.94**	**<0.001**	**3.31**	**1.90**	**5.75**	**<0.001**	**2.59**	**1.75**	**3.84**	**<0.001**
First Degree Family History of Ovarian Cancer	No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
	Yes	**5.57**	**2.99**	**10.35**	**<0.001**	**11.02**	**4.70**	**25.88**	**<0.001**	**3.44**	**1.43**	**8.28**	**0.006**

Dorling et al., submitted

Which clinical criteria?

Model	NCCN Criteria	MCG Criteria	MCGplus Criteria	Expanded NCCN Criteria	Modified MCGplus Criteria
Sensitivity (%)	**67.0**	**67.0**	-	-	**67.0**
Specificity (%)	65.0	65.0	-	-	70.0
Patients to be screened (%)	36.0	37.0	-	-	32.0
Detection ratio	13 : 1	13 : 1	-	-	11 : 1
Sensitivity (%)	-	-	**76.0**	-	**76.0**
Specificity (%)	-	-	54.0	-	56.0
Patients to be screened (%)	-	-	47.0	-	46.0
Detection ratio	-	-	15 : 1	-	14 : 1
Sensitivity (%)	-	-	-	**96.0**	-
Specificity (%)	-	-	-	11.0	-
Patients to be screened (%)	-	-	-	89.0	-
Detection ratio	-	-	-	22 : 1	-

Significant proportion of Asian BRCA carriers missed by NCCN Criteria

Ang et al., in prep

Which clinical criteria?

Model	NCCN Criteria	MCG Criteria	MCGplus Criteria	Expanded NCCN Criteria	Modified MCGplus Criteria	Model A	Model B
Sensitivity (%)	**67.0**	**67.0**	-	-	**67.0**	**67.0**	**67.0**
Specificity (%)	65.0	65.0	-	-	70.0	76.0	75.0
Patients to be screened (%)	36.0	37.0	-	-	32.0	23.0	54.0
Detection ratio	13 : 1	13 : 1	-	-	11 : 1	8 : 1	19 : 1
Sensitivity (%)	-	-	**76.0**	-	**76.0**	**76.0**	**76.0**
Specificity (%)	-	-	54.0	-	56.0	65.0	65.0
Patients to be screened (%)	-	-	47.0	-	46.0	33.0	65.0
Detection ratio	-	-	15 : 1	-	14 : 1	10 : 1	20 : 1
Sensitivity (%)	-	-	-	**96.0**	-	**96.0**	**96.0**
Specificity (%)	-	-	-	11.0	-	18.0	17.0
Patients to be screened (%)	-	-	-	89.0	-	86.0	97.0
Detection ratio	-	-	-	22 : 1	-	21 : 1	24 : 1

Model built using data from population-based cohort outperforms clinical criteria

Ang et al., in prep

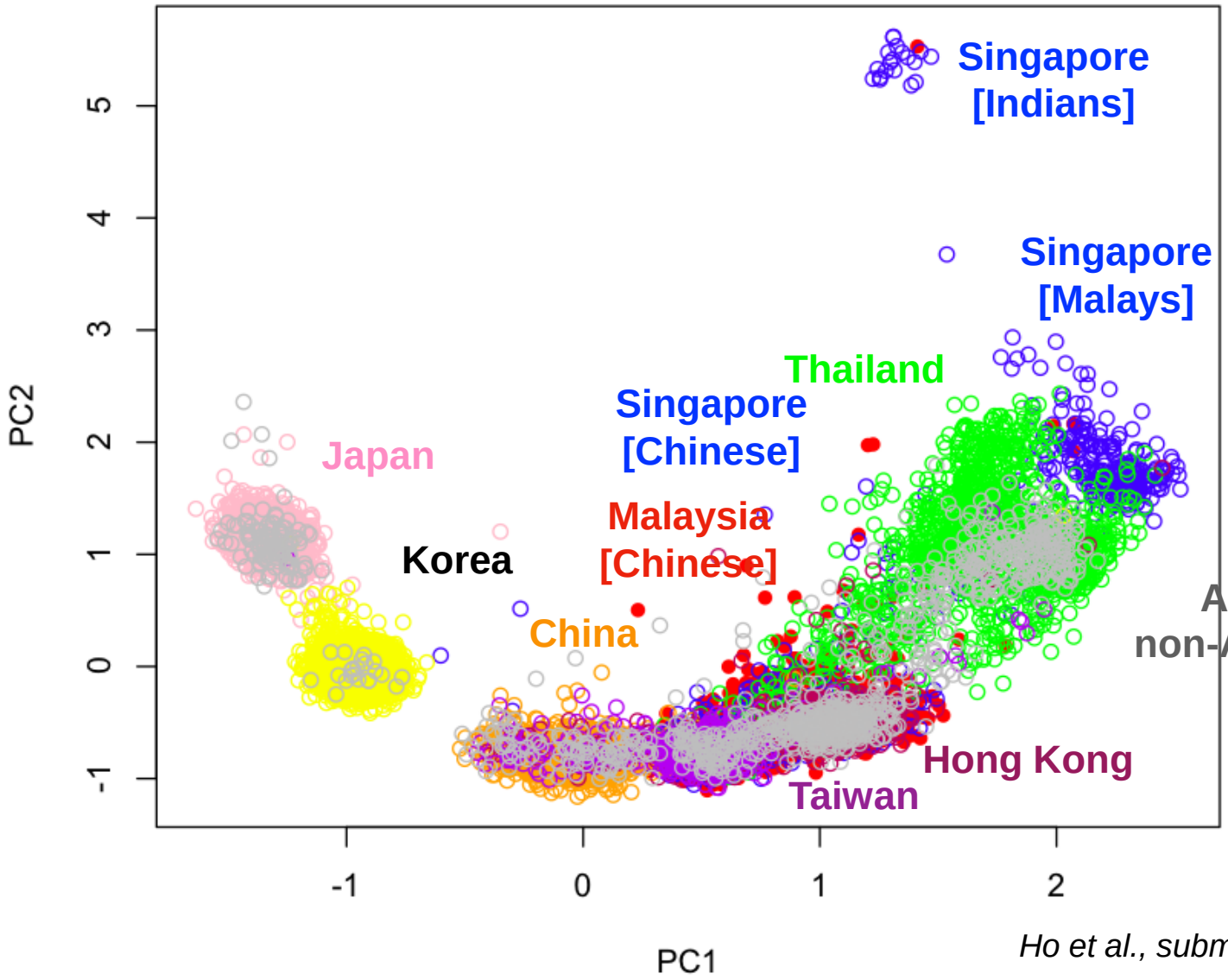
Common variants

- Asian cases and controls
  - Case control: 17,262 cases, 17,695 controls
  - Prospective: 10,255 controls, 413 incident cases

- Genotyping
  - OncoArray, Illumina

Ho et al., submitted

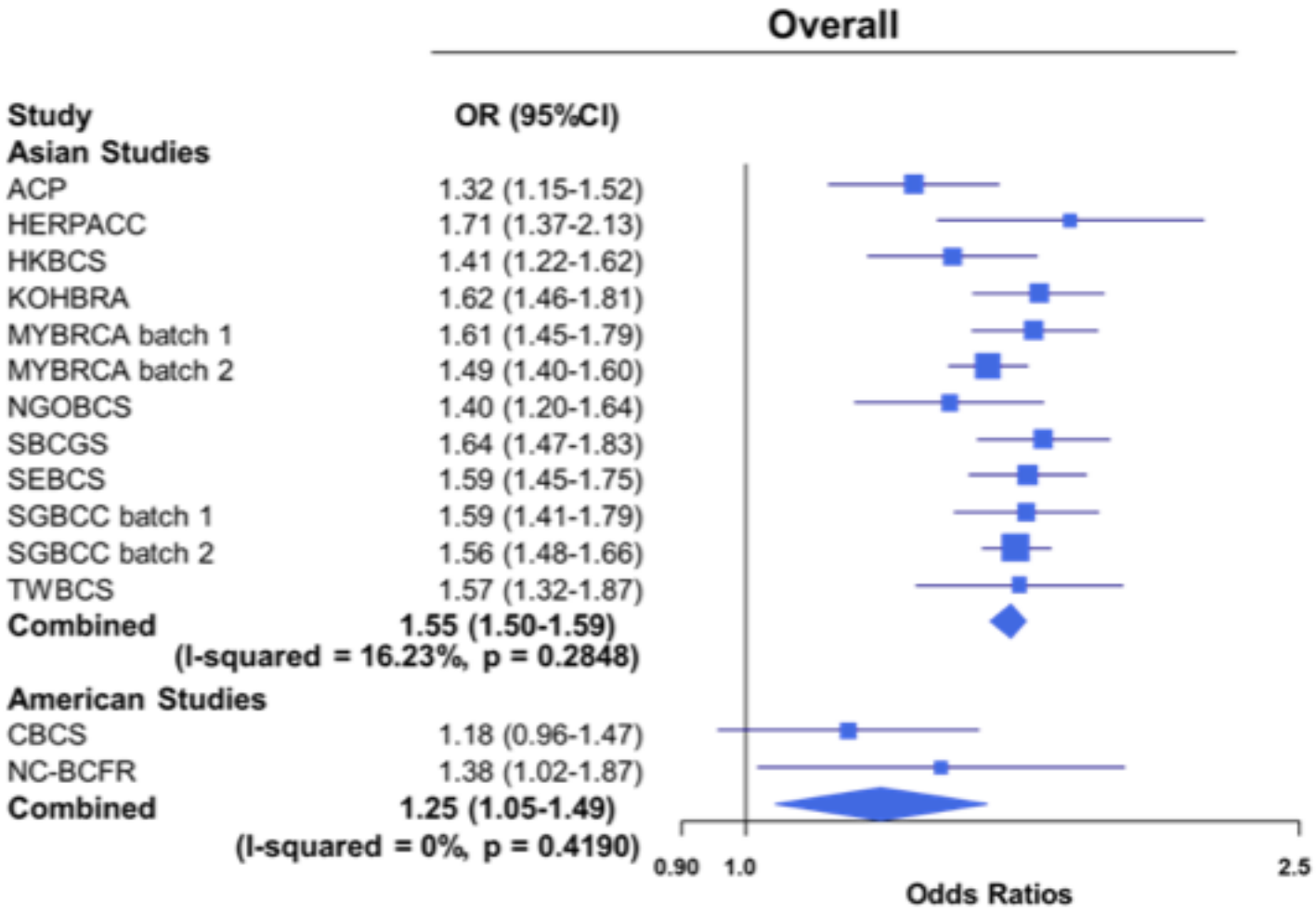
Common variants



Asians in non-Asian study

Ho et al., submitted

Eur PRS is predictive in Asians



Ho et al., submitted

Eur PRS is predictive in Asians

	Cases, N	Controls, N	287-SNP PRS		229-SNP PRS	
			OR per SD†	AUC	OR per SD†	AUC
(a) Asian studies in BCAC						
Overall BC	16,983	16,483	1.52 (1.49-1.56)	0.613	1.49 (1.45 - 1.52)	0.611
ER-positive	10,477	16,483	1.62 (1.57-1.67)	0.627		
ER-negative	4,764	16,483	1.41 (1.36-1.46)	0.594		
(b) Asians within American Studies in BCAC						
Overall BC	1,507	1,212	1.36 (1.25 - 1.49)	0.577	1.33 (1.22 - 1.45)	0.579
ER-positive	1,022	1,212	1.38 (1.25 - 1.53)	0.586		
ER-negative	280	1,212	1.49 (1.26 - 1.76)	0.587		
(c) Prospective cohort						
Overall BC	413	9,842			1.49 (1.33 - 1.67)	0.610
(d) European studies						
Overall BC	11,225	17,788	1.61 (1.57 - 1.66)	0.63	1.59 (1.55 - 1.64)	0.627
ER-positive	7,809	17,788	1.68 (1.64 - 1.73)	0.642		
ER-negative	1234	17,788	1.44 (1.36 - 1.53)	0.6		

Ho et al., submitted

Eur PRS is predictive in Asians

		Chinese			Malay			Indian	
Percentile (%)	**OR**	**Lifetime risk**	**Age†**		**Lifetime risk**	**Age†**		**Lifetime risk**	**Age†**
<1	0.38	0.02	NR		0.02	NR		0.02	NR
1-5	0.48	0.03	NR		0.02	NR		0.02	NR
5-10	0.54	0.03	NR		0.03	NR		0.03	NR
10-20	0.67	0.04	NR		0.03	NR		0.03	NR
20-40	0.83	0.05	NR		0.04	NR		0.04	NR
40-60	1	0.06	NR		0.05	NR		0.05	NR
60-80	1.2	0.07	NR		0.06	NR		0.06	NR
80-90	1.51	0.09	44		0.08	NR		0.07	NR
90-95	1.82	0.11	40		0.09	43		0.09	46
95-99	2.22	0.13	37		0.11	38		0.11	31
>99	2.72	0.16	35		0.13	35		0.13	39

Ho et al., submitted

The Challenge

- Current work will address population-based estimates of mutation prevalence and penetrance.

BUT:

- Lack of access to *BRCA* testing.

  Currently in Malaysia:

  - *BRCA testing is traditionally offered through familial cancer clinics*
  - *Only 4 clinical genetics services are available*
- Hesitation among healthcare professionals about
  - trade off between benefit of treatment/risk management and the consequences of genetic discrimination
  - How to interpret complex test results.
- Lack of knowledge about the impact of genetics on the individual and the family:
  - Psychosocial barriers, especially in a multi-racial and multi-religious context.

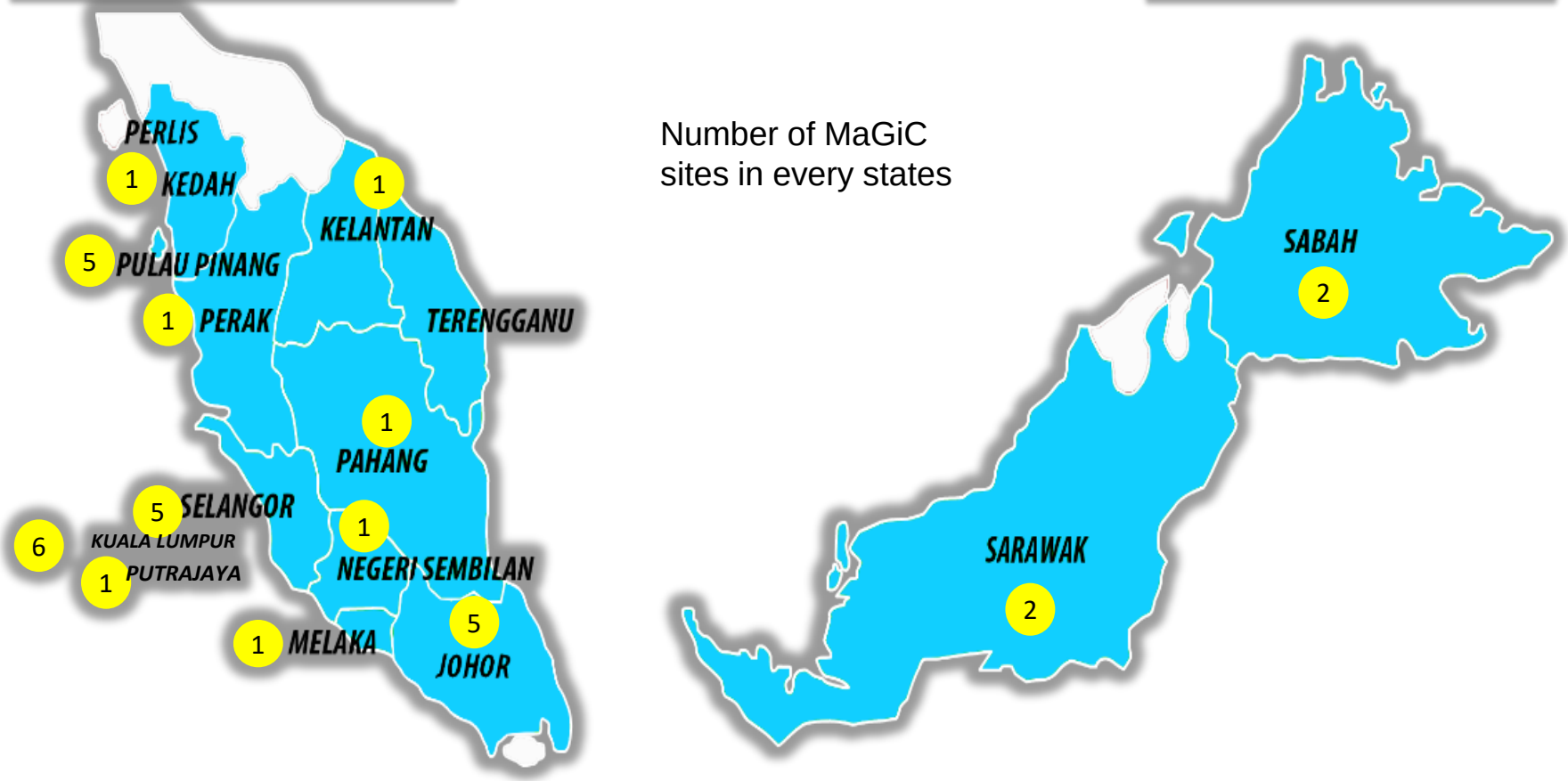
Mainstreaming genetic counselling for BRCA1 and BRCA2 in Malaysia: MaGiC

cancer research malaysia

33 sites
- 13 Government hospitals
- 16 Private hospitals
- 3 University hospitals
- 1 NGO

23 active sites
- 18 Pathway 1 (Mainstreaming)
- 5 Pathway 2 (Genetic)

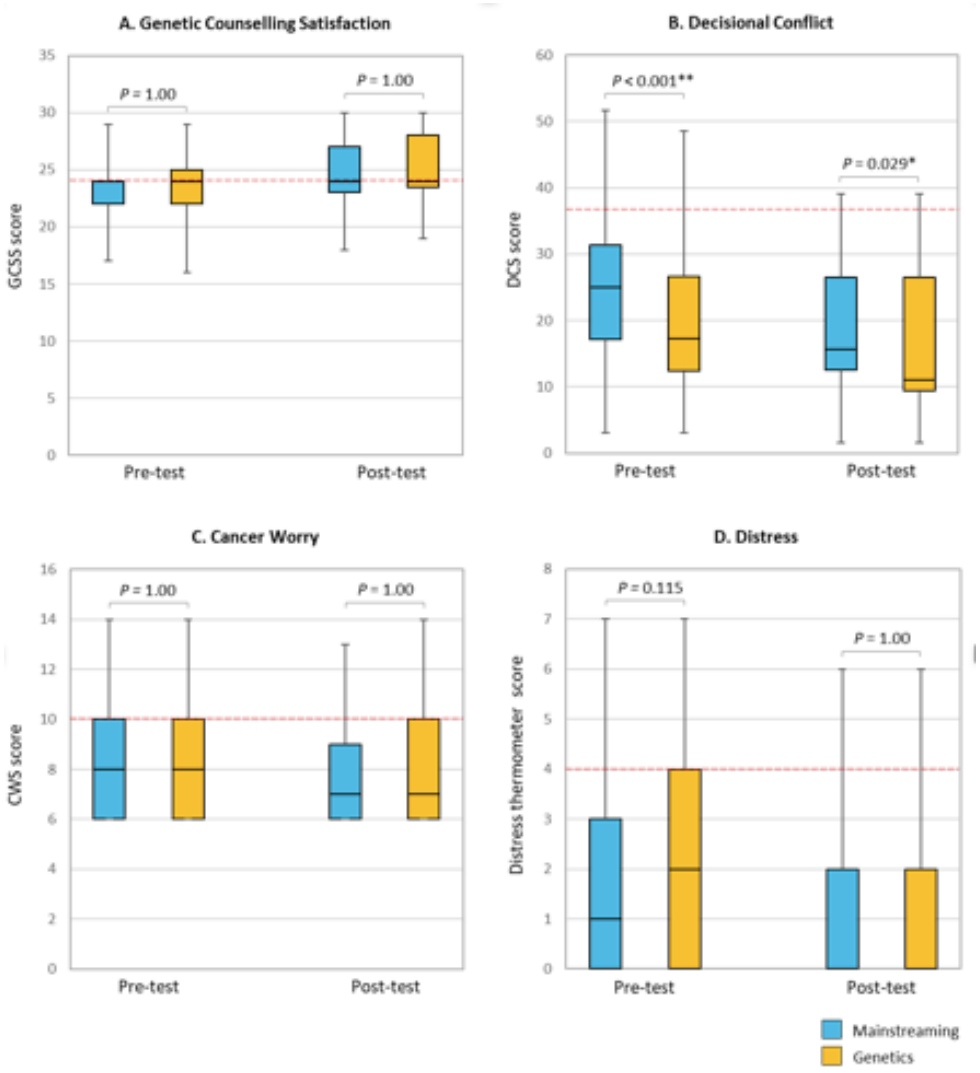
68 clinicians trained
- 36 Gynaeoncologists
- 32 Oncologists
- 54 Mainstreaming
- 14 Genetics



Number of MaGiC sites in every states

Yoon et al., submitted

Mainstreaming genetic counselling for BRCA1 and BRCA2 in Malaysia: MaGiC



Yoon et al., submitted

Summary and Conclusions

- Age-specific genetic predisposition in Asian women is largely similar to that in women of European descent
  - Rare variants contribute to 4-6% of breast cancers overall
  - Polygenic risk scores built on European data largely works in Asians, only 30% of population may benefit from screening
  - Mainstreaming genetic counselling increases access to genetics from 2% to 65%, without affecting psychosocial outcomes

- Genomic profiles of Asian breast cancers are largely similar to that in women of European descent, but
  - Higher prevalence of TP53 mutations
  - Higher prevalence of HER2 subtypes
  - Higher prevalence of immune enrich subtypes

What is appropriate for LMIC Asians?

- Start with those with **family history** of breast cancer
  - But majority do not have FH and FH poorly reported

- Start with **genetics** [panel test of rare and common variants]
  - But major challenges in genetic discrimination, mainstreaming and affordability

- Start with a **baseline mammogram at 40** to determine screening frequency
  - But current measures of density for risk and masking effects need further development for Asians

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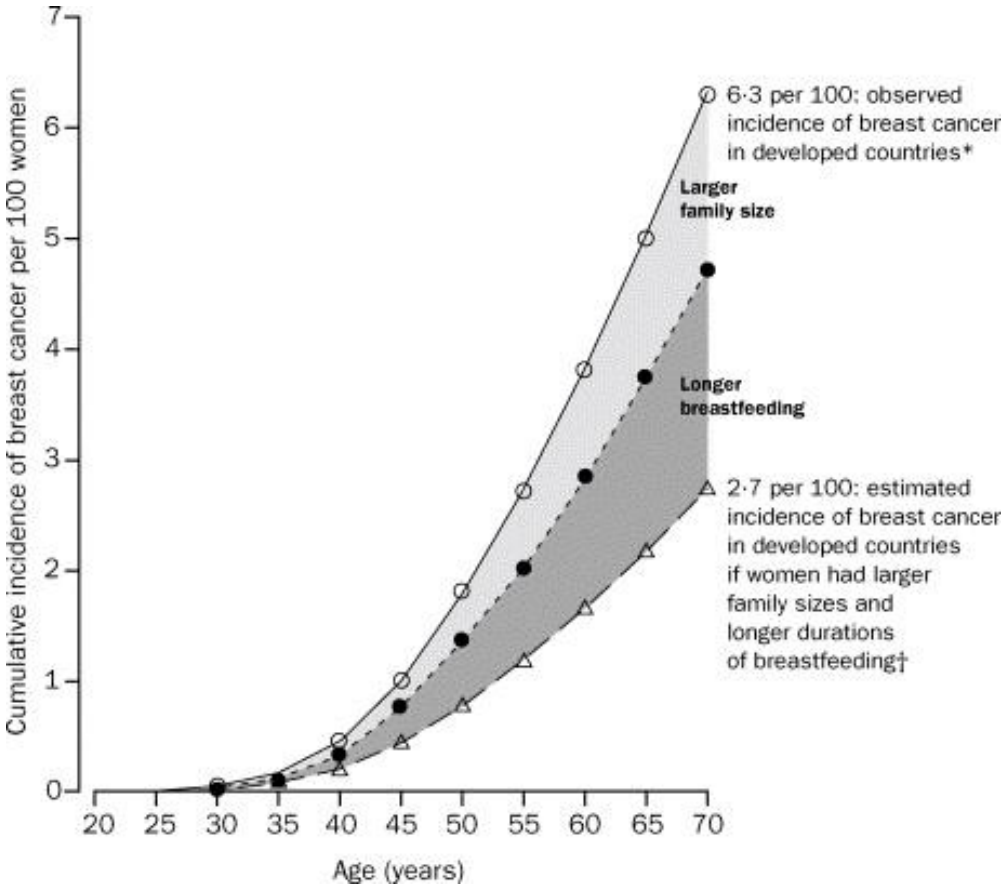
ADDITIONAL SLIDES

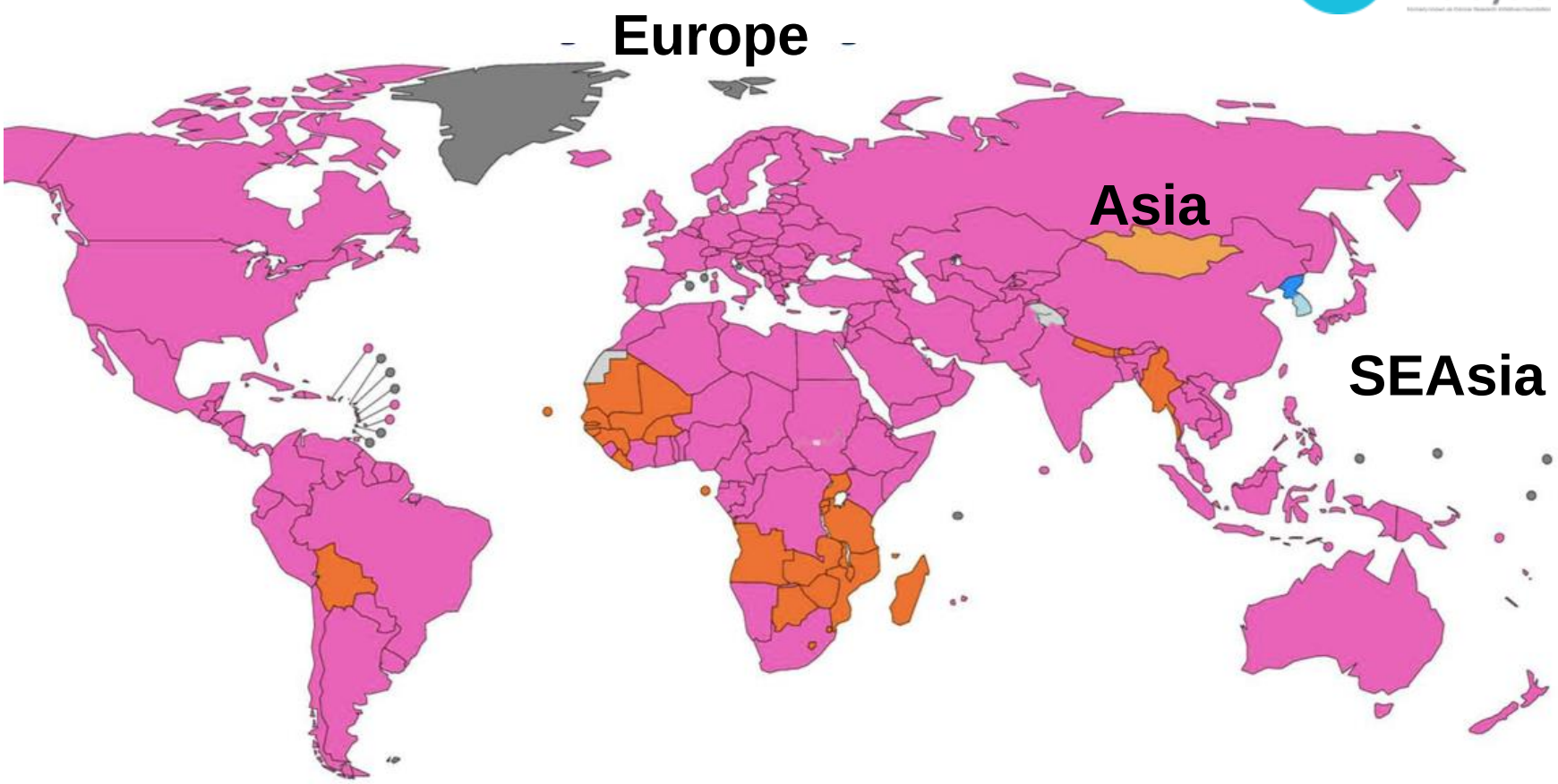
Breastfeeding reduces cancer risk

Having a child reduces breast cancer risk by 7%
Breastfeeding for 1 year reduces breast cancer risk by 4%

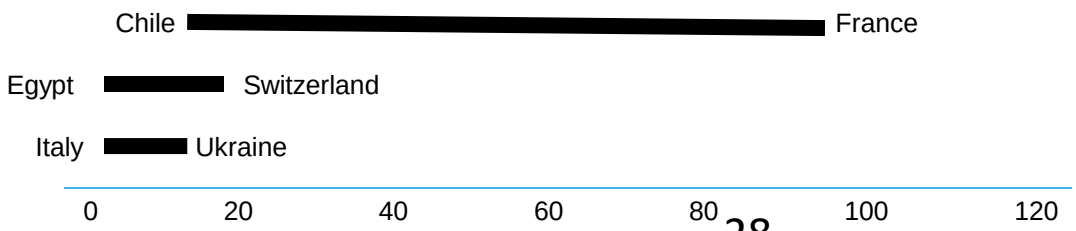


Collaborative Group of Hormonal Factors in breast cancer, Lancet 2002

Global variations by cancer type



	Relative mag
Breast	**2.9**
Ovary	**2.1**
Cervical	**3.3**



Bray et al., IJC 2015