Ethic Differences in the Treatment Landscape of Breast Cancer: Western vs Asians

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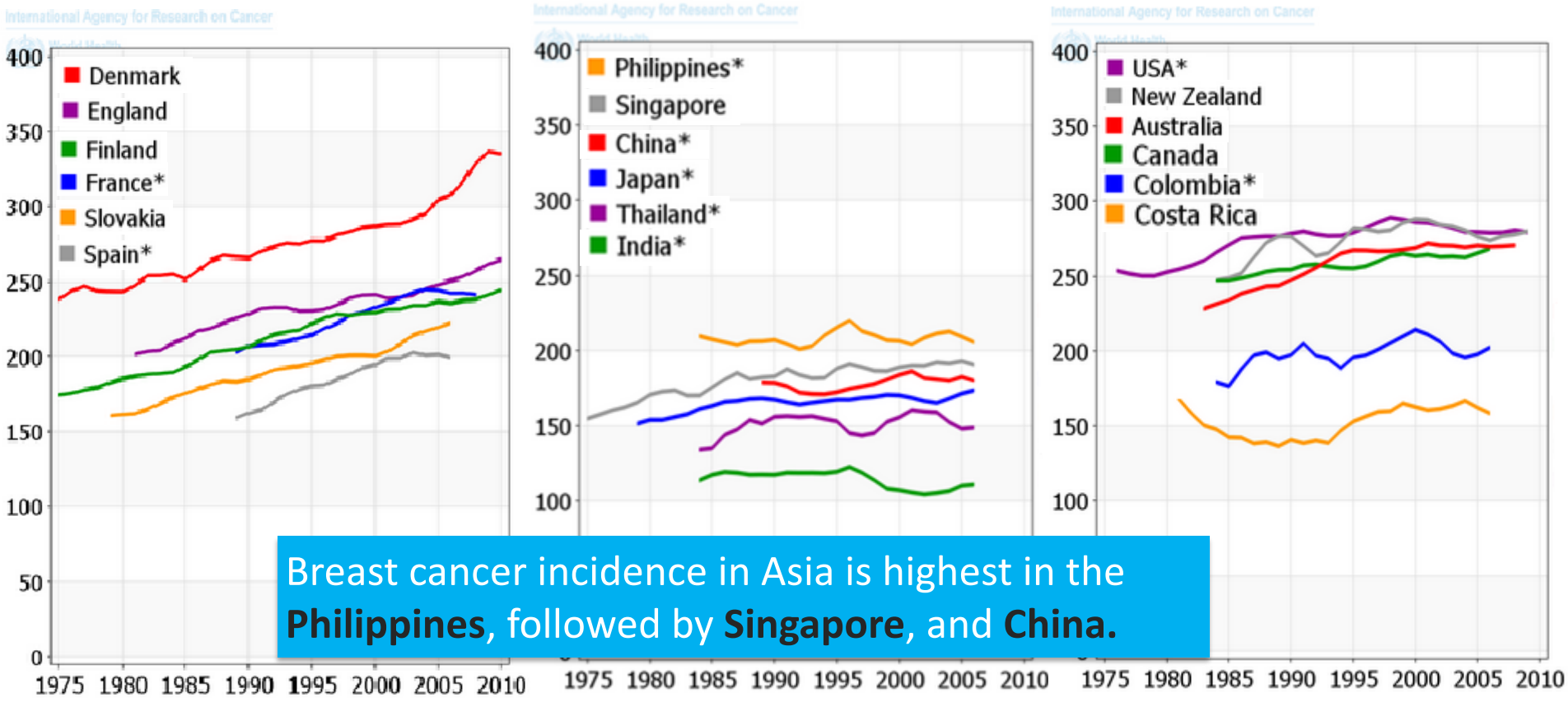
INCIDENCE

Breast Cancer Incidence

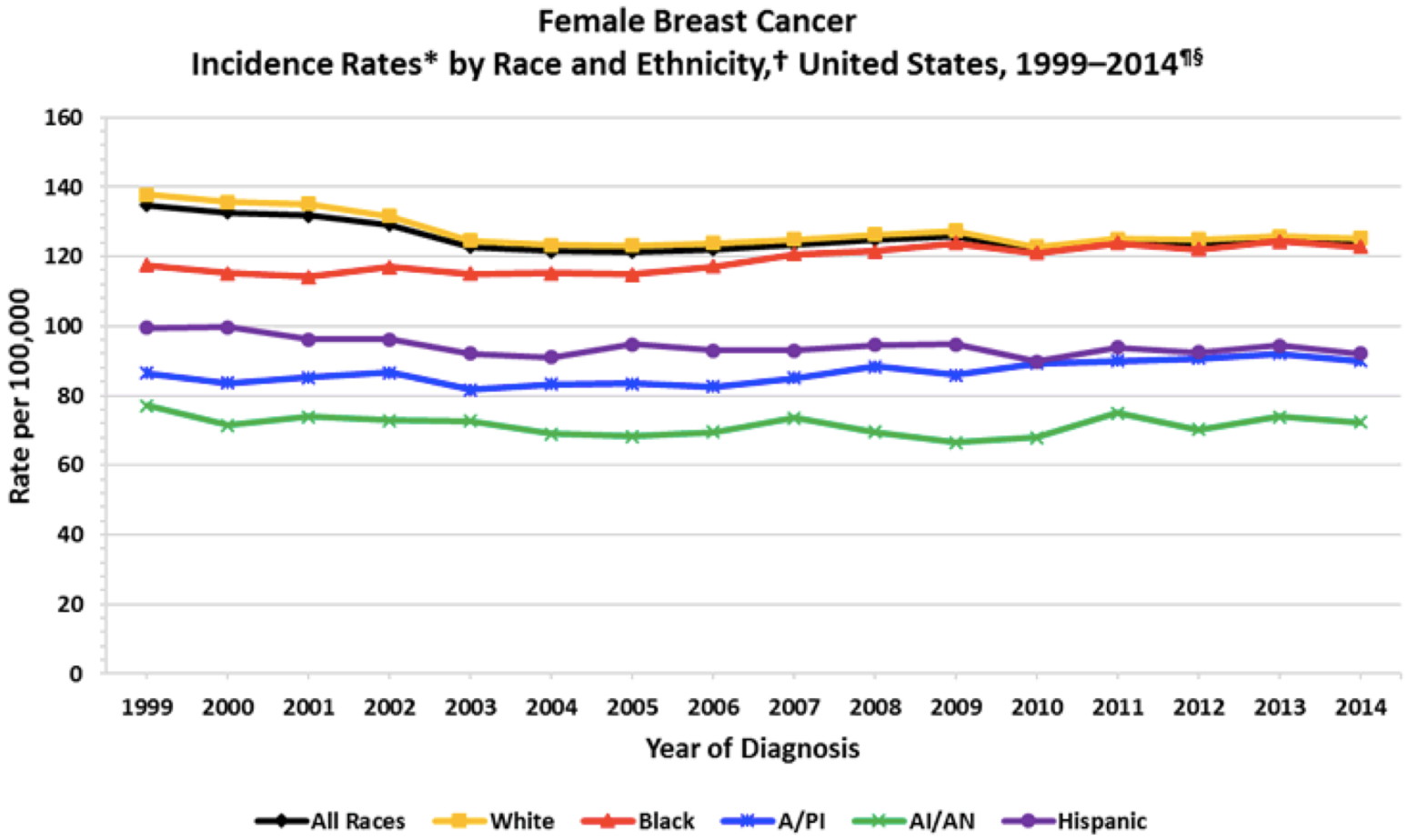


Breast cancer incidence in Asia is highest in the **Philippines**, followed by **Singapore**, and **China.**

Tam CY, Martin LJ, Hislop G, et al. *Breast Cancer Res* 2001

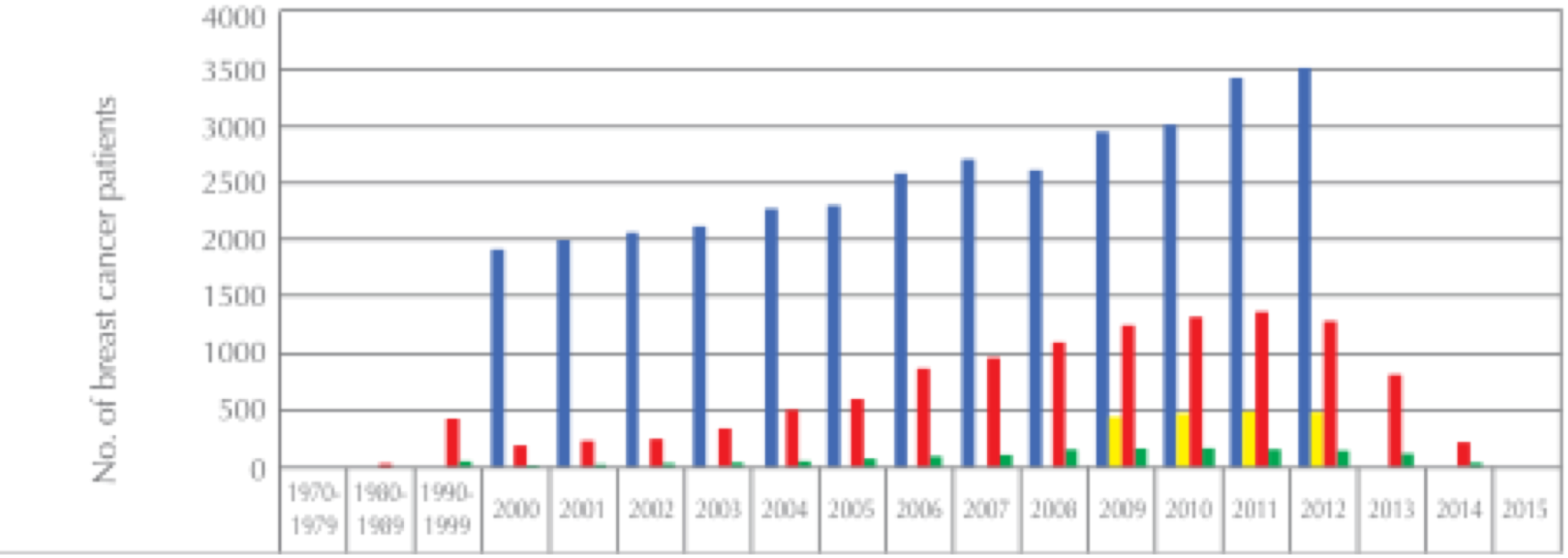
Liu Q, Loo WTY, Yip AYS, Chow LWC, et al. *Chinese Journal of Breast Disease* 2013

Incidence Rates

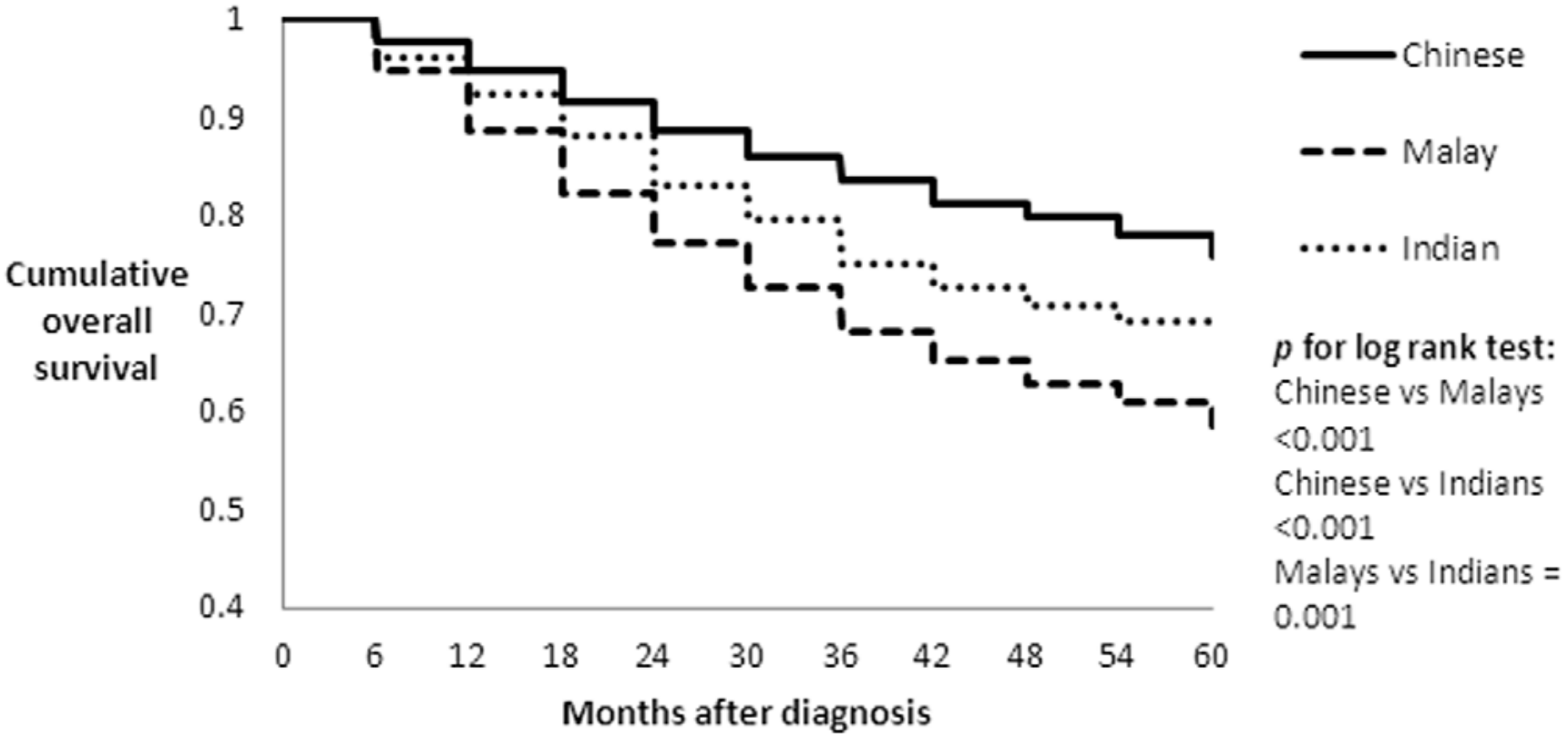


Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Incidence (HK)



Cumulative overall survival by ethnicity in 5,264 South East Asian women with breast cancer



Five year overall survival:
Chinese (75.8%; 95%CI: 74.4%–77.3%); **Indians** (68.0%; 95%CI: 63.8%–72.2%); **Malays** (58.5%; 95%CI: 55.2%–61.7%)

Bhoo-Pathy, *et al. PLoS ONE* 7(2):e30995.

Breast cancer in Asia

- The incidence of breast cancer in Hong Kong is among the highest in Asia, on par with Singapore and Japan

- Breast cancer incidence in Hong Kong was 41 per 100,000 persons from 1998 to 2002

Tam CY, Martin LJ, Hislop G, et al. *Breast Cancer Res* 2001
Liu Q, Loo WTY, Yip AYS, Chow LWC, et al. *Chinese Journal of Breast Disease* 2013

Genetic Ancestry

- European ancestry
  - Associated with higher risk of breast cancer
    - OR: 1.36

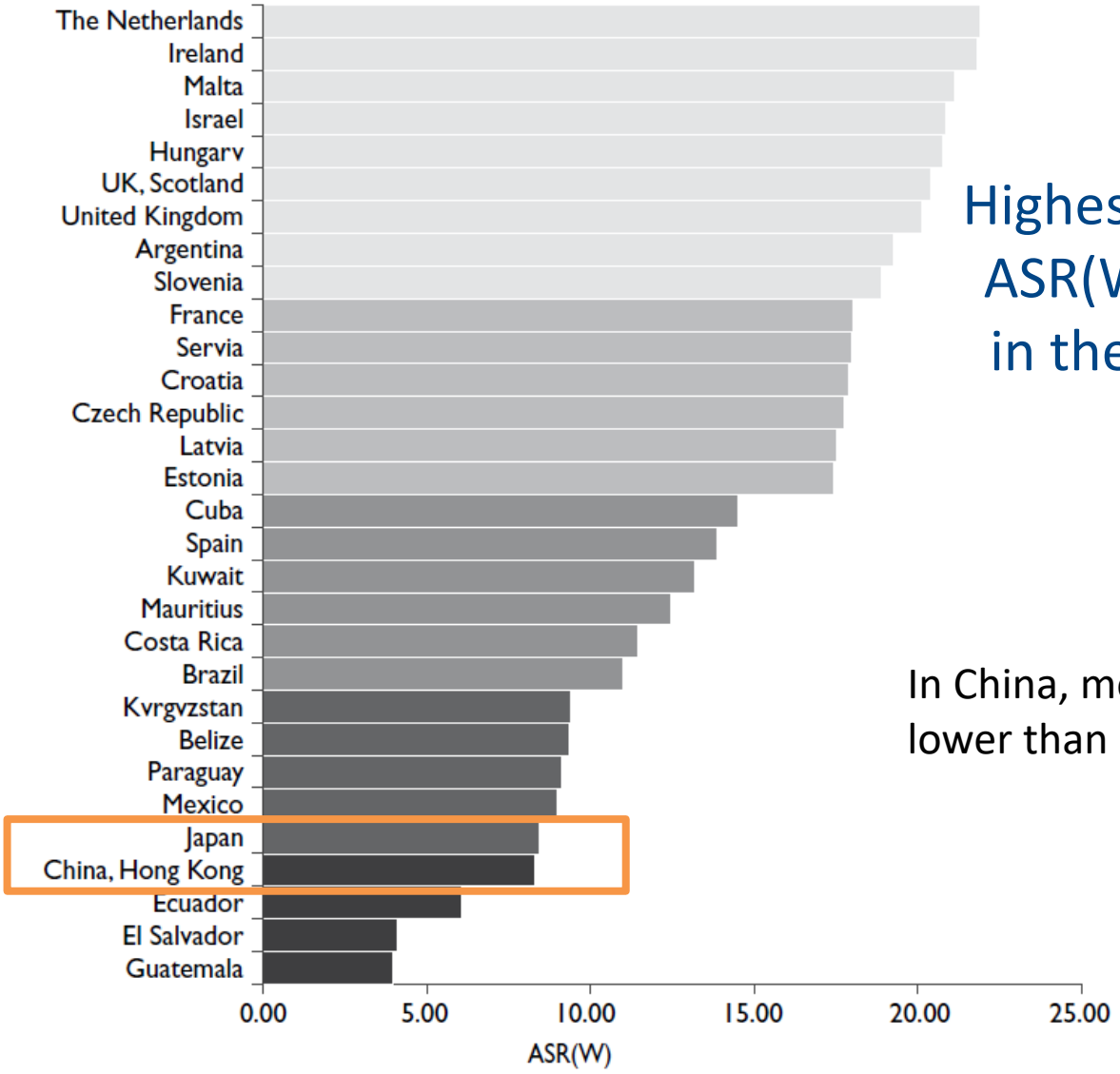
    Fejerman L, Cancer Res 2008; 68:9723-28

  - Every 25% of European ancestry was associated with increased risk of breast cancer
    - OR: 1.20 (compared with women with <25%)

    Fejerman L, Cancer Epidemiol Biomarkers Prev 2010

MORTALITY

Breast Cancer Mortality

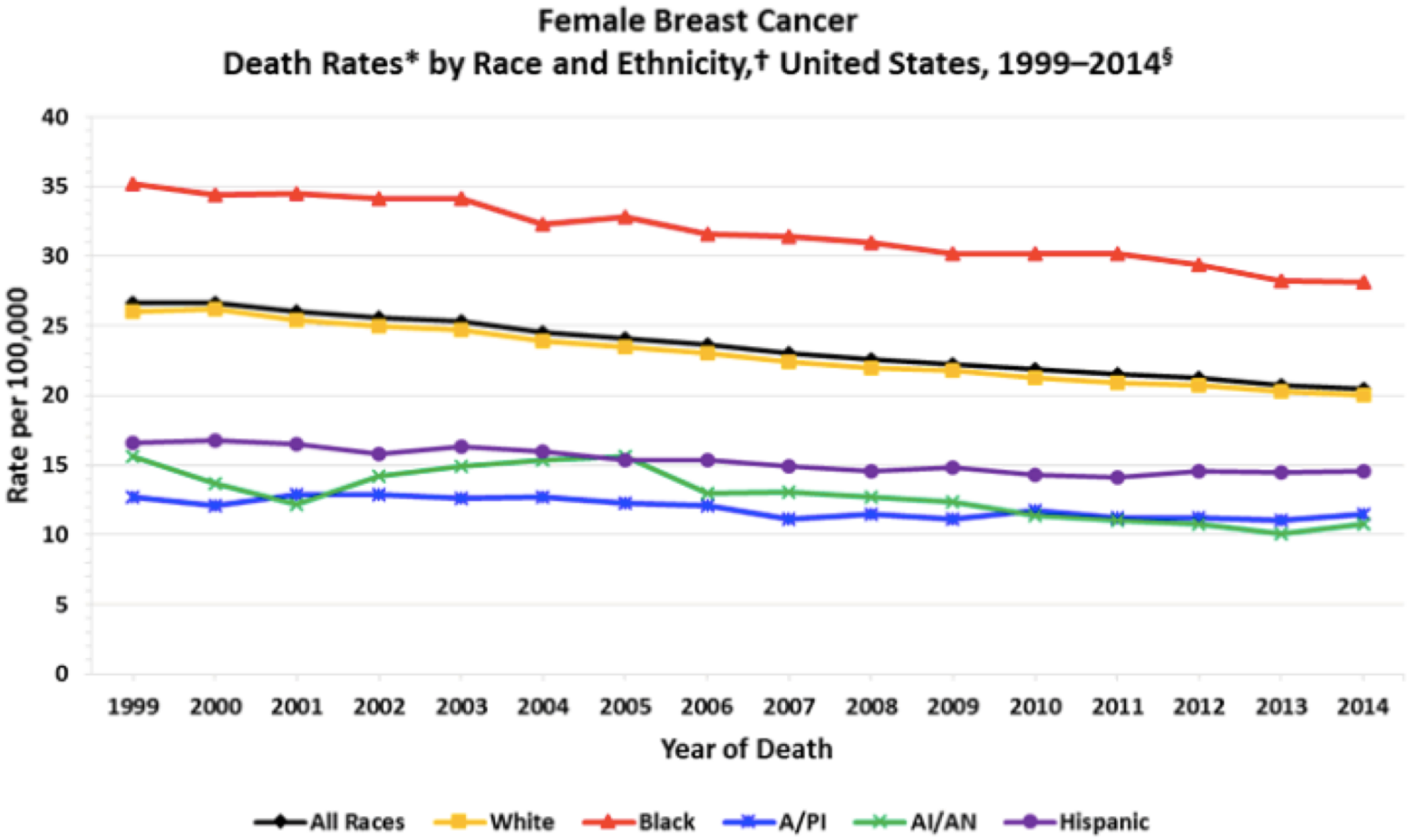


Highest and lowest mortality ASR(W) from breast cancer in the world for the period 1998-2006

In China, mortality rates for breast cancer are lower than in Western population.

Curado MP. Salud Publica Mex 2011

Death Rates



CDC Centers for Disease Control and Prevention
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BJC

FULL PAPER

British Journal of Cancer (2013) 109, 1302–1309 | doi: 10.1038/bjc.2013.387

Keywords: Asian; breast cancer; disparities; clinicopathologic; survival; young age

Table 3. Survival (5-year and 10-year) rates for each ethnic group of women aged 18–39 years with breast cancer

	NHW (*n* = 35 101) (%)	Black (*n* = 8215) (%)	HW (*n* = 7067) (%)	Asian (*n* = 4770) (%)	Filipino (*n* = 1040) (%)	Japanese (*n* = 602) (%)	Chinese (*n* = 995) (%)	Hawaiian/ Pacific Islander (*n* = 540) (%)	Korean (*n* = 339) (%)	Asian Indian/ Pakistani (*n* = 410) (%)	Vietnamese (*n* = 307) (%)	Other (*n* = 537) (%)
Disease-specific survival												
5-Year	81.4	71.8	79.1	84.6	82.9	86.0	85.6	76.1	89.3	84.9	85.6	90.3
10-Year	73.0	63.9	70.3	77.2	73.0	80.2	78.3	67.9	83.8	73.8	80.6	86.5
Overall survival												
5-Year	80.0	69.4	77.0	83.5	81.1	86.0	84.8	74.6	88.3	82.5	86.1	89.5
10-Year	70.6	60.2	67.2	74.7	69.9	79.1	76.5	65.2	80.7	68.7	80.8	82.4

Abbreviations: HW = Hispanic white; NHW = non-Hispanic white.

Breast Cancer Mortality Rates

- Caucasian □
- Chinese □

Annual percent change (APC) in the **mortality rates** of breast cancer among females by country and broad age group, 1980-2011

	Trend 1		Trend 2		Trend 3	
Country	Year	APC	Year	APC		
China	1987-1995	+0.4	1995-2000	+4.1		
Hong Kong	1980-2011	-0.1				
Singapore	1980-2011	+0.3				
South Korea	1985-1994	+5.5	1994-2011	+2.1		
Japan	1980-1990	+1.5	1990-1997	+3.3*	1997-2011	+1.1
Australia	1985-1994	–0.4	1994-2000	-3.2	2000-2011	-1.7
New Zealand	1980-1989	+0.4	1989-2009	–2.1		

Youlden DR *et al*. *Cancer Biol Med*. 2014

AGE AT DIAGNOSIS

Age distribution of patients with breast cancer

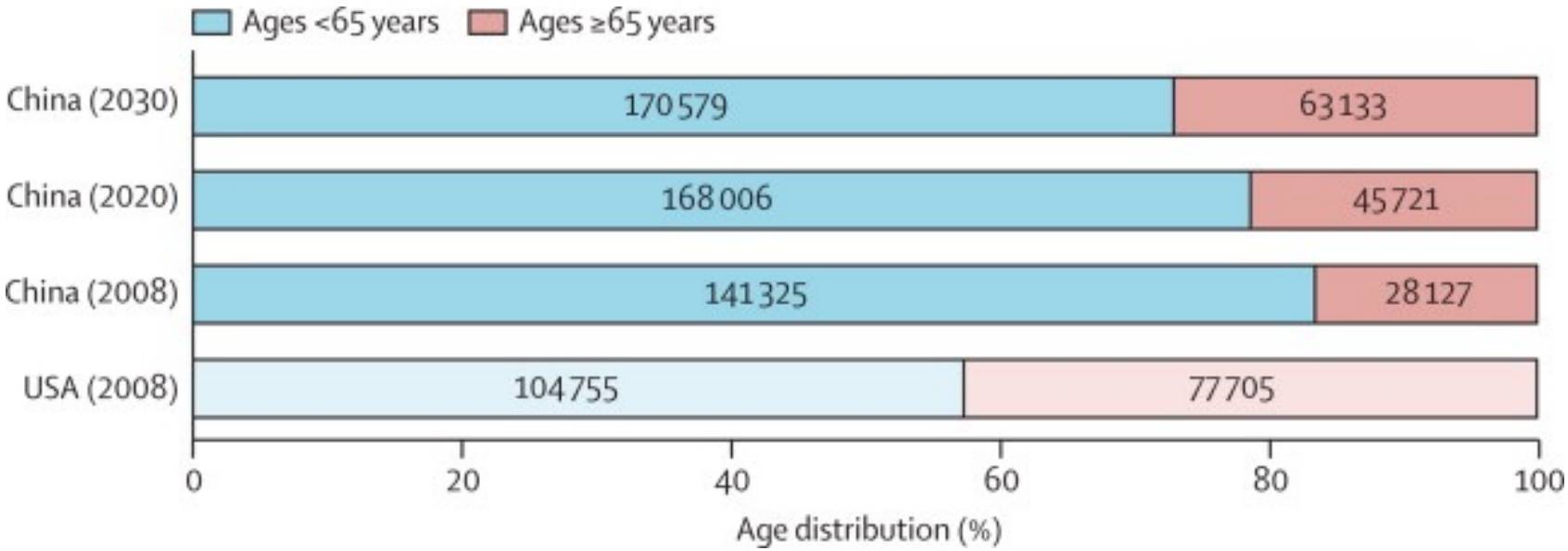


Figure shows age distribution in China and the USA in 2008, and estimated distributions in China in 2020 and 2030; based on data from the WHO China country profile.

- The mean age at diagnosis of breast cancer in China is 45–55 years.
- Similar situation have been reported in East such as Taiwan and Hong Kong, and have been attributed to shifts in risk-factor profiles of younger women.

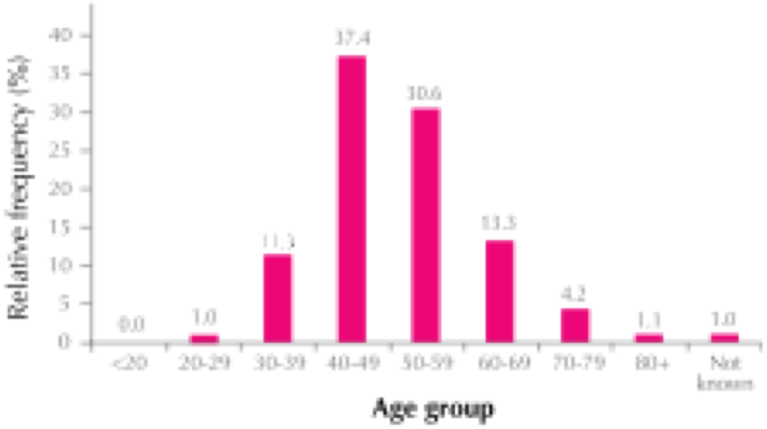
- **Compare:** The median age at diagnosis of breast cancer in USA is 62 years with 68% of women diagnosed after their 54th year of life.

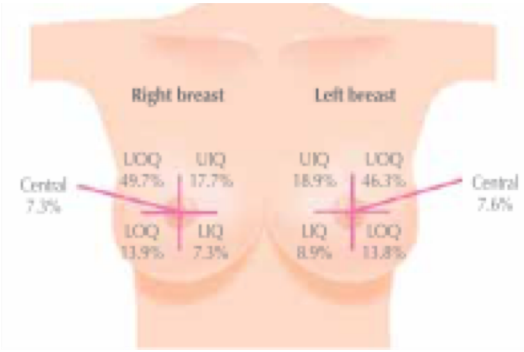
Lei Fan et al. Lancet Oncol 2014
NIH SEER, visited 06/2016

Age distribution of patients with breast cancer

- Onset and aetiology of breast cancer in Chinese women is different.
- Vast majority of luminal tumours is diagnosed at younger age
    - Before menopause;
    - Higher proliferative;
    - Poorer prognosis.

- Over 50% breast cancers in Asia are diagnosed in premenopausal females





STAGE

Breast cancer stage at diagnosis

AJCC stage of initial presentation	St I: 15.7% Mostly stage II 50% StIII-IV 21.1%	St I: 1–8%; St II: 23–58%; St III: 29–52%; St IV: 6–24%	43.6% presented with Stage II disease	St I: 36% St II: 40% St III: 5%	Localized (Stage 1) 65%	Localized (Stage 1) 60–70%

In Asia,

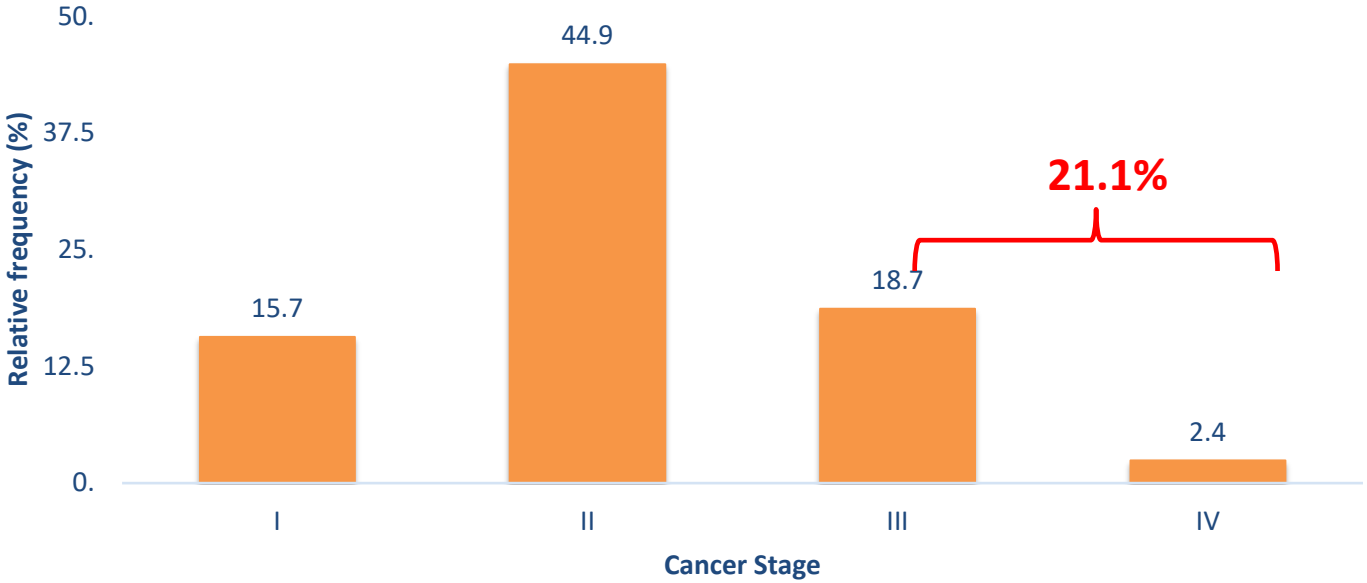
- Lower rates of monitoring and screening for breast cancer
- Delays in diagnosis (more advanced stage of disease)

Stanley P. L. Leong et al. World J Surg. 2010

Breast cancer stage at diagnosis

In China

Data from a retrospective study by multiple clinical centre in China



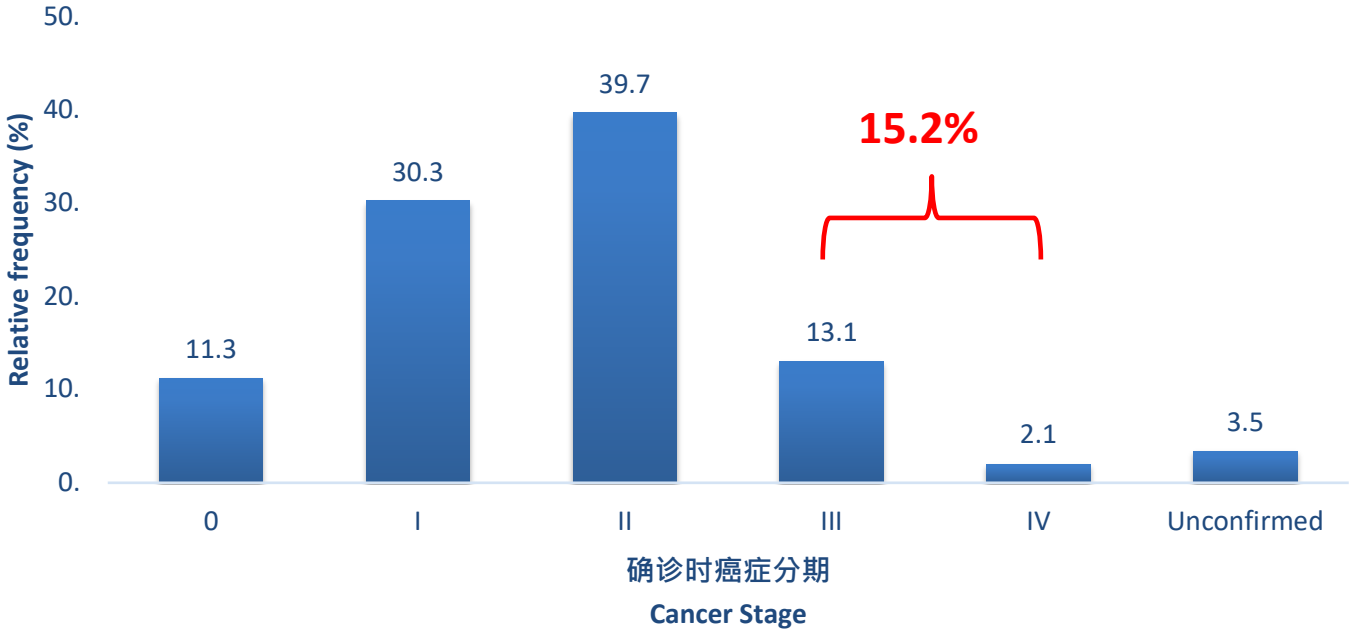
- At diagnosis, the most common cancer stage was stage II (44.9%)
- Advanced cancer (stage III-IV) contribute to 21.1%. (v.s. Hong Kong, 15.3%)
- Stage I contribute to 15.7% (v.s. Hong Kong, 30.3%)
- By contrast, 60%-70% of women in the USA present with localised stage I disease.

Li J, Zhang BN, Fan JH, et al. BMC Cancer 2011; 11: 364

Breast cancer stage at diagnosis

In Hong Kong

Data from Hong Kong Breast Cancer Registry Report No. 6 (Issue 2014)

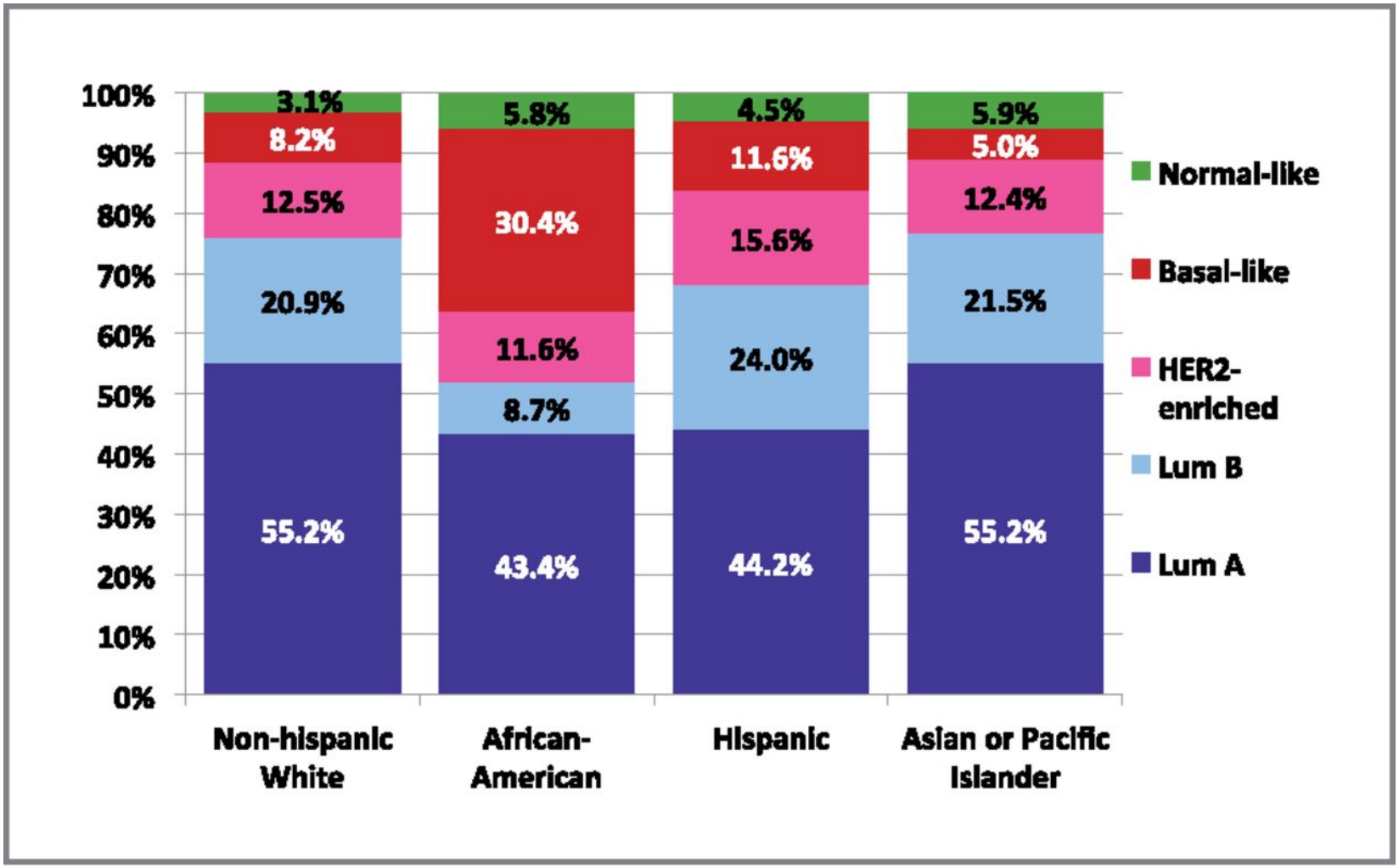


- At diagnosis, the most common cancer stage was stage II (39.7%)
- Advanced cancer (stage III-IV) contribute to 15.2%.
- 11.3% patient were diagnosed with in situ cancer

Data from Breast Cancer Registry Report No. 6 (Issue 2014)

SUBTYPES AND BIOLOGY

Distribution of breast cancer intrinsic subtypes from PAM50 assay in a population-based cohort by race and ethnicity, LACE and Pathways studies.



Carol Sweeney et al. Cancer Epidemiol Biomarkers Prev 2014;23:714-724

AACR American Association for Cancer Research
Cancer Epidemiology, Biomarkers & Prevention

Differences in Breast Cancer Subtypes among Asian-American Women with Invasive Breast Cancer in New York City

Ethnicity	Luminal A	Luminal B	HER-2+/ER-	Basal like	All HER-2+	Age (yrs)
Chinese	66.7%	15.3%	9.5%	8.5%	24.9%	51+/-13
Filipino	47.1%	20.6%	25.0%	5.9%	45.6%	52+/-10
Japanese	77.8%	11.1%	2.8%	5.6%	13.9%	47+/-11
Korean	47.1%	11.8%	17.6%	23.5%	29.4%	39+/-11

K. McCarville et al, SABCS 2009

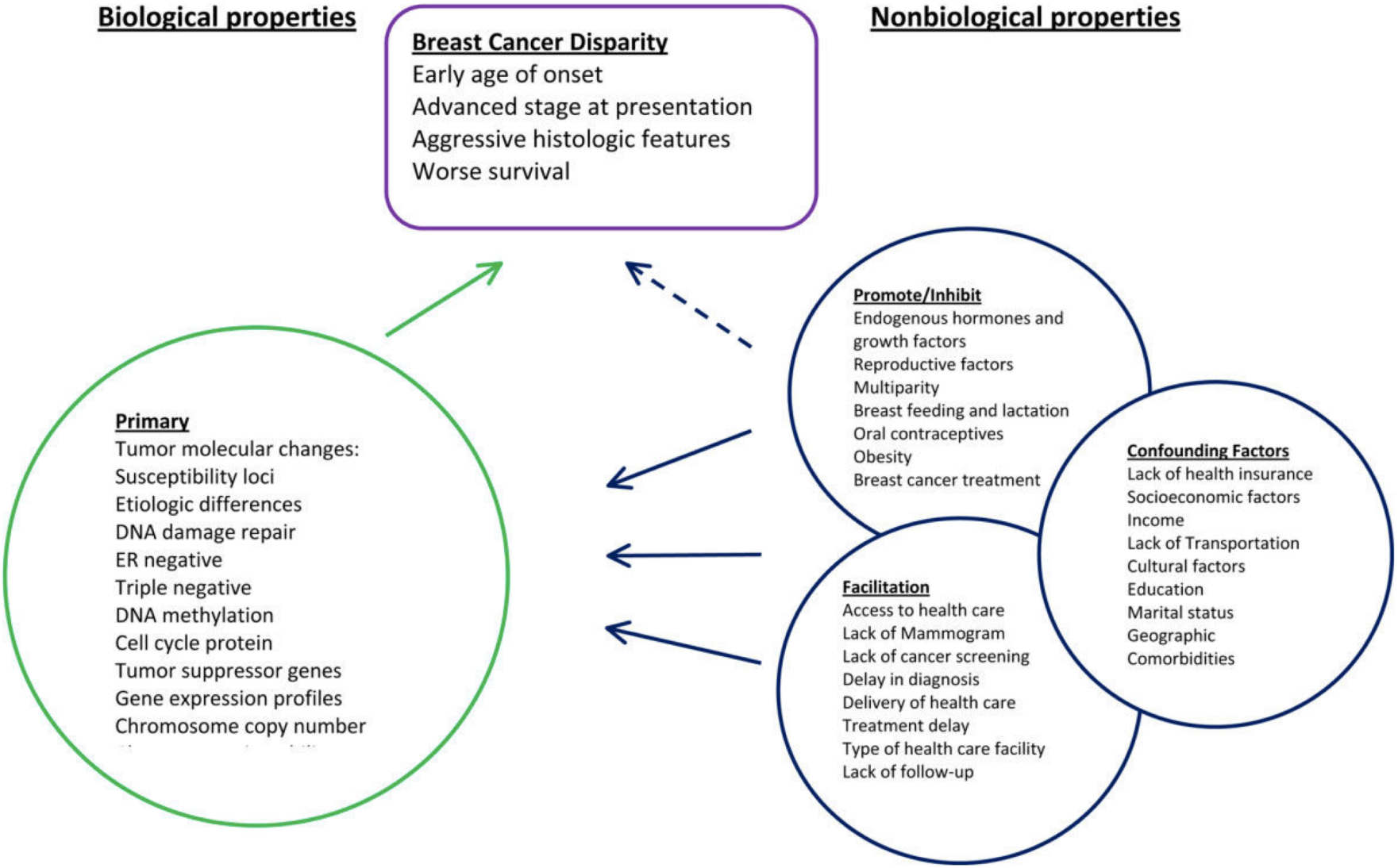
Breast density: Western vs. East population

	No. (%) of Patients in BI-RADS Category[a]				Total No. of Patients (%)
	1	2	3	4	
Asian	4 (0.92)	69 (15.86)	244 (56.09)	118[b] (27.13)	435 (2.84)
White	831 (6.54)	3,463 (27.26)	6,825 (53.72)	1,585 (12.48)	12,704 (83.1)
African American	47 (8.38)	174 (31.02)	290 (51.69)	50 (8.91)	561[c] (3.67)
Other[d]	150 (9.42)	465 (29.21)	830 (52.14)	147 (9.23)	1,592 (10.4)
Total	1,032	4,171	8,189	1,900	15,292

[a]BI-RADS categories converted to the following numeric values: 1, breast is almost entirely fat; 2, breast has scattered fibroglandular dense tissue; 3, breast tissue is heterogeneously dense; and 4, breast tissue is extremely dense.
[b]**Asian women had a statistically meaningful higher breast density ($p < 0.0001$).**
[c]African American women had a statistically meaningful lower breast density ($p < 0.0001$).
[d]Racial background not specified, American Indian, and Caribbean race.

del Carmen, Marcela G., et al. American Journal of Roentgenology 2007

Disparities in breast cancer outcomes



Danforth DN, Breast Cancer Research 2013

SURGERY

Operable Challenge
For The Chinese Population

Western vs. Chinese population:

- breast volume consideration

Chinese average cup size: A cup

Yarkko, Target Map

Table 6 Treatment patterns of breast cancer cases

Therapy	Total (N = 4211)	
	n	%
Surgery		
No	107	2.5
Radical Mastectomy	3740	88.8
Breast Conservative Surgery	231	5.5
Simple Mastectomy	46	1.1
Others	61	1.5
Unknown	26	0.6
Radiotherapy		
No	2723	64.7
Yes	952	22.6
Unknown	536	12.7
Chemotherapy		
No	626	14.9
Yes	3428	81.4
Unknown	157	3.7
Endocrine Therapy		
No	2092	49.7
Yes	1599	38.0
Unknown	520	12.4

Treatment Pattern in China

- Surgery was the most common treatment. Radical mastectomy was widely perceived as the only curative treatment
- Radiotherapy and endocrine therapy were much less, which indicates that adjuvant therapy, especially radiotherapy and endocrine therapy are of great unmet needs.

Li J, Zhang BN, Fan JH, et al. BMC Cancer 2011

Western vs. Asian population: surgical treatment comparison

Parameters	China	India	Japan	S. Korea	Europe (Sweden)	Canada	USA
Mastectomy rate (%)	60-80	*>90	45.3	64.7	#40	#20	46
Lumpectomy Rate (%)	15-30	*<10	48-40	35.3	#60	#80	52
Lumpectomy + AxLND (%)	15-30	*<5	48	42.6	53	#80	9
Lumpectomy + SLNB (%)	>5	#2	48	42.6	#57	#80	33
Modified RM (%)	75	#80	45	50	46	5%-10	21
Radical (%)	5	Rare	1-2	1	Occasional	Extremely rare	0

Higher rates of mastectomy performed in China compared to western countries

AxLND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; RM, radical mastectomy
*Estimate; #approximate

Leong SPL, Shen ZZ, Liu TJ, et al. World J Surg (2010)

Types of surgical operations in the patient in Hong Kong (N=12,023)
Data From Breast Cancer Registry Report No. 6 (Issue 2014)

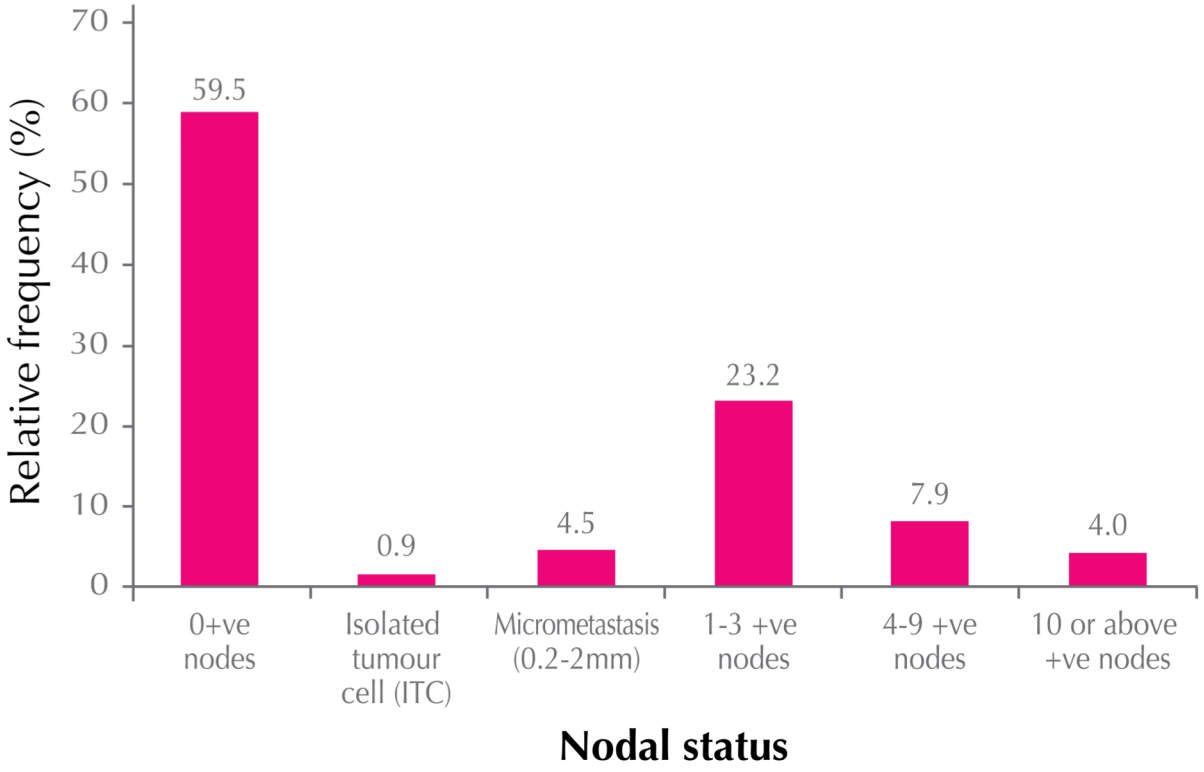
No surgery	174	(1.4)
Breast- conserving surgery	4217	(35.1)
Mastectomy	7582	(63.1)
Nodal surgery only	5	(0.0)
Type of surgery not known	16	(0.1)
Not known if surgery done	29	(0.2)

Data From Breast Cancer Registry Report No. 6 (Issue 2014)

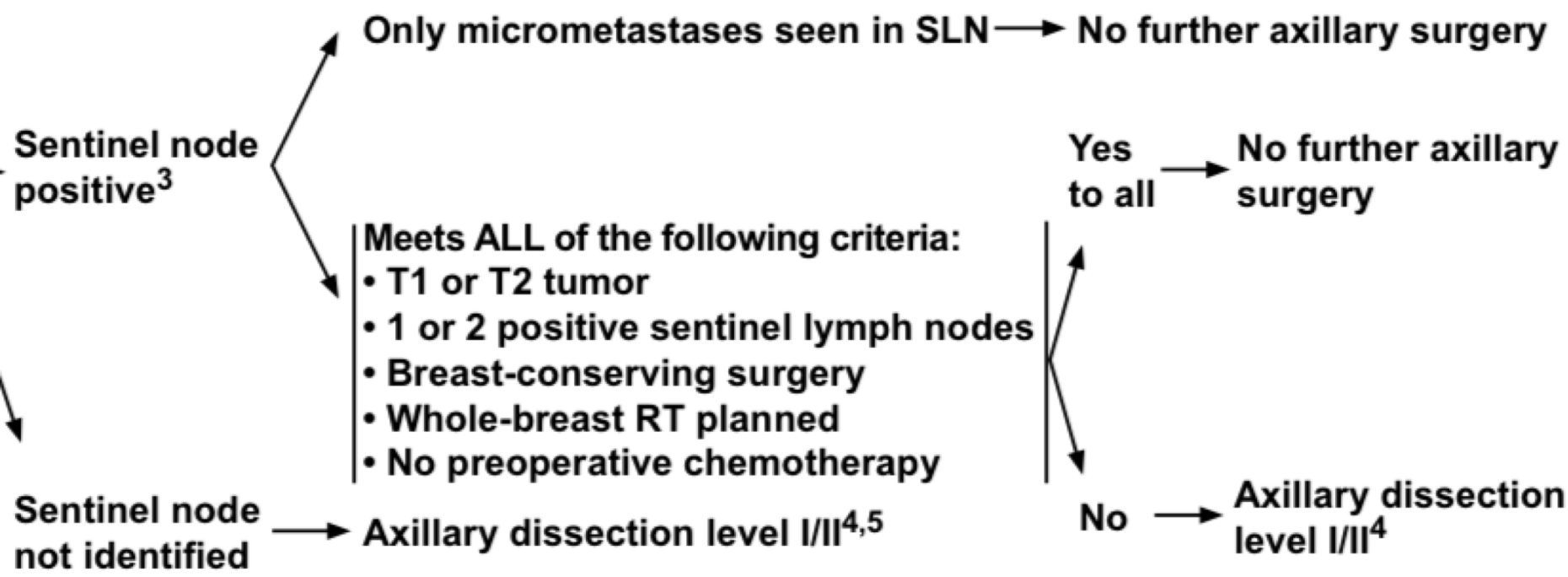
Types of surgical operations in Chinese population

- The rate of BCS in Chinese population is relatively low compared to that of Western countries
- Age, marital status, and educational level were found to be independent significant factors affecting the choice of BCS
- Suitability and acceptance of BCS by Chinese women should increase with better understanding and education.

Can we totally apply the Z11 results?



NCCN Guidelines



Patients had a low nodal burden

	ALND (n=420)	SLND (n=436)	p
Median nodes removed	**17**	**2**	**<.001**
Positive Nodes, n (%)			
0	**4 (1.2)**	**29 (7)**	**<.001**
1	**199 (58)**	**295 (71)**	
2	**68 (19.8)**	**76 (18.3)**	
>3	**72 (21)**	**15 (3.6)**	
Size of Metastasis, n (%)			
Micro	**137 (37.5)**	**164 (44.8)**	**.05**
Macro	**228 (62.5)**	**202 (55.2)**	
Additional Positive Non-Sentinel Nodes			
All	**97 (27.3)**	**N/A**	
Micromet	**14 (10)**		

65% only one positive LN

41% micromet

- In those undergoing ALND, 27% had additional positive LNs and 14% had 4 or more positive LNs

ACOSOG Z011

Table 1. Baseline Patient and Tumor Characteristics by Study Group

Characteristic	No. (%) ALND (n = 420)	No. (%) SLND Alone (n = 436)
Age, median (range), y	56 (24-92)	54 (25-90)
Missing	7	10
Clinical T stage		
T1	284 (67.9)	303 (70.6)
T2	134 (32.1)	126 (29.4)
Missing	2	7
Tumor size, median (range), cm	1.7 (0.4-7.0)	1.6 (0.0-5.0)
Missing	6	14
Receptor status		
ER+/PR+	256 (66.8)	270 (68.9)
ER+/PR–	61 (15.9)	54 (13.8)
ER–/PR+	3 (0.8)	4 (1.0)
ER–/PR–	63 (16.5)	64 (16.3)
Missing	37	44
LVI		
Yes	129 (40.6)	113 (35.2)
No	189 (59.4)	208 (64.8)
Missing	102	115
Modified Bloom-Richardson score		
1	71 (22.0)	81 (25.6)
2	158 (48.9)	148 (46.8)
3	94 (29.1)	87 (27.5)
Missing	97	120
Tumor type		
Infiltrating ductal	344 (82.7)	356 (84.0)
Infiltrating lobular	27 (6.5)	36 (8.5)
Other	45 (10.8)	32 (7.5)
Missing	4	12

<u>Hong Kong Figures</u>

65% > 50 yo — 50% > 50 yo

69% T1 — 30% T1

83% ER+ve — 77% ER+ve

35% LVI +ve — 55% LVI +ve

84% IDC — 93% IDC

Non-sentinel lymph node metastasis

- 31% with non-SLN +ve disease
- Factors include:
  - tumors >3 cm,
  - more than 1 metastatic SLN,
  - presence of extracapsular spread

Hung WK, et al ANZ J Surg. 2005

CHEMOTHERAPY

EJC
EUROPEAN JOURNAL OF CANCER

Racial differences in acute toxicities of neoadjuvant or adjuvant chemotherapy in patients with early-stage breast cancer

Han HS, Reis IM, Zhao W, Kuroi K, Toi M, Suzuki E, Syme R, **Chow L**, Yip AY, Glück
Eur J **Cancer**. 2011 Nov;47(17):2537-45

- Ethnic differences in treatment-related toxicities exist between Eastern and Western patients
- Our previous retrospective study has demonstrated racial differences in acute toxicities in patients receiving anthracycline-based chemotherapy

EUROPEAN JOURNAL OF CANCER 47 (2011) 2537–2545

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

ELSEVIER

EJC

Racial differences in acute toxicities of neoadjuvant or adjuvant chemotherapy in patients with early-stage breast cancer

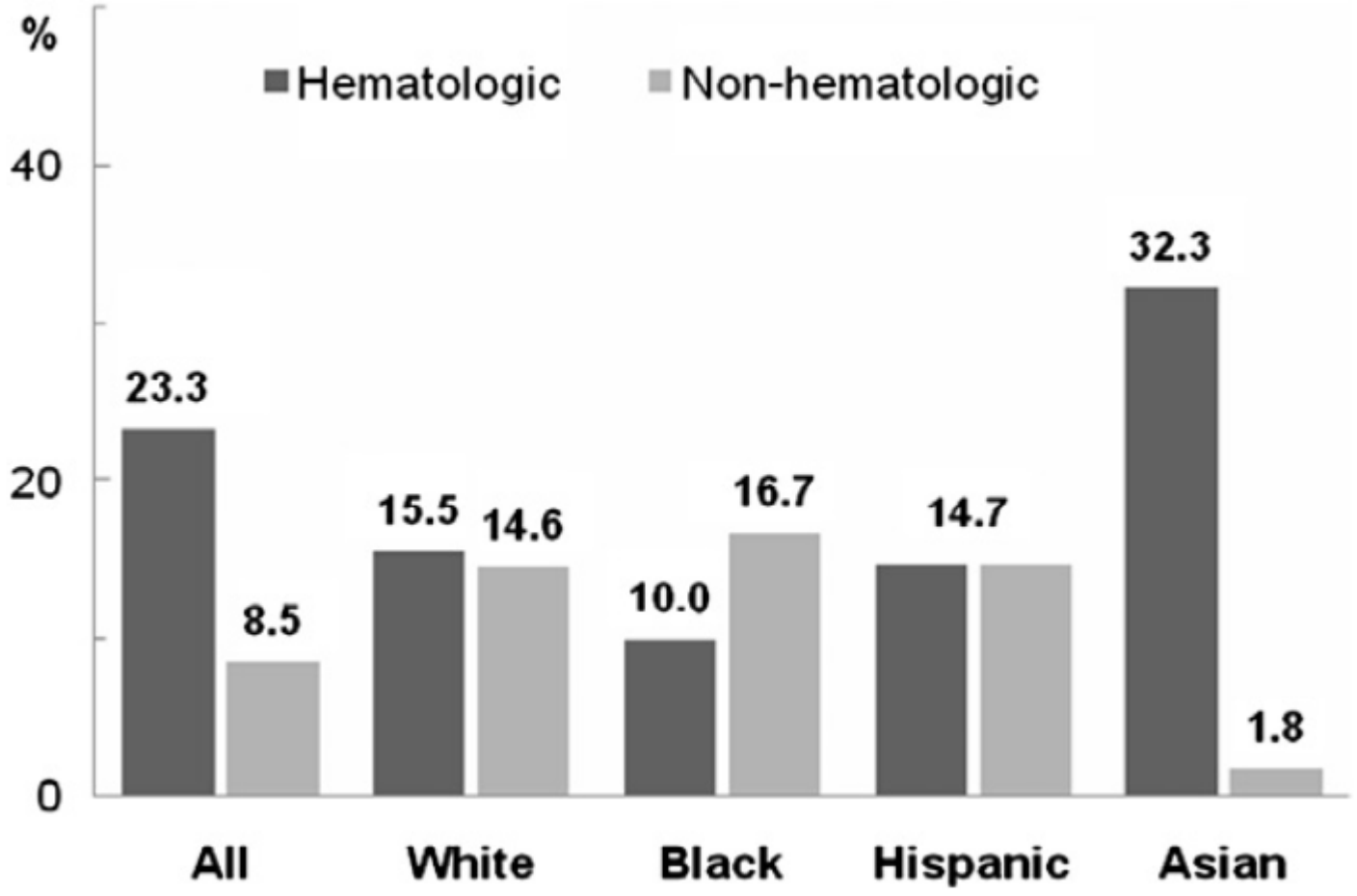
Hyo Sook Han [a], Isildinha M. Reis [b,c], Wei Zhao [c], Katsumasa Kuroi [d], Masakazu Toi [e], Eiji Suzuki [d], Rachel Syme [f], Louis Chow [g,h], Adrian Y.S. Yip [g], Stefan Glück [i,]*

"… Asians had a significantly higher rate of grade 3 hae-matologic toxicity than Caucasians, African Americans or Hispanic women (32%, 16%, 10%, and 15%, respectively; p<0.05)"

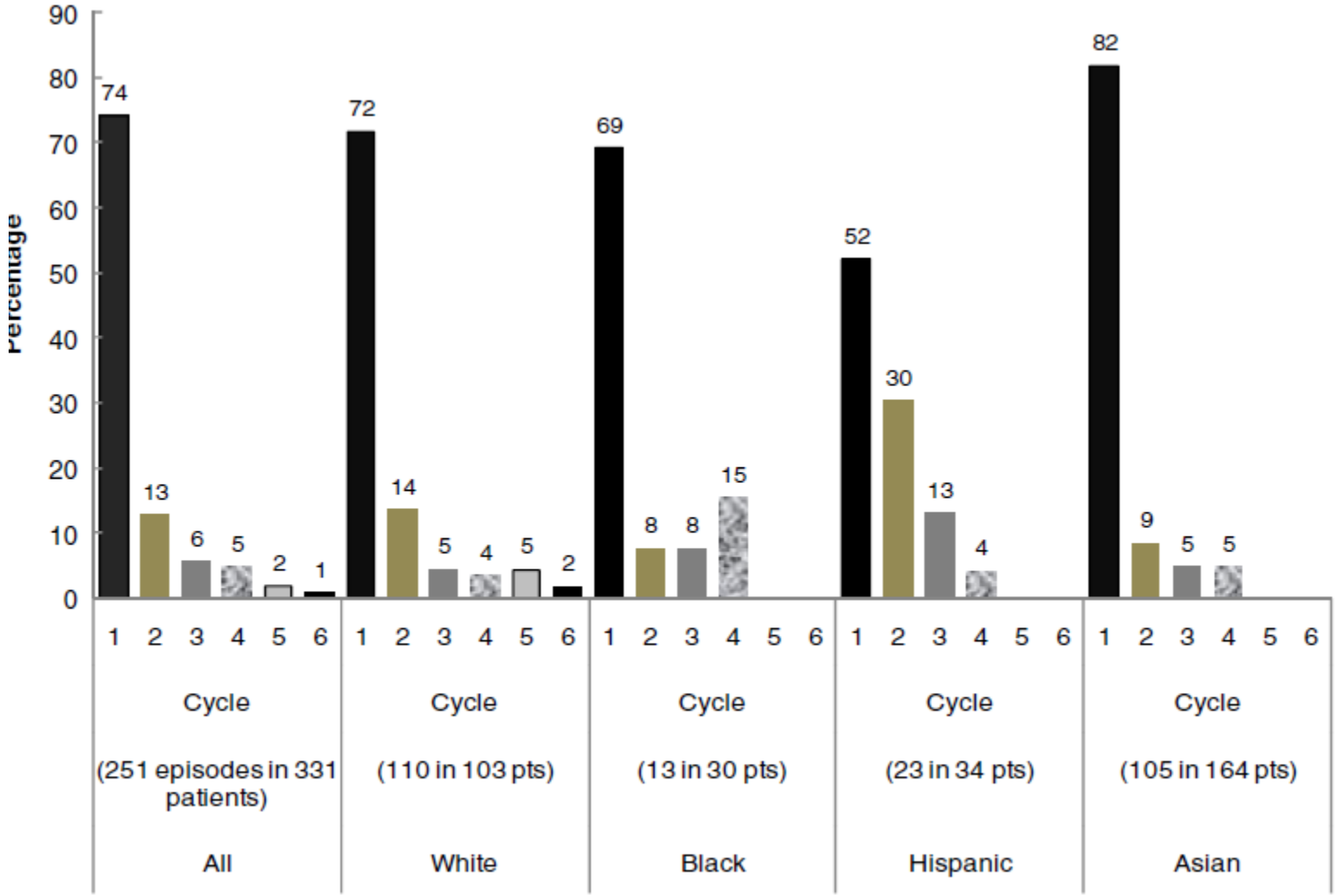
- *EJC* 2011

Grade >3 Toxicity by type, race and ethnicity

Neo/Adjuvant chemotherapy: FEC 100



Toxicity by Cycle and Race/Ethnicity % relative to total episodes



Asia–Pacific Journal of
Clinical Oncology

ORIGINAL ARTICLE

Toxicity profile differences of adjuvant docetaxel/cyclophosphamide (TC) between Asian and Caucasian breast cancer patients

Chow lWC et al
Asia Pac J Clin Oncol. 2017 Dec;13(6):372-378

Results

- From March 2004 to July 2013, data of **246** patients were included. **19** patients were excluded because of insufficient data
- Patients from six countries (China, Hong Kong SAR, Japan and Taiwan as **Asian group** whereas Italy and United States as **Caucasian group**)
  - **Asian group** 127 Asians
  - **Caucasian group** 100 Caucasian

- With respect to body mass index (BMI), there were significantly more overweight and obese patients in the Caucasian population, but more underweight and normal weight patients represented by Asian cohorts.

- There were significantly more cardiac predispositions in Caucasians.

Patient Characteristics

Demographics	Asian (N = 127)		Caucasian (N = 100)		
	N	(%)	N	(%)	P-value
Age, years					
< 55	68	(53.5)	42	(42.0)	0.108
≥55	59	(46.5)	58	(58.0)	
Menopausal status					
Pre-menopausal	61	(48.4)	30	(31.6)	0.013
Post-menopausal	65	(51.6)	65	(68.4)	
Body mass index, kg/m^2					
Underweight	15	(11.8)	4	(4.0)	<0.001
Normal weight	84	(66.1)	41	(41.0)	
Overweight	22	(17.3)	34	(34.0)	
Obese	6	(4.7)	21	(21.0)	
ECOG PS					
0	126	(99.2)	90	(91.8)	0.011
1	1	(0.8)	6	(6.1)	
2	0	-	2	(2.0)	
Comorbidities					
Diabetes	3	(2.4)	7	(7.0)	0.111
Hypertension	24	(18.9)	23	(23.0)	0.510
Hepatitis	2	(1.6)	0	-	0.505
Cardiac	2	(1.6)	14	(14.0)	<0.001
Respiratory	3	(2.4)	3	(3.0)	1.000
Gastrointestinal	8	(6.3)	3	(3.0)	0.355
Genitourinary	0	-	2	(2.0)	0.193

Louis WC Chow *et al*. "Toxicity profile differences of adjuvant docetaxel/cyclophosphamide (TC) between Asian and Caucasian breast cancer patients" has been submitted to *Annals of Oncology*

- A majority of patients receiving the TC regimen were treated for early-stage breast cancer
- The histological grades were more advanced for the Caucasian population than Asians
- There were significantly more ER+ (84.3% vs. 68%, *p*=0.004) and PR+ (74% vs. 51%, *p*<0.001) breast tumours among Asians.

Disease Characteristics

Disease Characteristics	Asian (N=127)		Caucasian (N=100)		
	N	(%)	N	(%)	P-value
AJCC Stage					
Stage I	49	(38.6)	46	(46.9)	<0.001
Stage IIA	65	(51.2)	26	(26.5)	
Stage IIB	10	(7.9)	10	(10.2)	
Stage IIIA	3	(2.4)	15	(15.3)	
Stage IIIC	0	-	1	(1.0)	
Histologic Grade					
1	18	(14.4)	4	(4.1)	0.027
2	53	(42.4)	47	(48.0)	
3	54	(43.2)	47	(48.0)	
Hormone Receptor*					
ER+	107	(84.3)	68	(68.0)	0.004
PR+	94	(74.0)	51	(51.0)	<0.001
CerbB2 Status*					
HER2+	15	(11.8)	17	(17.0)	0.337

*Measured by immunohistochemistry (IHC); HER-2 status of IHC 3+ was defined as HER2+

Louis WC Chow *et al*. "Toxicity profile differences of adjuvant docetaxel/cyclophosphamide (TC) between Asian and Caucasian breast cancer patients" has been submitted to *Annals of Oncology*

First episodes of grade 2 or higher toxicities during 4 cycles of TC

Toxicity	Asian (N = 127)		Caucasian (N = 100)		
	No. of episodes	(%)	No. of episodes	(%)	P-value
Febrile Neutropenia	19	(15.0)	9	(9.0)	0.223
Neutropenia	58	(45.7)	6	(6.0)	<0.001
Thrombocytopenia	0	-	0	-	N/A
Anemia	1	(0.8)	6	(6.0)	0.046
Nausea	7	(5.5)	8	(8.0)	0.592
Vomiting	7	(5.5)	1	(1.0)	0.081
Diarrhea	13	(10.2)	7	(7.0)	0.483
Mucositis	7	(5.5)	5	(5.0)	1.000
Hepatotoxicity	2	(1.6)	1	(1.0)	1.000
Hand-foot syndrome	10	(7.9)	5	(5.0)	0.433
Others*	1	(0.8)	0	-	1.000
*One patient experience grade 2 malaise at the last cycle of TC					

A significantly higher incidence of grade 2 and above hematological events were experienced by Asian patients.

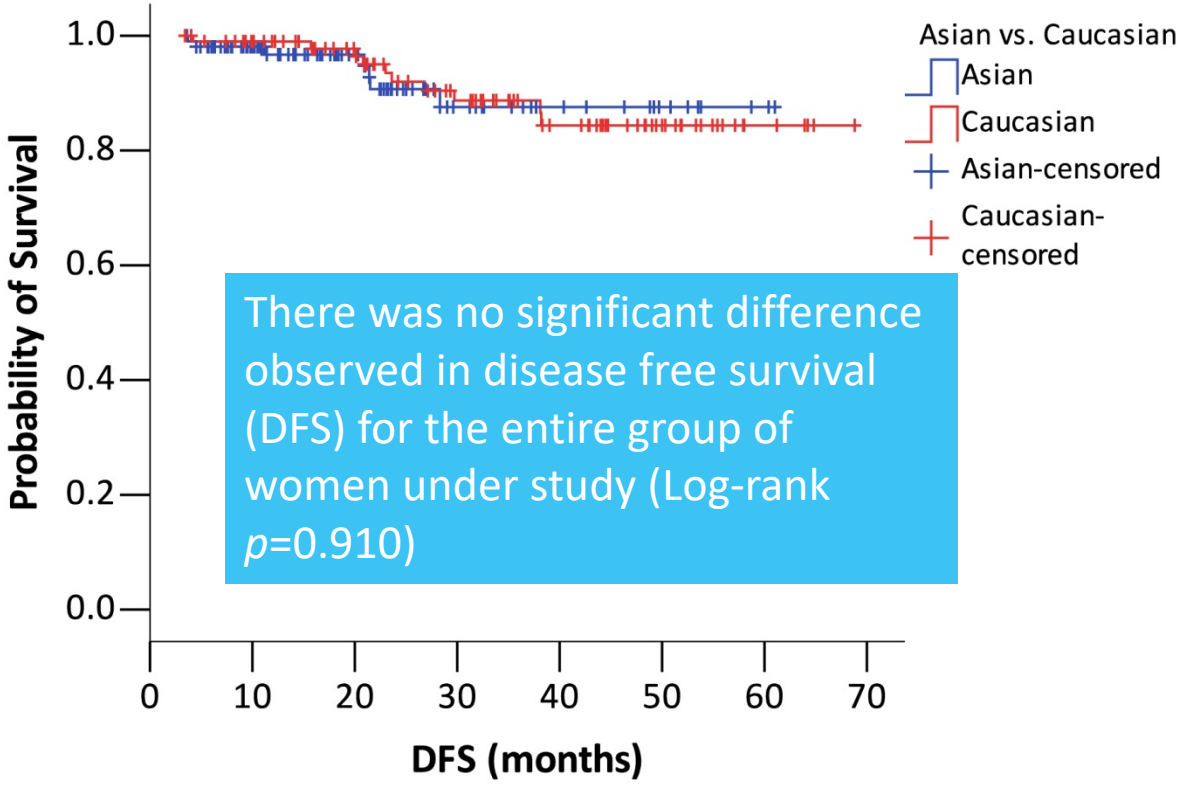
- During the given four-cycle TC adjuvant chemotherapy, significantly more grade 2 or higher neutropenia events were observed in Asians when compared to Caucasian patients (45.7% vs.6.0, $p<0.001$).
- The incidence rates of grade 3 and 4 neutropenia were 30.7% and 4.0% respectively among Asian and Caucasian patients ($p < 0.001$).

Louis WC Chow *et al*. "Toxicity profile differences of adjuvant docetaxel/cyclophosphamide (TC) between Asian and Caucasian breast cancer patients" has been submitted to *Annals of Oncology*

Patient Status at Follow-up	Asian (N=105)		Caucasian (N=100)	
	N	(%)	N	(%)
Disease-free	98	(93.3)	90	(90.0)
Relapse	3	(2.9)	7	(7.0)
Lost to Follow-up	4	(3.8)	1	(1.0)
Death	0	-	2	(2.0)

A total of 188 females were disease-free at median follow-up of 23 months, while 3 Asian patients and 7 Caucasian women had a relapse

Comparison of Disease-free Survival (DFS) between Asians and Caucasians



Louis WC Chow *et al*. "Toxicity profile differences of adjuvant docetaxel/cyclophosphamide (TC) between Asian and Caucasian breast cancer patients" has been submitted to *Annals of Oncology*

POSSIBLE REASONS

Cancer Science
Japanese Cancer Association JCA
Open Access

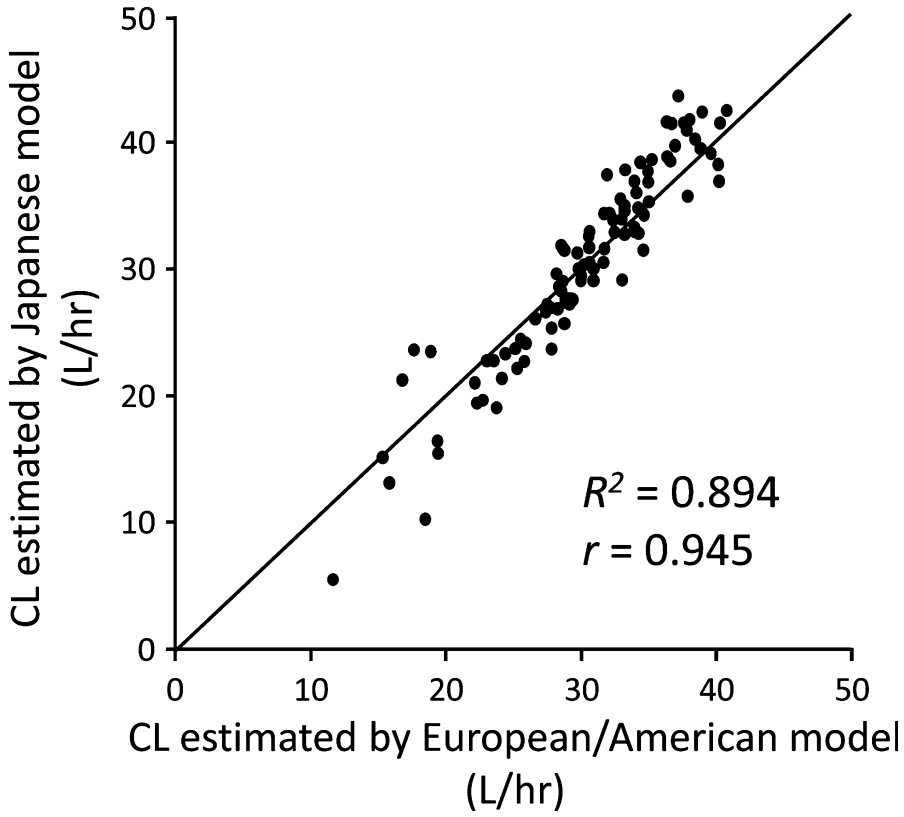
Review Article

Pharmacokinetics, dynamics and toxicity of docetaxel: Why the Japanese dose differs from the Western dose

Hirotsugu Kenmotsu[1,2] and Yusuke Tanigawara[1]

Docetaxel (Taxotere") has been one of the most important chemotherapeutic drugs for cancer treatment since 1996. Although a large number of clinical stud- ies have been conducted in various cancer fields, there is a discrepancy in the standard dose between Japan and Western countries. This article reviews the pharmacokinetic, pharmacodynamic and toxicological profiles of docetaxel, and explains why there exists an ethnic difference in dose, and further discusses which direction we should go forward to solve this problem. The original recommended dose was 100 mg／m2 every 3 weeks in US and European populations, while a Japanese phase I study suggested the recommended dose as 60 mg／m2 every 3 weeks. A prospective population pharmacokinetic analysis of docetaxel conducted in both the USA／Europe and Japan, indicated an absence of ethnic difference in the pharmacokinetics. Both analyses demonstrated that docetaxel clearance is related to a1-acid glycoprotein level, hepatic function, age and body surface area. The relationship was observed between increasing docetaxel dose and increased tumor response rates across the dose range of 60 to 100 mg／m2. The area under the serum concentration time curve (AUC) of docetaxel at the first cycle was significantly related to time to progression. Hematological toxicities were well correlated with the AUC of docetaxel, and severe hematological toxicities were more frequently observed in Japanese patients treated with 60 mg／m2, compared to the US／European patients treated with 75–100 mg／m2 dose. The Japanese population seems more susceptible to the toxicity of docetaxel. A docetaxel dose of 75 mg／m2 is now standard not only in global trials but also in recent Japanese trials. Although the optimal dose of docetaxel is still unclear, we need to continue to seek the appropriate dose of docetaxel depending on patient status and the goals of chemotherapy.

Pharmacokinetics



Other Factors

- Docetaxel clearance is related to:
  - hepatic function
    - patients with grade 2 and 3 elevations of transaminases at baseline in conjunction with elevation of alkaline phosphatase (grade ≥1) showed 22% and 38% lower clearances, respectively
  - age
  - body surface area
- Pharmacogenomics
  - Transporters of docetaxel:
    - ABCB1 (P-glycoprotein, multidrug resistance 1),
    - ABCC2 (MRP2)
    - SLCO1B3 (OATP1B3, OATP8)
  - the homozygous allele T of C1236T polymorphism in the ABCB1 gene was significantly correlated with a decreased docetaxel clearance (25%; P = 0.0039).
  - ABCC2 and SLCO1B3 have cooperative roles in the docetaxel transport process in the liver
    - A Japanese case-control association study indicated a significant association of both rs12762549 in ABCC2 (P = 0.00022) and rs11045585 in SLCO1B3 (P = 0.00017) with docetaxel-induced leukopenia／neutropenia

HORMONAL THERAPY

original article

Annals of Oncology 17: 1637–1643, 2006
doi:10.1093/annonc/mdl177
Published online 25 August 2006

Clinical outcomes of ethnic minority women in MA.17: a trial of letrozole after 5 years of tamoxifen in postmenopausal women with early stage breast cancer

B. Moy[1]*, D. Tu[2], J. L. Pater[2], J. N. Ingle[3], L. E. Shepherd[2], T. J. Whelan[4] & P. E. Goss[1]

[1]*Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA;* [2]*National Cancer Institute of Canada Clinical Trials Group, Kingston, ONT, Canada;* [3]*Mayo Clinic, Rochester, MN, USA;* [4]*McMaster University, Hamilton, ONT, Canada*

- **Background:** Aromatase inhibitors are widely employed in the adjuvant treatment of early stage breast cancer. The impact of aromatase inhibitors has not been established in ethnic minority women.
- **Patients and methods:** The purpose of this study was to evaluate the impact of letrozole on minority women in MA.17, a placebo-controlled trial of letrozole following 5 years of tamoxifen in postmenopausal women with early stage breast cancer. Retrospective comparison of disease-free survival (DFS), side effects, and mean changes in quality of life (QOL) scores from baseline between Caucasian and minority women was performed.
- **Results:** Minority (n = 352) and Caucasian (n = 4708) women were analyzed. There was no difference between these groups in DFS (91.6% versus 92.4% respectively for 4 year DFS). Letrozole, compared with placebo, significantly improved DFS for Caucasians (HR = 0.55; P < 0.0001) but not for minorities (HR = 1.39; P = 0.53). Among women who received letrozole, minorities had a significantly lower incidence of hot flashes (49% versus 58%; P = 0.02), fatigue (29% versus 39%; P = 0.005), and arthritis (2% versus 7%; P = 0.006) compared with Caucasians. Mean change in QOL scores for minority women who received letrozole demonstrated improved mental health at the 6-month assessment (P = 0.02) and less bodily pain at the 12-month assessment (P = 0.046).
- **Conclusion:** Letrozole improved DFS in Caucasians but a definite benefit in minority women has not yet been demonstrated. Minority women tolerated letrozole better than Caucasians in terms of toxicity. These results need confirmation in other trials of aromatase inhibitors.

Ethnic Minority

- Total = 5170 patients,
- Ethnic minority = 462 (8.9%)
  - Black = 179 (3.5%) were
  - Hispanic = 77 (1.5 %)
  - Asian or Pacific Islander = 73 (1.4%)
  - Native North American or Native Alaskan = 23 (0.4%)
  - ‘other’ = 31 (0.6%)
  - ‘unknown’ = 44 (0.9%)
  - Missing ethnic data = 35 (0.7%)

Patient's Characteristics & Co-Morbidities

	Minority women $n = 351$	Caucasian women $n = 4708$	P-value (two-sided)
Age (years)			
Mean	61.3	62.3	0.03
Range	35.4–84.5	32.4–94.7	
<65	216 (61.5%)	2754 (58.5%)	
≥65	135 (38.5%)	1954 (41.5%)	
Duration of prior tamoxifen (years)			
Mean	5.1	5.0	0.0002
Range	4.2–6.1	0–6.3	
≤5	137 (38.9%)	2182 (46.4%)	
>5	215 (61.1%)	2518 (53.6%)	
Geographical region			
US	285 (81.0%)	3300 (70.1%)	<0.0001
Canada	65 (18.5%)	1287 (27.3%)	
Other	2 (0.6%)	121 (2.6%)	
T stage			
1	190 (54.3%)	2744 (58.5%)	0.19
2	122 (34.9%)	1570 (33.5%)	
3	24 (6.9%)	248 (5.3%)	
4	10 (2.9%)	72 (1.5%)	
X	4 (1.1%)	55 (1.2%)	
N stage			
0	171 (48.7%)	2337 (49.8%)	0.54
1	160 (45.6%)	2064 (44.0%)	
2	8 (2.3%)	71 (1.5%)	
3	0 (0%)	10 (0.2%)	
X	12 (3.4%)	211 (4.5%)	

	Minority women	Caucasian women	P-value
Prior treatment (modality)			
Surgery only	86 (24.6%)	1086 (23.1%)	0.004
Surgery & radiation	81 (23.6%)	1491 (31.7%)	
Surgery & chemo	76 (21.7%)	790 (16.8%)	
Surgery & radiation & chemo	106 (30.6%)	1331 (28.3%)	
Comorbidity			
Osteoporosis	28 (8.0%)	497 (10.8%)	0.12
Arthritis	34 (9.7%)	575 (12.5%)	0.15
Thyroid disease	32 (9.1%)	603 (13.2%)	0.04
Liver disease	6 (1.7%)	99 (2.2%)	0.61
Uterine cancer	2 (0.6%)	20 (0.4%)	0.69
IBD	1 (0.3%)	63 (1.4%)	0.09
Hypertension	194 (55.4%)	1978 (43.1%)	<0.0001
Heart attack	5 (1.4%)	80 (1.7%)	0.69
Stroke	4 (1.1%)	54 (1.2%)	0.99
Neuromuscular disease	2 (0.6%)	70 (1.5%)	0.15
Diabetes	120 (34.3%)	1320 (28.8%)	0.02
Kidney disease	0	40 (0.9%)	0.08
Phlebitis/thrombophlebitis	2 (0.6%)	26 (0.6%)	0.97
Respiratory disease	19 (5.4%)	207 (4.5%)	0.38
Other cancer	7 (2.0%)	84 (1.8%)	0.78
Number of past major medical problems			
0	119 (33.8%)	1999 (42.5%)	0.004
1–6	233 (66.2%)	2709 (57.5%)	

Race	Letrozole		Placebo		Hazard ratio[b] (95% CI) *P*-value
	n	4 year DFS (%)	*n*	4 year DFS (%)	
Minority	183	89.5	169	93.7	1.39 (0.50, 3.91) $P = 0.53$
Caucasian	2339	94.9	2369	89.7	0.55 (0.41, 0.72) $P < 0.0001$

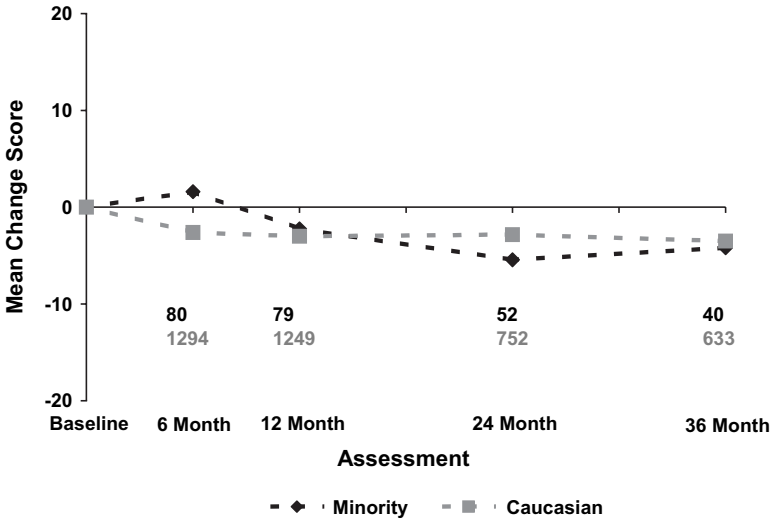
	Univariate analysis		Log-rank *P*-value	Multivariate analysis	
	4 year DFS (%)	Hazard ratio (95% CI)		Hazard ratio (95% CI)	*P*-value (Cox regression)
Race			0.88		0.90[b]
Minority ($n = 352$)	91.6	0.95[a] (0.56, 1.60)		0.96[a] (0.57, 1.62)	
Caucasian ($n = 4708$)	92.3				

Adverse Effects

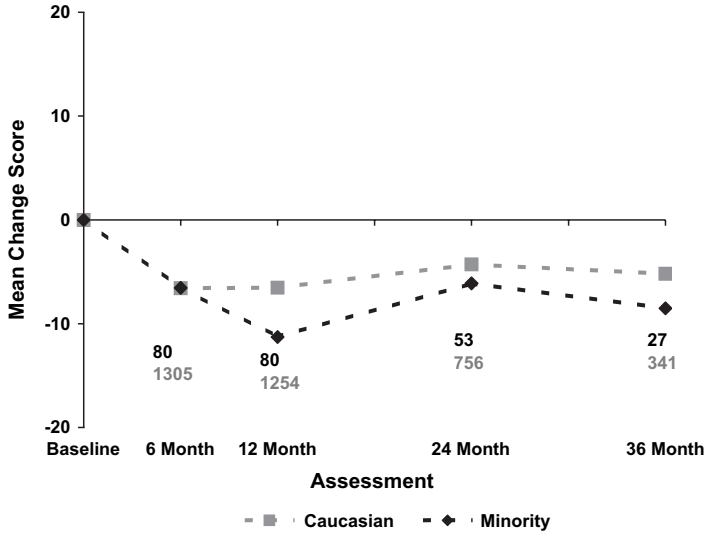
Toxicity	Minority (n = 183)					Caucasian (n = 2339)					P value[†]
	Grade 1	Grade 2	Grade 3	Grade 4	Total, no. (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total, no. (%)	
Edema	40	4			44 (24)	422	91	5		518 (22)	0.55
Hypertension	9	1	7		17 (9)	44	20	48		112 (5)	0.008
Hot flashes/flushes	59	30	1		90 (49)	740	616	1		1357 (58)	0.02
Fatigue	46	7			53 (29)	739	170	14	1	924 (39)	0.005
Sweating	4	10			54 (30)	494	219			713 (30)	0.78
Anorexia	8	1			9 (5)	104	25	1		130 (6)	0.71
Constipation	23	2			25 (14)	270	57	6		333 (14)	0.83
Diarrhea	4	1			5 (3)	117	27	14		158 (7)	0.033
Nausea	21				21 (12)	240	35	6		281 (12)	0.83
Vaginal bleeding	5	1			6 (3)	115	20	2		137 (6)	0.15
Infection without neutropenia	3	4			7 (4)	29	59	27		115 (5)	0.51
Arthritis	2			1	3 (2)	107	45	9		161 (7)	0.006
Hypercholesterolemia	25	2	1		28 (15)	346	33	1		380 (15)	0.90
Dizziness	29	5			34 (19)	352	52	13		417 (18)	0.80
Insomnia	7	2			9 (5)	108	42	2		152 (6)	0.40
Depression	7	1			8 (4)	77	41	14	2	134 (6)	0.44
Headache	43	9			52 (28)	487	129	22		638 (27)	0.74
Arthralgia	34	11	1		46 (25)	340	229	24		593 (25)	0.95
Myalgia	15	9			24 (13)	216	112	18		346 (15)	0.54
Bone pain	5	2	1	1	9 (5)	74	44	12		130 (6)	0.25
Dyspnea		11	4		15 (8)		129	9	4	142 (6)	0.25
Alopecia	9				9 (5)	101	12			113 (5)	0.96
Vaginal dryness	6	5			11 (6)	63	64			127 (5)	0.74

Quality of life scores

Bodily Pain



Mental health



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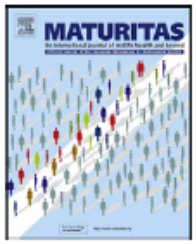


A cross-sectional study of elderly Asian and European women with primary operable breast cancer aged 70 and older. Are there differences?

Muy-Kheng M. Teaa[b,*], Lichen Tang[a], Gen-Hong Di[a], Dana Muin[b], Stefan Steurer[b,c], James W. Delancey[d], Zhi-Ming Shao[a], Christian F. Singer[b]

[a] *Fudan University Shanghai, Cancer Institute, Department of Breast Surgery, Shanghai, China*
[b] *Medical University of Vienna, Department of OB/GYN, Division of Senology, Vienna, Austria*
[c] *Medical University Eppendorf, Institute for Pathology, Hamburg, Germany*
[d] *Tulane University, Department of Health Systems Management, New Orleans, USA*

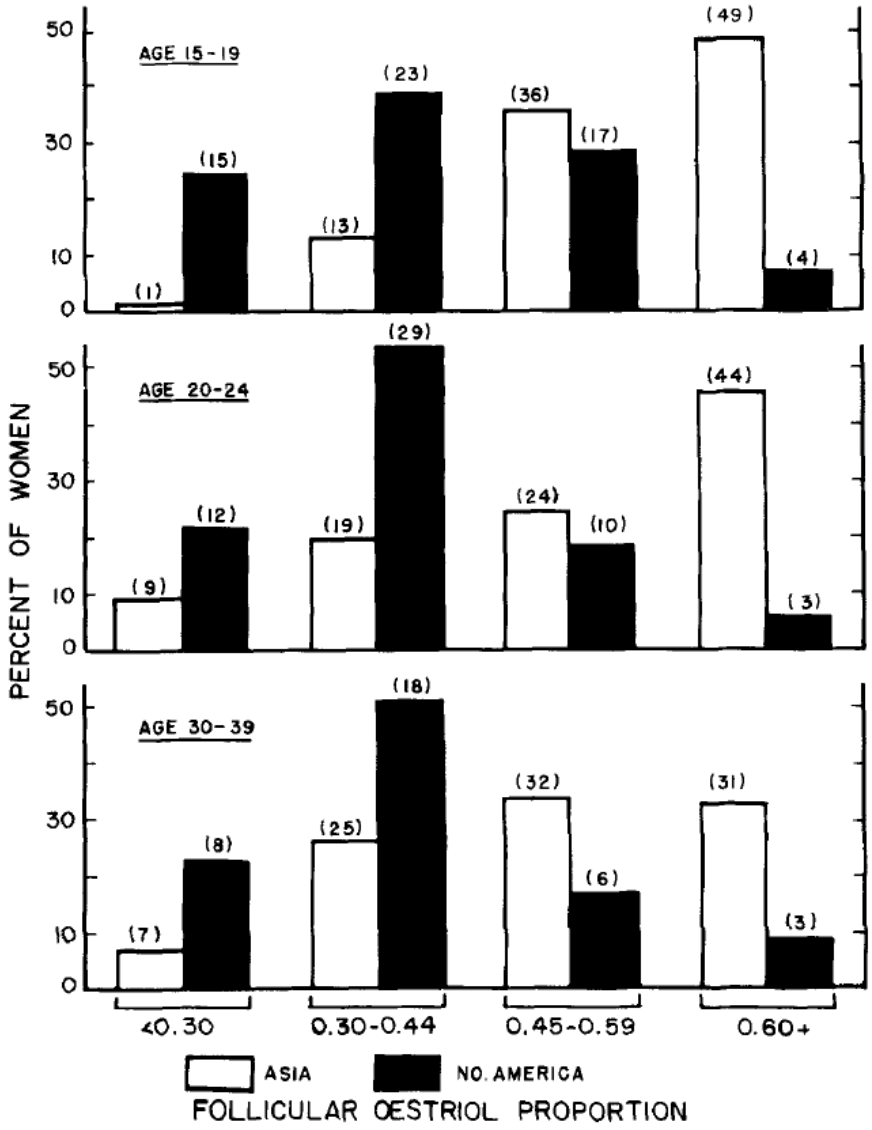
Maturitas 2012, **73:** 251– 254

Distribution of tumor size, axillary nodal status, receptor expression, and histological grading in geriatric Asian compared to Caucasian breast cancer cases

	Shanghai, n (%)	Vienna, n (%)	*P*-value
Mean age	75.3	75.3	0.934
[Minimum–maximum age]	[70-105]	[70-105]	
Tumor size			
≤2 cm	193 (53.3)	105 (61.4)	0.079
>2 cm	169 (46.7)	66 (38.6)	
Axillary lymph node status			
Negative	264 (66.3)	113 (68.5)	0.245
Positive	134 (33.7)	52 (31.5)	
Grading			
G1	23 (7.3)	46 (24.1)	G1 + G2 vs. G3 **< 0.001**
G2	250 (79.6)	93 (48.7)	
G3	41 (13.1)	52 (27.2)	
Receptor status			
ER[a] positive	261 (73.7)	144 (84.2)	**<0.001**
ER[a] negative	93 (26.3)	27 (15.8)	
PR[a] positive	236 (66.5)	103 (60.2)	0.162
PR[b] negative	119 (33.5)	68 (39.8)	
HER2[c] positive	21 (5.9)	16 (9.7)	0.129
HER2[c] negative	333 (94.1)	149 (90.3)	
Triple negative	74 (20.9)	19 (11.5)	**0.027**

[a] ER (estrogen-receptor); [b] PR (progesterone-receptor); [c] HER2 (human epidermal growth factor 2-receptor).

Percentage distribution of women according to urine oestriol proportion, by continent and age group



( ) Numbers of women

MacMahon B, *et al. Int J Cancer.* 1974;14:161-167

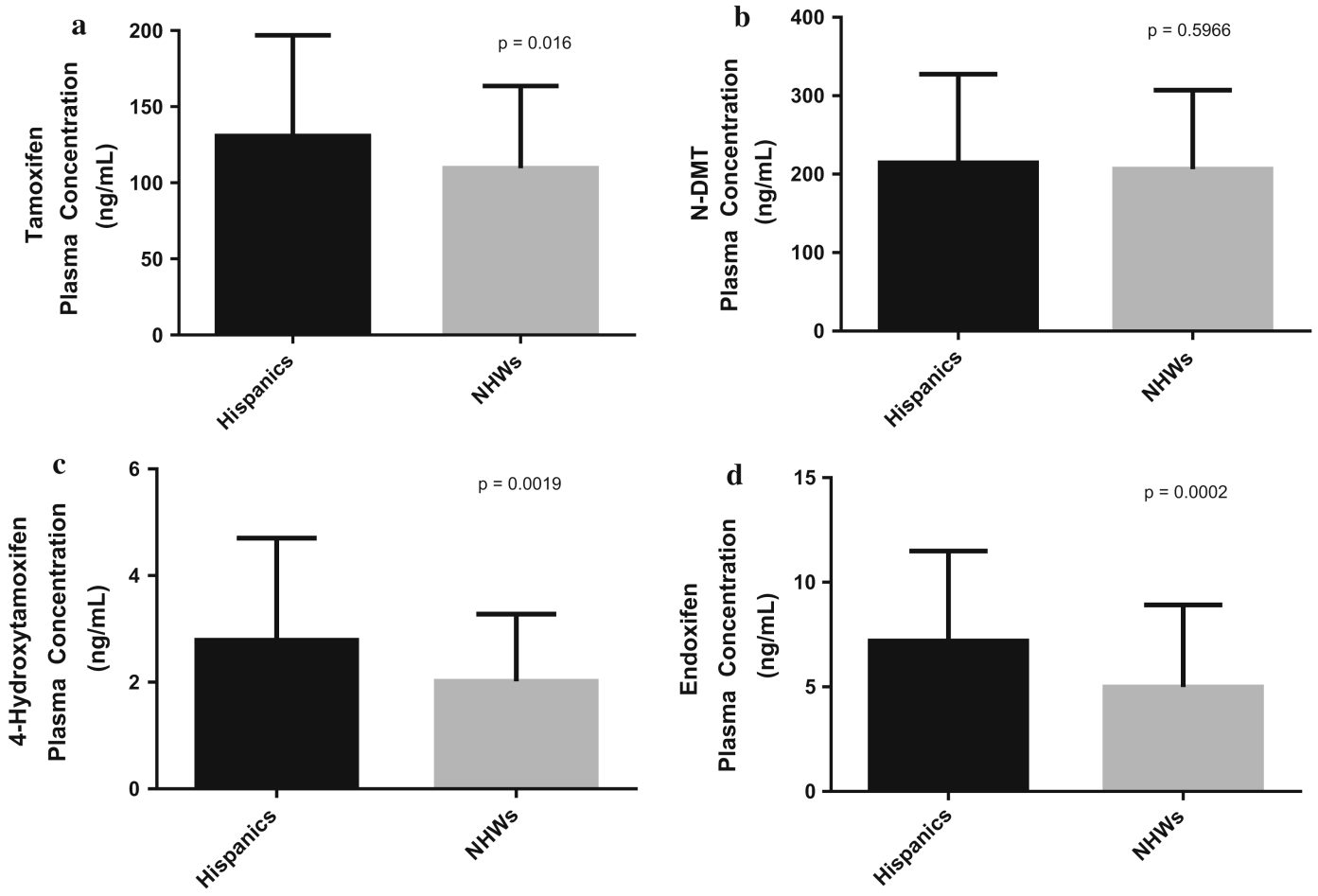
Breast Cancer Res Treat, Dec 2014

Pharmacogenomic diversity of tamoxifen metabolites and estrogen receptor genes in Hispanics and non-Hispanic whites with breast cancer

Leticia B. A. Rangel, Jodi L. Taraba, Christopher R. Frei, Lon Smith, Gladys Rodriguez, John G. Kuhn

Ethnic differences in patient genetics and breast cancer (BC) biology contribute to ethnic disparities in cancer presentation and patient outcome. We prospectively evaluated SNPs within phase I and phase II tamoxifen (TAM) metabolizing enzymes, and the estrogen receptor gene (ESR1), aiming to identify potential pharmacogenomic ethnicity patterns in an ER-positive BC cohort constituted of Hispanic and Non-Hispanic White (NHW) women in South Texas. Plasma concentrations of TAM/metabolites were measured using HPLC. CYP2C9, CYP2D6 and SULT1A1 genotypes were determined by DNA sequencing/Pyrosequencing technology. ESR1 PvuII and XbaI SNPs were genotyped using Applied Biosystems Taqman® Allelic Discrimination Assay. Hispanics had higher levels of TAM, 4-hydroxytamoxifen, and endoxifen than NHWs. There was a higher prevalence of CYP2D6 EM within Hispanics than NHWs, which corresponded to higher endoxifen levels, but no differences were verified with regard to CYP2C9 and SULT1A1. We found a higher incidence of the wild type forms of the ESR1 in Hispanics than NHWs. The performance status, the disease stage at diagnosis, and the use of aromatase inhibitors might have overcome the overall favorable pharmacogenomics profile of Hispanics when compared to NHWs in relation to TAM therapy responsiveness. Our data strongly point to ethnical peculiarities related to pharmacogenomics and demographic features of TAM treated Hispanics and NHWs. In the era of pharmacogenomics and its ultimate goal of individualized, efficacious and safe therapy, cancer studies focused on the Hispanic population are warranted because this is the fastest growing major demographic group, and an understudied segment in the U.S.

Tamoxifen & metabolites plasma concentration



The Oncologist®

Epidemiology, Access, and Outcomes

Interethnic Differences in Genetic Polymorphisms of CYP2D6 in the U.S. Population: Clinical Implications

Stephen Bernard,[a] Kathleen A. Neville,[b] Anne T. Nguyen,[b] David A. Flockhart[b]

[a]Division of Hematology and Medical Oncology, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA;
[b]Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana, USA

Phenotype	Effect on metabolism	Potential consequences
Poor metabolizer	Slowed drug metabolism	Greater potential for drug–drug interactions and adverse events Slower conversion to active metabolites, potentially lower efficacy
Ultrarapid metabolizer	Accelerated drug metabolism	Greater rates of drug elimination Potentially lower drug efficacy

Population	PM phenotype (%)	Diminished activity of IMs (%)	UM phenotype (%)	Reference
White		1–2		[1]
American	7.7		4.3	[20, 40]
British	8.9			[26]
Polish	8.3			[73]
Swiss	10			[25]
Danish			0.8	[22]
German	7.7		0.8	[49]
Swedish			1	[50]
Spanish			10	[23]
Turkish	1.5		8.7	
Croatian	3.0		4.0	[74]
African				
African-American	1.9–7.3		4.9	[20, 39–42]
Nigerian	0–8.1			[35, 36]
Ghanaian	6.0			[37]
Ethiopian	1.8		29	[21]
South African	19			[38]
Asian		51		[1]
Japanese	0			[29]
Chinese	<1.0		0.9	[28, 75]
Thai	1.2			[27]
Indian	1.8–4.8			[30–33]
Saudi Arabian	1–2	3–9	21.0	[1, 51, 76]
Hispanic				
Colombian	6.6		1.7	[47]
Mexican	3.2			[46]
Panamanian (Amerindian)	2.2–4.4			[45]
Nicaraguan	3.6			[48]

Abbreviations: IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

VOLUME 25 · NUMBER 25 · SEPTEMBER 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinical Implications of CYP2D6 Genotypes Predictive of Tamoxifen Pharmacokinetics in Metastatic Breast Cancer

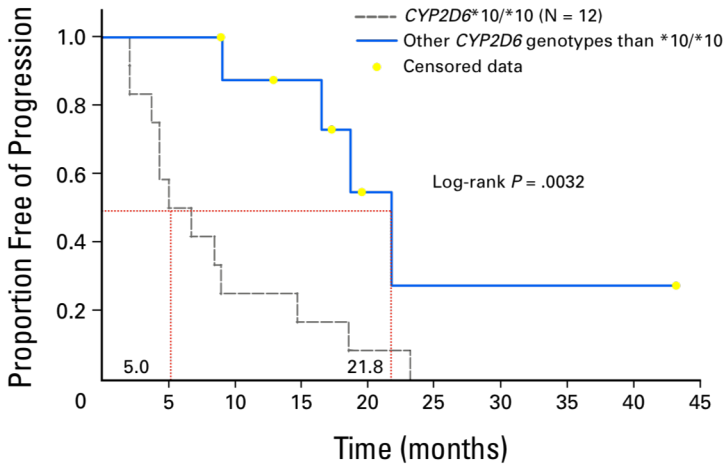
Hyeong-Seok Lim, Han Ju Lee, Keun Seok Lee, Eun Sook Lee, In-Jin Jang, and Jungsil Ro

Outcome	*CYP2D6* genotypes: Wt/Wt or Wt/*10 No.	%	*10/*10 No.	%	*P**
CR	0		0		.01860
PR	1		0		
SD ≥ 24 wk	8		6		
Clinical benefit	9	100	6	50	
SD < 24 wk	0		3		
PD	0		3		
No clinical benefit	0	0	6	50	
Total	9	100	12	100	

NOTE. Clinical benefit is defined as CR, PR, or SD ≥ 24 wks.

Abbreviations: Wt, wild type; CR, complete response; PR, partial response; SD, stable disease; wk, week; PD, progressive disease.

*Fisher's exact test for the association between the *CYP2D6* genotypes and clinical benefit.



Oncogene (2000) 1919, 1329–1333

www.nature.com/onc

Genetic variants of *CYP19* (aromatase) and breast cancer risk

Vessela Nedelcheva Kristensen[1], Nobuhiro Harada[2], Noriko Yoshimura[2], Ellen Haraldsen[1], PE Lønning[4], Bjørn Erikstein[3], Rolf Kåresen[5], Tom Kristensen[6] and Anne-Lise Børresen-Dale*[,1]

- The frequency of the polymorphic T allele was particularly high among patients presenting with high stage disease and with tumors larger than 5 cm and was significantly associated with mRNA levels as well as a switch from the normally used adipose promoter to ovary promoter

- Individuals homozygous for this allele may have accelerated production of tissue estrogen and therefore higher risk for developing tumors with rapid local growth

The Oncologist®
Breast Cancer
2008:13; 751-60

The *CYP19* TTTA Repeat Polymorphism Is Related to the Prognosis of Premenopausal Stage I–II and Operable Stage III Breast Cancers

CHIUN-SHENG HUANG,[a] SUNG-HSIN KUO,[b,d,e] HUANG-CHUN LIEN,[c] SHI-YI YANG,[f] SAN-LIN YOU,[f] CHEN-YANG SHEN,[g] CHING-HUNG LIN,[b,d] YEN-SEN LU,[b,d] KING-JENG CHANG[a]

Premenopausal women with the long allele have a greater survival rate and may not gain benefit from adjuvant chemotherapy

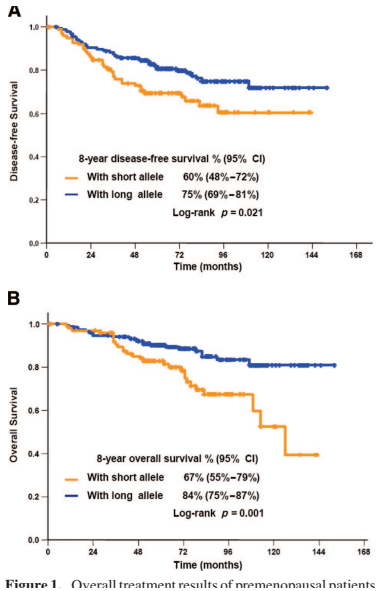


Figure 1. Overall treatment results of premenopausal patients

PLOS ONE

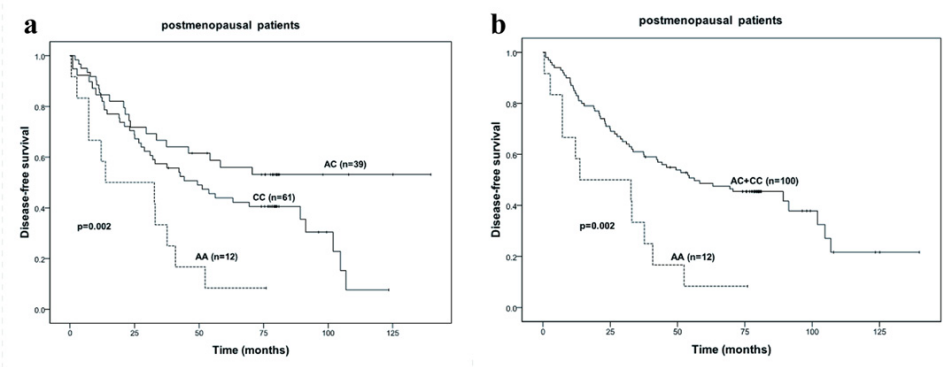
Mar 20, 2015

RESEARCH ARTICLE

The *CYP19* RS4646 Polymorphism Is Related to the Prognosis of Stage I–II and Operable Stage III Breast Cancer

Xiying Shao[1], Yong Guo[2], Xiaohong Xu[3], Yabing Zheng[1], Jiwen Wang[4], Zhanhong Chen[1], Jian Huang[1], Ping Huang[1], Jufen Cai[1], Xiaojia Wang[1]*

- CYP19 rs4646 polymorphism is related to DFS in early breast cancer
- The prognosis index of the homozygous for the minor allele (AA) may depend on menopause status



MTOR INHIBITOR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

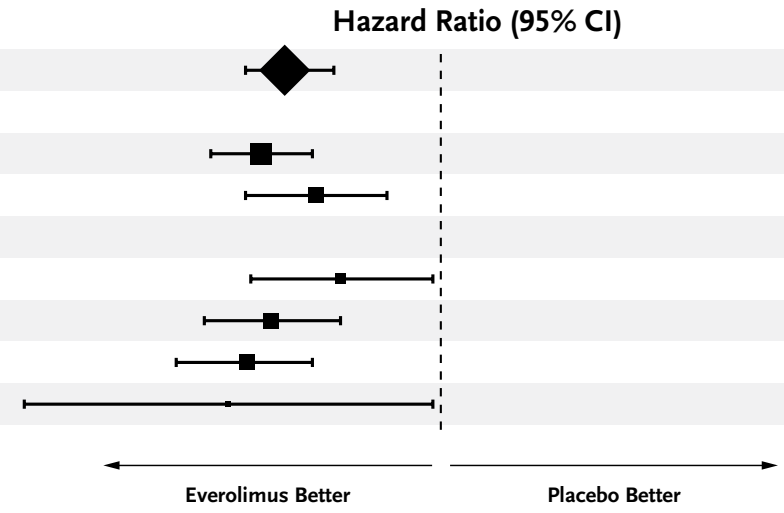
Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

Table 1. Patient and Tumor Characteristics at Baseline.*

Characteristic	Everolimus and Exemestane (N = 485)	Placebo and Exemestane (N = 239)
Age (yr)		
Median	62	61
Range	34–93	28–90
Race (%)†		
White	74	78
Black	3	1
Asian	20	19
Other	3	2

Subgroup	No.
All patients	724
Age	
<65 yr	449
≥65 yr	275
Region	
Asia	137
Europe	275
North America	274
Other	38



Breast Cancer (2014) 21:703–714
DOI 10.1007/s12282-013-0444-8

ORIGINAL ARTICLE

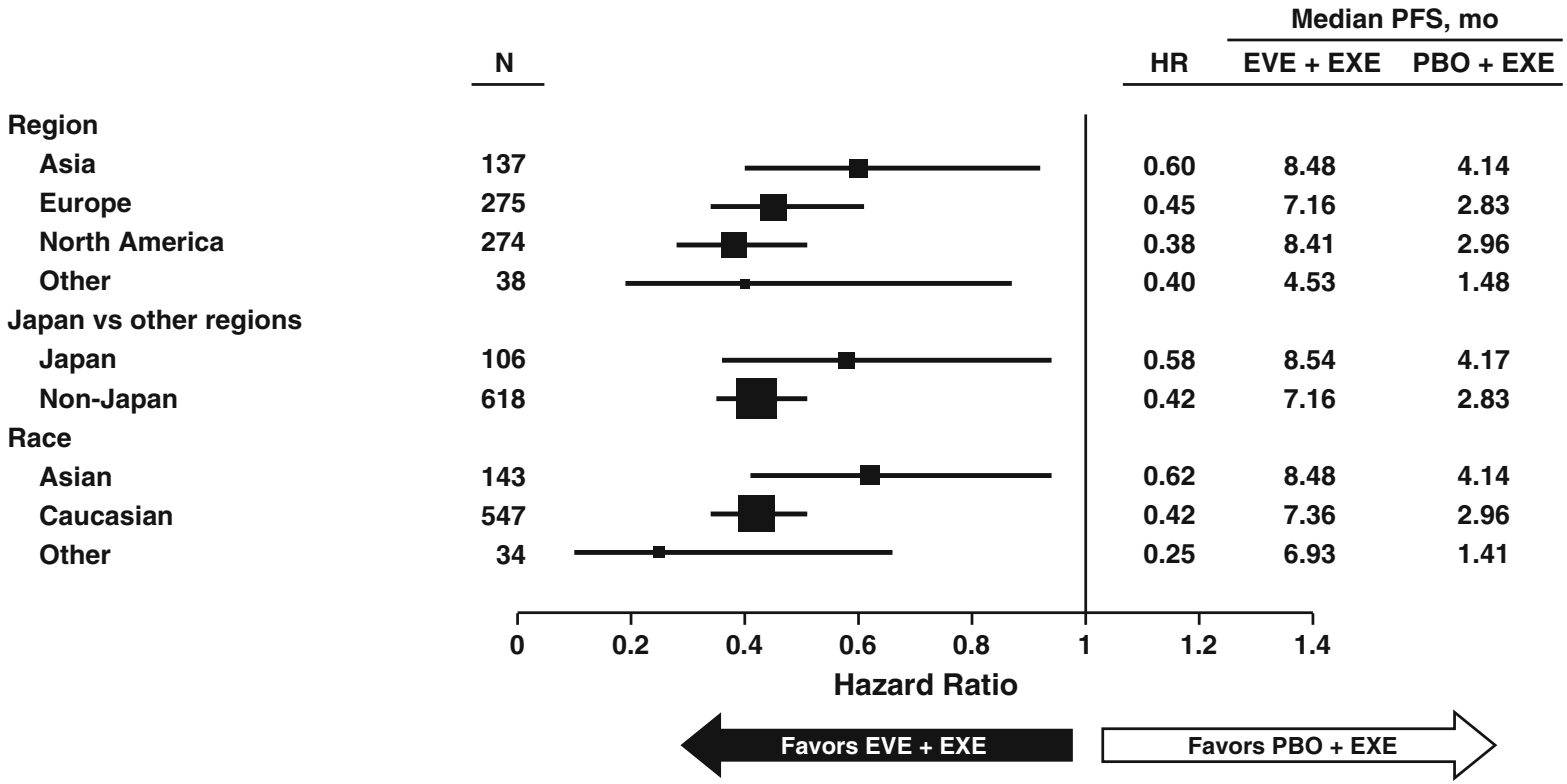
Efficacy of everolimus with exemestane versus exemestane alone in Asian patients with HER2-negative, hormone-receptor-positive breast cancer in BOLERO-2

Shinzaburo Noguchi · Norikazu Masuda · Hiroji Iwata · Hirofumi Mukai · Jun Horiguchi · Puttisak Puttawibul · Vichien Srimuninnimit · Yutaka Tokuda · Katsumasa Kuroi · Hirotaka Iwase · Hideo Inaji · Shozo Ohsumi · Woo-Chul Noh · Takahiro Nakayama · Shinji Ohno · Yoshiaki Rai · Byeong-Woo Park · Ashok Panneerselvam · Mona El-Hashimy · Tetiana Taran · Tarek Sahmoud · Yoshinori Ito

Results: Of 143 Asian patients, 98 received EVE + EXE and 45 received PBO + EXE. Treatment with EVE + EXE significantly improved median PFS versus PBO + EXE among Asian patients by 38 % (HR = 0.62; 95 % CI, 0.41–0.94). Median PFS was also improved among non-Asian patients by 59 % (HR = 0.41; 95 % CI, 0.33–0.50). Median PFS duration among EVE-treated Asian patients was 8.48 versus 4.14months for PBO + EXE, and 7.33 versus 2.83 months, respectively, in non-Asian patients. The most common grade 3/4 adverse events (stomatitis, anemia, elevated liver enzymes, hyperglycemia, and dyspnea) occurred at similar frequencies in Asian and non-Asian patients. Grade 1/2 interstitial lung disease occurred more frequently in Asian patients. Quality of life was similar between treatment arms in Asian patients.

Forest plot of progression-free survival

(subgroup analysis by region and ethnicity)



Adverse events

	Asians (Im)	Asians (Noguchi)	Non-asians (Noguchi)
Stomatitis	66 (9)	82 (8)	14 (2)
Hyperlipidemia	26 (2)	8 (0)	3 (<1)
Hyperglycaemia	14 (5)	9(4)	4 (1.5)
Elevated liver enzymes	17 (6)	17 (3)	3 (0.8)
Pneumonitis	10 (<1)	23 (2)	4 (1)

Im, HY Im, ASCO 2015 abstract
Noguchi, S Noguchi, Breast Cancer, 2014
(), Gr3 toxivity

CDK 4/6 INHIBITORS

RIBOCICLIB PLUS GOSERELIN AND TAMOXIFEN OR A NON-STEROIDAL AROMATASE INHIBITOR FOR PREMENOPAUSAL WOMEN WITH HR+, HER2– ADVANCED BREAST CANCER IN THE RANDOMIZED PHASE III MONALEESA-7 TRIAL

Seock-Ah Im,[1] Joohyuk Sohn,[2] Debu Tripathy,[3] Louis Chow,[4] Marco Colleoni,[5] Fabio Franke,[6] Aditya Bardia,[7] Nadia Harbeck,[8] Sara Hurvitz,[9] Keun Seok Lee,[10] Kyung Hae Jung,[11] Young-Hyuck Im,[12] Nagi El Saghir,[13] Mei-Ching Liu,[14] Melissa Tripodi,[15] Rahul Tyagi,[15] Gareth Hughes,[16] Michelle Miller,[15] Yen-Shen Lu[17]

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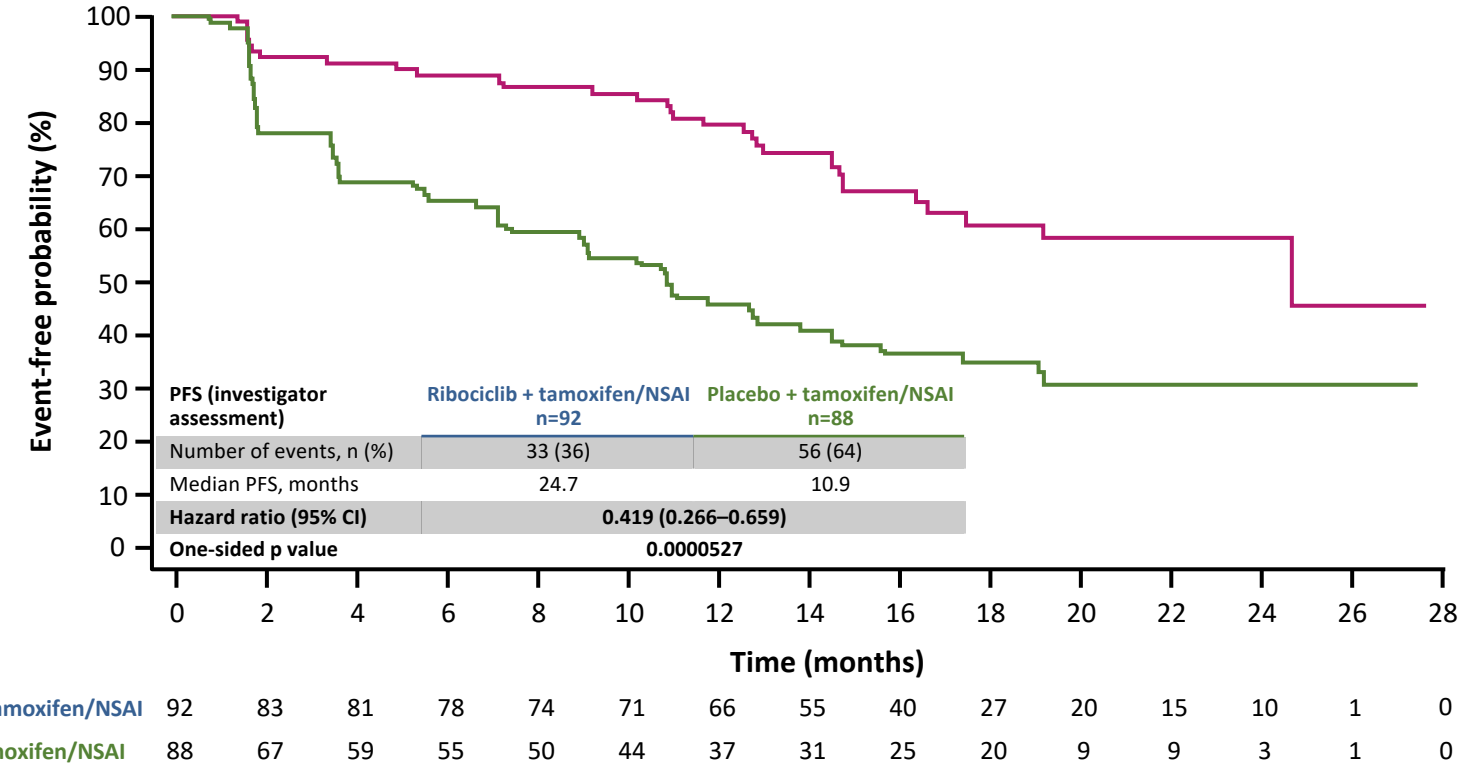
Presented on Friday April 5, 2018 (Invited Oral Presentation)

PFS: Asian subgroup analysis*

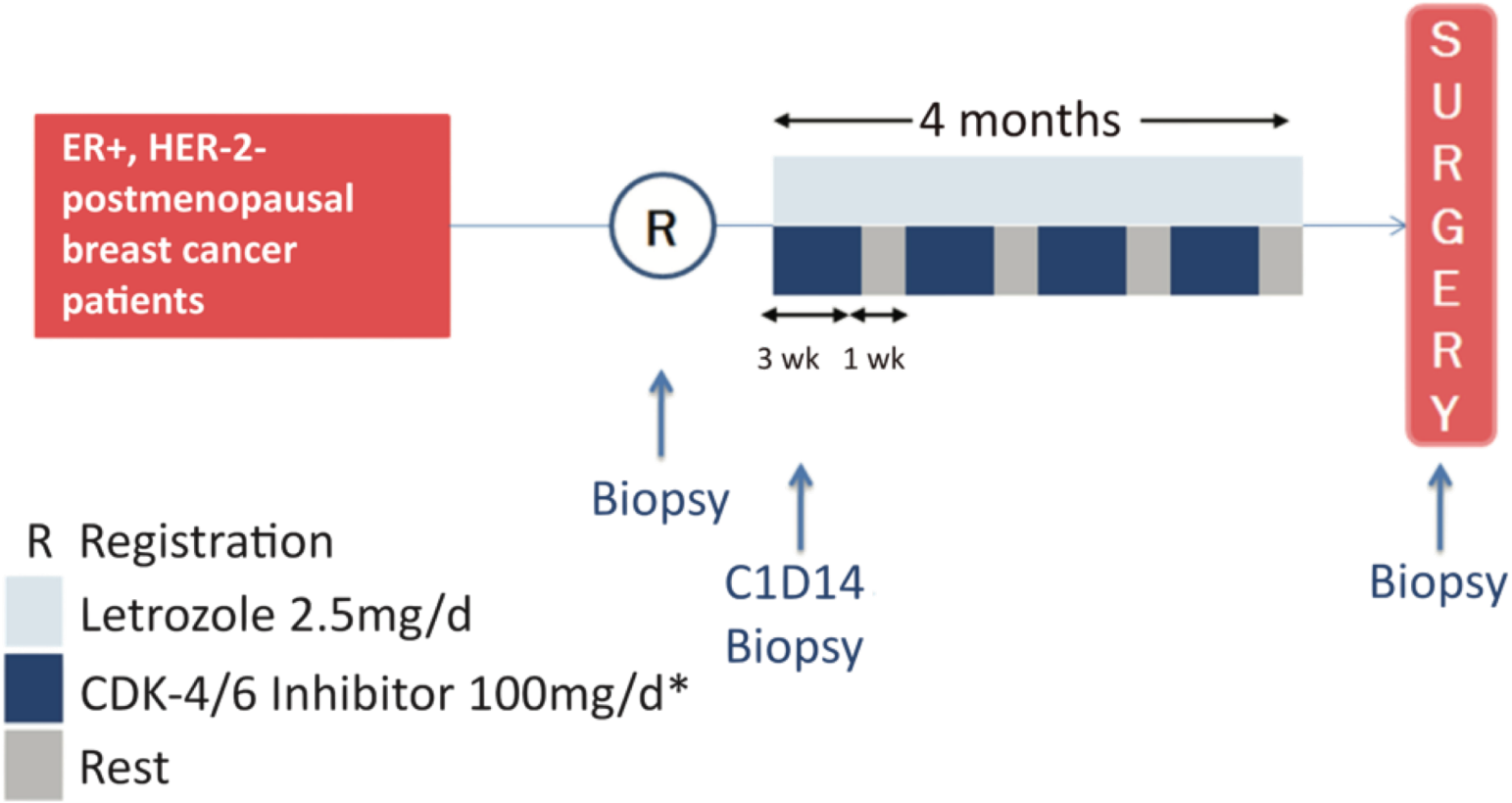


*Locally assessed PFS in Asian patients (by region).
Goserelin included in all combinations.

RESEARCH

Neoadjuvant palbociclib on ER+ breast cancer (N007): clinical response and EndoPredict's value

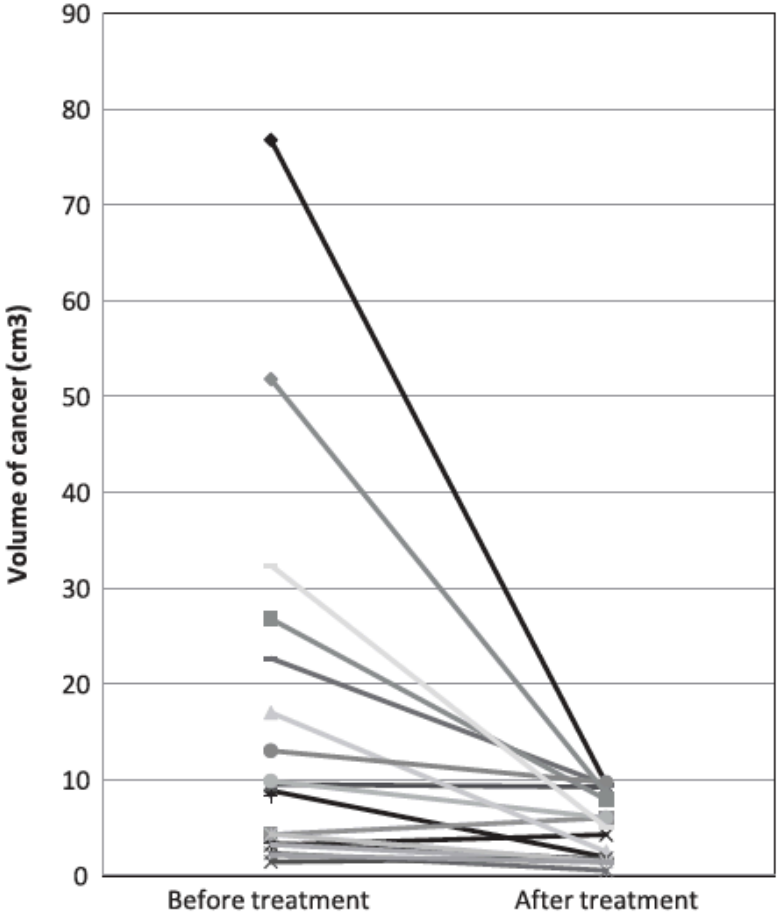
OOTR-N007 Study

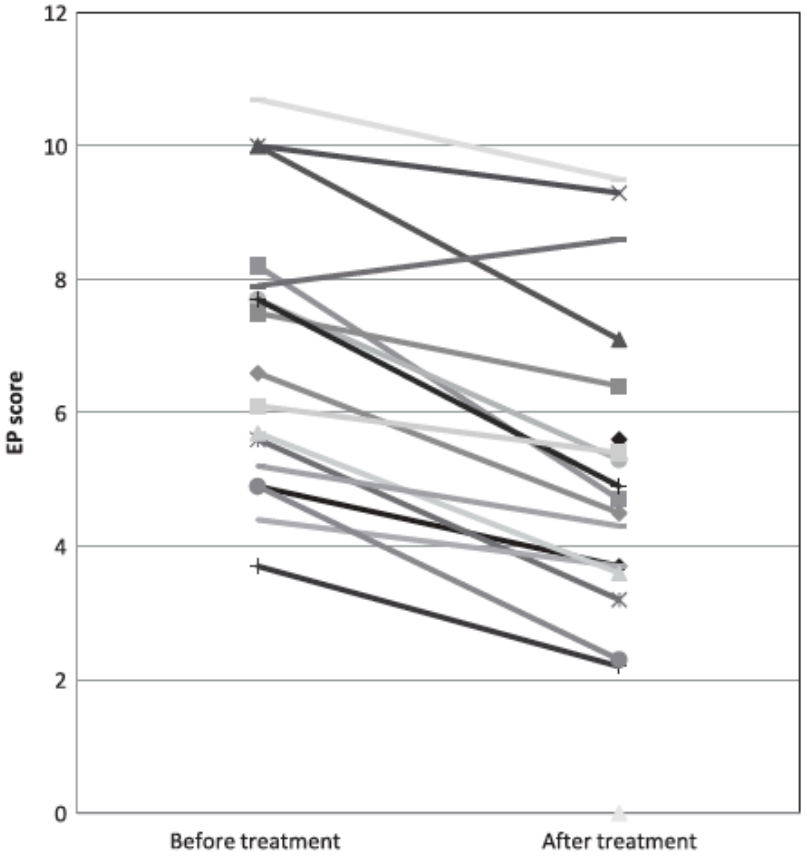


* If no dose-limiting toxcities is experienced at cycle 1, patient will be given 125mg/d at next cycle.

Patient will be given letrozole 2.5mg/d plus PD 0332991 (CDK-4/6 inhibitor) 125 mg/d for 3 out of 4 weeks in repeated cycles for 16 weeks (4 cycles) before surgery.

Changes in Volume and EP scores





Adverse Events in Pts on Palbociclib + Letrozole

Paloma-1 study: Palbociclib + Letrozole in 1st line ABC

- Finn et al. Lancet Oncol 2015; 16: 25–35

	Palbociclib plus letrozole (n=83)			Letrozole (n=77)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	19 (23%)	49 (59%)	14 (17%)	49 (64%)	16 (21%)	0
Neutropenia	17 (20%)	40 (48%)	5 (6%)	3 (4%)	1 (1%)	0
Leucopenia	20 (24%)	16 (19%)	0	2 (3%)	0	0

- Ethnicity: not reported
  - Only East-Asian 24/321 sites
- Dosing Palbociclib
  - 125 mg q3w / 28 d
- Stage: mostly stage IV BC
- Visceral Metastasis: 44%
- Bone Metastasis: 20%
- Other Metastasis: 30%
- CTx pre-treated: 40%
- Hormonal Pre-treated: 32%

OOTR-N007 Study: Palbociclib + Letrozole in Neoadjuvant Treatment of Breast Cancer

– Chow et al. AOS-OOTR-KBCCC Meeting, 2016 Poster Presentation

SIDE EFFECTS IN >20% OF PATIENTS

Adverse Events (n=20)	Neutropenia n (%)	Mucositis n (%)
Palbociclib	Grade 3/4	Grade 1
Starting Dose 125 mg	4/8 (50%)	4/8 (50%)
Starting Dose 100 mg	8/12 (75%)	3/12 (25%)
Total	**12/20 (60%)**	**7/20 (35%)**

- Ethnicity: Chinese
- Starting Dose Palbociclib:
  - Initially: 125 mg q3w / 28 d
  - Amended: 100 mg q3w / 28 d

ANTI-HER2 THERAPY (LAPATINIB)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer

Charles E. Geyer, M.D., John Forster, M.Sc., Deborah Lindquist, M.D., Stephen Chan, M.D., C. Gilles Romieu, M.D., Tadeusz Pienkowski, M.D., Ph.D., Agnieszka Jagiello-Gruszfeld, M.D., John Crown, M.D., Arlene Chan, M.D., Bella Kaufman, M.D., Dimosthenis Skarlos, M.D., Mario Campone, M.D., Neville Davidson, M.D., Mark Berger, M.D., Cristina Oliva, M.D., Stephen D. Rubin, M.D., Steven Stein, M.D., and David Cameron, M.D.

End Point	Lapatinib plus Capecitabine (N=163)	Capecitabine Alone (N=161)	Hazard Ratio (95% CI)	P Value
Median time to progression — mo	8.4	4.4	0.49 (0.34–0.71)	<0.001†
Median progression-free survival — mo	8.4	4.1	0.47 (0.33–0.67)	<0.001†
Overall response — % (95% CI)	22 (16–29)	14 (9–21)		0.09‡
Complete response — no. (%)	1 (<1)	0 (0)		
Partial response — no. (%)	35 (21)	23 (14)		
Clinical benefit — no. (%)	44 (27)	29 (18)		
Death — no. (%)	36 (22)	35 (22)		

Event	Lapatinib plus Capecitabine (N=164)				
	Grade 1	Grade 2	Grade 3	Grade 4†	Any Grade
					number of events
Diarrhea	44 (27)	33 (20)	19 (12)	2 (1)	98 (60)
Nausea	48 (29)	21 (13)	3 (2)	0	72 (44)
Vomiting	30 (18)	10 (6)	3 (2)	0	43 (26)
Stomatitis	17 (10)	7 (4)	0	0	24 (15)
Abdominal pain	13 (8)	10 (6)	2 (1)	0	25 (15)
Hand–foot syndrome	16 (10)	52 (32)	12 (7)	0	80 (49)

Breast Cancer (2015) 22:192–200
DOI 10.1007/s12282-013-0475-1

ORIGINAL ARTICLE

Efficacy, safety, pharmacokinetics and biomarker findings in patients with HER2-positive advanced or metastatic breast cancer treated with lapatinib in combination with capecitabine: results from 51 Japanese patients treated in a clinical study

Hiroji Iwata · Hirofumi Fujii · Norikazu Masuda · Hirofumi Mukai · Yuichiro Nishimura · Koichi Katsura · Catherine E. Ellis · Robert C. Gagnon · Seigo Nakamura

Chinese Journal of Cancer

Original Article

Lapatinib plus capecitabine in treating HER2-positive advanced breast cancer: efficacy, safety, and biomarker results from Chinese patients

Bing-He Xu[1], Ze-Fei Jiang[2], Daniel Chua[3], Zhi-Min Shao[4], Rong-Cheng Luo[5], Xiao-Jia Wang[6], Dong-Geng Liu[7], Winnie Yeo[8], Shi-Ying Yu[9], Beth Newstat[10], Alka Preston[10], Anne-Marie Martin[10], Hai-Dong Chi[11] and Li Wang[11]

Table 4 Summary of tumor response in the ITT population

Best response, *n* (%)	
CR	0
PR	12 (24)
SD, ≥ 24 weeks	18 (35)
SD, < 24 weeks	14 (27)
PD	6 (12)
NE	1 (2)
ORR	24 % (95 %CI 12.8, 37.5)
CBR	59 % (95 %CI 44.2, 72.4)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* overall response rate, *CBR* clinical benefit rate (CR; PR; SD ≥ 24 weeks)

Japanese Study

1) median TTP was 9 months (95 % CI 27.1, 48.0)
2) median OS was 19.7 months (95 % CI 51.6, 103.0)

Chinese Study

Table 4. Investigator-assessed response rates by RECIST criteria v1.0 and PFS for 52 patients treated with lapatinib plus capecitabine

Endpoint	No. of patients (%)
Best response rate	
CR	0 (0)
PR	23 (44.2)
SD ⩾24 weeks	7 (13.5)
PD	4 (7.7)
Unknown	2 (3.8)
CBR (CR + PR + SD ⩾24 weeks)	
% (95% CI)	57.7 (43.2–71.3)
PFS	
Median, months (95% CI)	6.34 (4.93–9.82)
6-month rate, % (95% CI)	53.4 (39.4–67.4)
Median time to response (months)	4.07
Median duration of response (months)	6.93
First site of relapse	
Any new lesion(s)	13 (25.0)
CNS disease as site of first relapse	2 (3.8)

Adverse events

Japanese study

Adverse event, *n* (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total
PPE syndrome	18 (35)	16 (31)	5 (10)	0	39 (76)
Diarrhea	26 (51)	7 (14)	1 (2)	0	34 (67)
Stomatitis	21 (41)	0	0	0	21 (41)
Rash	13 (25)	6 (12)	1 (2)	0	20 (39)
Pruritus	16 (31)	1 (2)	0	0	17 (33)
Nausea	15 (29)	2 (4)	0	0	17 (33)
Fatigue	16 (31)	1 (2)	0	0	17 (33)
Anorexia	15 (29)	1 (2)	1 (2)	0	17 (33)

Chinese study

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total
PPE	25 (48.1)	6 (11.5)	0	0	31 (59.6)
Diarrhea	20 (38.5)	4 (7.7)	0	0	25 (48.1)[a]
Rash	22 (42.3)	1 (1.9)	2 (3.8)	0	25 (48.1)
Hyperbilirubinemia	4 (7.7)	12 (23.1)	2 (3.8)	0	18 (34.6)
Fatigue	11 (21.2)	4 (7.7)	1 (1.9)	0	16 (30.8)
Nausea	9 (17.3)	1 (1.9)	0	0	10 (19.2)
Neutropenia	0	4 (7.7)	1 (1.9)	2 (3.8)	7 (13.5)

Summary

- Asians tolerate less well the Caucasian dose of docetaxel
- Asians may fare better with tamoxifen
- Asians may have a lower EVE + EXE efficacy and slightly different toxicity profiles than Caucasians
- Efficacy of lapatinib + capecitabine may have higher CBR and and toxicities than Caucasians

Thank You