Rules of management of patients with BRCA1 gene mutation

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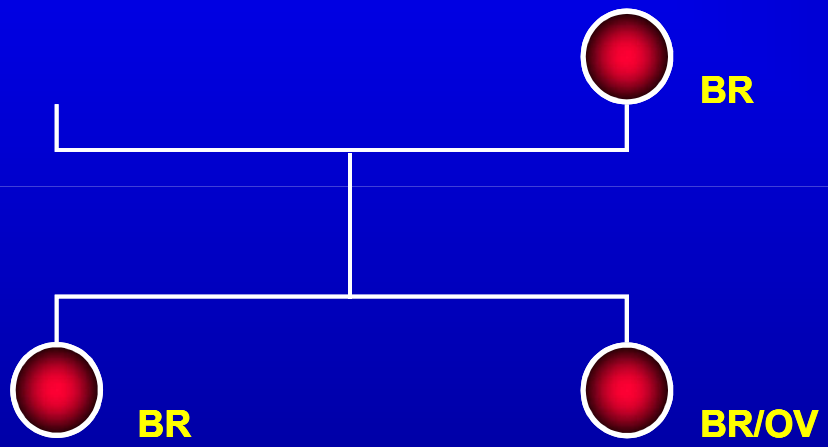
15. 03. 2019. Poznań

HEREDITARY BREAST CA



N= 200 FAMILIES

Table 2. Germ-line mutations detected in BRCA1 and BRCA2 genes in breast or/and ovarian cancer families from Poland.

Family	Mutation			Site and number of cancers in a family		
	Exon	Codon	Alteration	breast	ovarian	other sites
	BRCA1					
4506	20	1756	5382insC	3	-	-
3311	20	1756	5382insC	3	-	-
4412	20	1756	5382insC	3	-	-
1633	20	1756	5382insC	3	-	colon
4508	20	1756	5382insC	2	1	-
3319	20	1756	5382insC	2	1	-
3088	20	1756	5382insC	2	2	lymphoma
3572	20	1756	5382insC	3	-	-
4545	20	1756	5382insC	3	-	colon, stomach
1738	20	1756	5382insC	4	3	colon
1582	20	1756	5382insC	3	-	prostate
4478	20	1756	5382insC	3	-	-
1387	20	1756	5382insC	4	1	colon
2863	20	1756	5382insC	4	2	-
4968	20	1756	5382insC	-	4	stomach, cancer site unknown

5715	20	1756	5382insC	-	3	-
5726	20	1756	5382insC	1	2	-
4030	20	1756	5382insC	3	-	lung, leukemia
1581	5	61	C61G	2	2	cancer site unknown
1888	5	61	C61G	4	-	-
4859	5	61	C61G	3	-	-
3804	5	61	C61G	7	-	-
4858	5	61	C61G	4	-	-
5850	5	61	C61G	2	1	-
4854	5	61	C61G	3	-	skin
2984	11	1345	4153delA	2	1	-
4278	11	1345	4153delA	-	4	-
3080	11	1345	4153delA	2	2	colon,
5939	11	1345	4153delA	-	4	leukemia
1601	2	23	185delAG	3	-	-
703	2	23	185delAG	3	-	lung
3910	11	1234	3819del5	3	-	-
5763	11	1234	3819del5	2	2	colon, lung
5746	5	64	C64R	4	1	lung, lung colon, leukemia

Górski B. et al. AJHG, June 2000

TEST BRCA1

- 5382 insC,
- C61G,
- 4153 delA

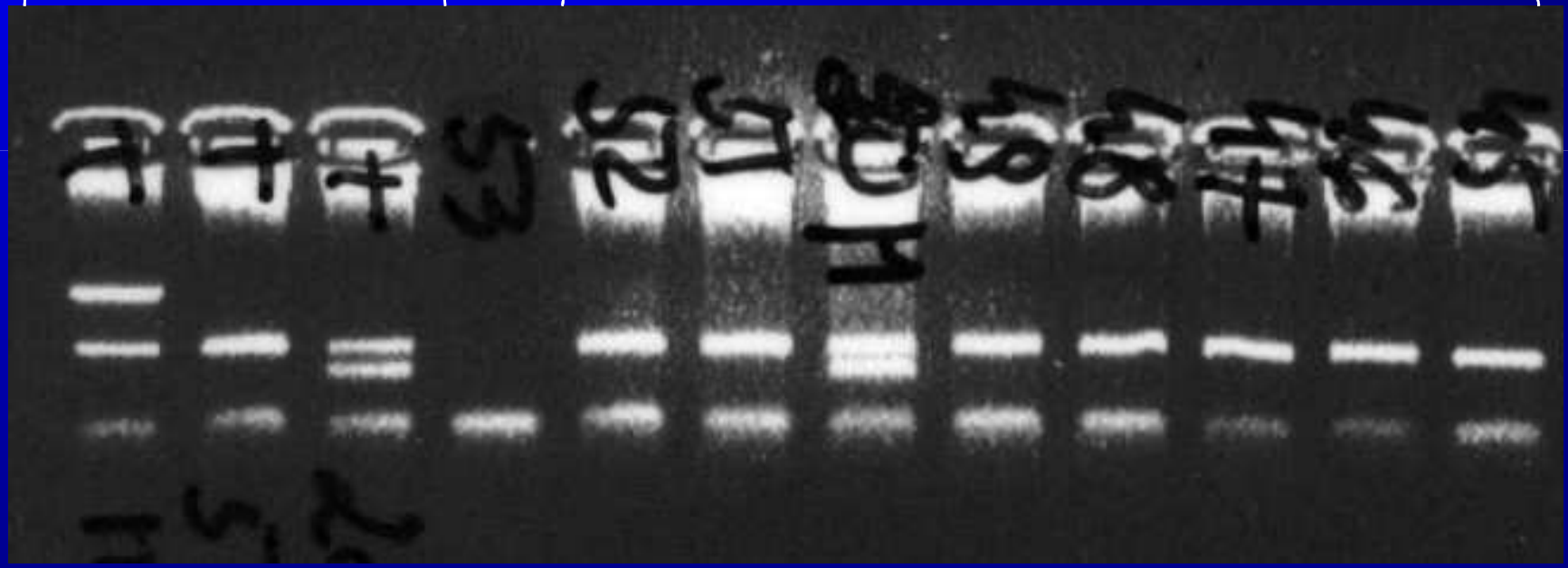
111/123

- **Sensitivity of BRCA1 test ~90%**

BRCA1 MULTIPLEX PCR

controls

patients



4153 delA

C61G

5382 insC

(-) DNA

5382 insC

BRCA1 – POSITIVE BREAST CANCERS IN YOUNG WOMEN IN POLAND

Lubiński J. et al. Br Can Res Treat 2005

BRCA1 mutations in patients with breast cancer <51yrs

- 4780 patients
- 3629 (75,9%) blood samples
- 3612 BRCA1 tests
- 199 (5,5%) mutations

Pathologic/ clinical features of cancers

Feature	Group	
	BRCA1 – (+)	BRCA1 – (-)
1. H-p		
a. medullary	30,11% (53/176)	4,15% (8/193)
b. ductal G3	18,75% (33/176)	10,36% (20/193)
c. ductale G1-G2	10,8% (19/176)	12,95% (25/193)
d. tubulo-lobular	- (0/176)	6,22% (12/193)
e. lobular	5,68% (10/176)	27,98% (54/193)
f. other	3,41% (6/176)	8,81% (17/193)
g. post CHTH	23,86% (42/176)	23,32% (45/193)
h. undefined	7,39% (13/176)	6,22% (12/193)
2. Tumour size		
a. the largest diameter	2,44cm (n=113)	1,99cm (n=118)
b. $\leq$ 1 cm	14,16% (16/113)	15,25% (18/118)

Pathologic/ clinical features of cancers

Feature	Group	
	BRCA1 – (+)	BRCA1 – (-)
3. Multicentricity	12,37% (12/97)	24,79% (30/124)
4. Bilaterality	18,13% (33/182)	2,22% (4/180)
5. LN metastases	36,09% (48/133)	48,65% (72/148)
6. Family history (probant and I or II° relatives)		
a. breast CA	55,31% (99/182)	12,22% (22/180)
b. ovarian CA	25,14% (45/182)	6,11% (11/180)
c. breast or ovarian CA	**57,14%** (104/182)	15,56%(28/180)
7. ER	15,08% (19/126)	58,33% (91/156)

About 43% no family history

POPULATION SCREENING FOR CANCER FAMILY SYNDROMES IN WEST – POMERANIA, POLAND

WEST – POMERANIA HEALTH CARE INS. COMP

FAMILY DOCTORS

IHCC POMERANIAN MEDICAL UNIVERSITY, SZCZECIN

FAMILY DOCTORS – PROJECT INITIATORS

1. Andrzej Raczyński NPZOZ „Asklepios” Bobolice
2. Jarosław Kopciewicz - SPZOZ Pyrzyce
3. Cygal Lucyna - SZOZ nr 3 Kołobrzeg
4. Krzysztof Jankowiak - NZOZ „Zdrowie” Drawsko Pomorskie
5. Wiesława Fabian - NZOZ Szczecin
6. Józef Dmochowski - ZOZ „Zdrowie” Barwice
7. Paweł Szycko - NZOZ Podimed - Szczecinek.
8. Tadeusz Cieślak - NZOZ - „Hipokrates” - Złocieniec.

Szanowny(a) Pan(i)

Onkologiczna Poradnia Genetyczna prowadzi badania mające na celu wykrycie i objęcie opieka lekarska rodzin, w których występują nowotwory. Badania genetyczne pozwalają wykryć zagrożenie nowotworowe na kilka lub kilkanaście lat przed pojawieniem się objawów klinicznych, zwiększając przez to szansę całkowitego wyleczenia.

Nazwisko i imię .....**wiek** .....

Adres (dokładny + tel., fax, e-mail) .....

Zdrowy / chory (podkreślić) PESEL ..... Kasa Chorych .....

Rozpoznanie kliniczne .....

Pana(i) krewni	Chorował na nowotwór (guz, rak) wpisać **TAK, NIE** lub **NIE WIEM**	Lokalizacja nowotworu (zajęty narząd)	Wiek w jakim zachorował	Jeśli zmarł to w jakim wieku
Bracia				
Siostry				
Synowie				
Córki				
Wnuczki i wnuki				
Ojciec				
Bracia ojca				
Siostry ojca				
Dziadek ze str. ojca				
Babcia ze str. ojca				
Matka				
Bracia matki				
Siostry matki				
Dziadek ze str. matki				
Babcia ze str. matki				

Wyniki będą Państwu przekazane przez wskazaną przez nas Onkologiczną Poradnię Genetyczną lub - w wyjątkowych przypadkach - przesłane pocztą.

Z wyrazami szacunku - Prof. dr hab. n. med. Jan Lubiński

Adres zwrotny:

Międzynarodowe Centrum Nowotworów Dziedzicznych

ul. Połabska 4, 70 – 115 Szczecin, tel./fax: +91 466 1542 , e-mail: ihcc@wp.pl

Wyrażam świadomą zgodę na wykonanie badań genetycznych w tym testu DNA

.....

Podpis Ankietowanego

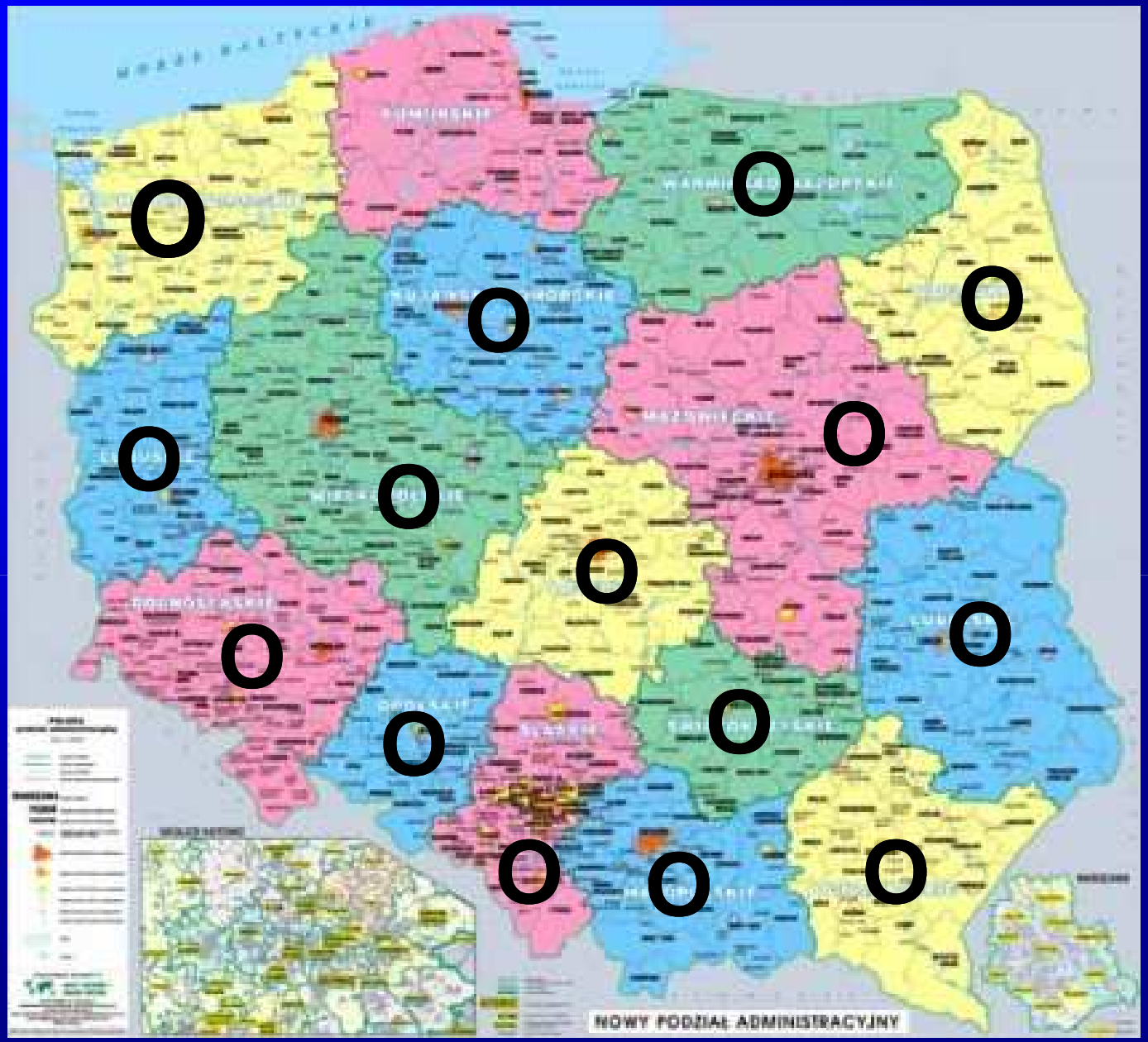
JANUARY 2001 – MAY 2002

- **1,258 mln questionaires out of 1,7 mln of inhabitants**
- the first worldwide large screening for hereditary cancers

Hereditary Cancer Sevicies in IHCC - Szczecin

Jacek Gronwald

International Hereditary Cancer Center,
Pomeranian Medical University,
Szczecin, Poland



O - Regions supervised by IHCC-Szczecin

BRCA1 – REGISTRY – SZCZECIN – POLAND

>7500 CARRIERS

THE LARGEST REGISTRY IN THE WORLD

Szczecin, September .2018

Indications for BRCA1 testing

- All patients with affected breast or ovarian cancer
- All adult females with at least one I^{o} or II^{o} relative affected by breast cancer or ovarian cancer dgn at any age

The MassARRAY system or Taq Man – for patients with pedigree / clinical symptoms of HBC

BRCA1	BRCA2
185delAG	488delCT
234T/C	886delGT
300T/G/A	1617delAG
794delT	3036del4
962del41806C/T	4075delGT
2985del5	5873C/A
3819-3875	6174delT
4153delA	6677delAA
5149del4	8138del5
5370-5382	8765delAG
	9068delA
	9325insA
	9630delC

Indications for BRCA1/2 NGS testing

- All patients diagnosed with breast or ovarian cancer with at least one I° or II° relative affected with breast or ovarian cancer one of breast cancers diagnosed <50

CANCER RISKS IN FIRST-DEGREE RELATIVES OF BRCA1 MUTATION CARRIERS: EFFECTS OF MUTATION AND PROBAND DISEASE STATUS

THE RISK OF BREAST CANCER IN WOMEN WITH BRCA1 MUTATION FROM NORTH AMERICA AND POLAND

J. Gronwald, JMG 2005

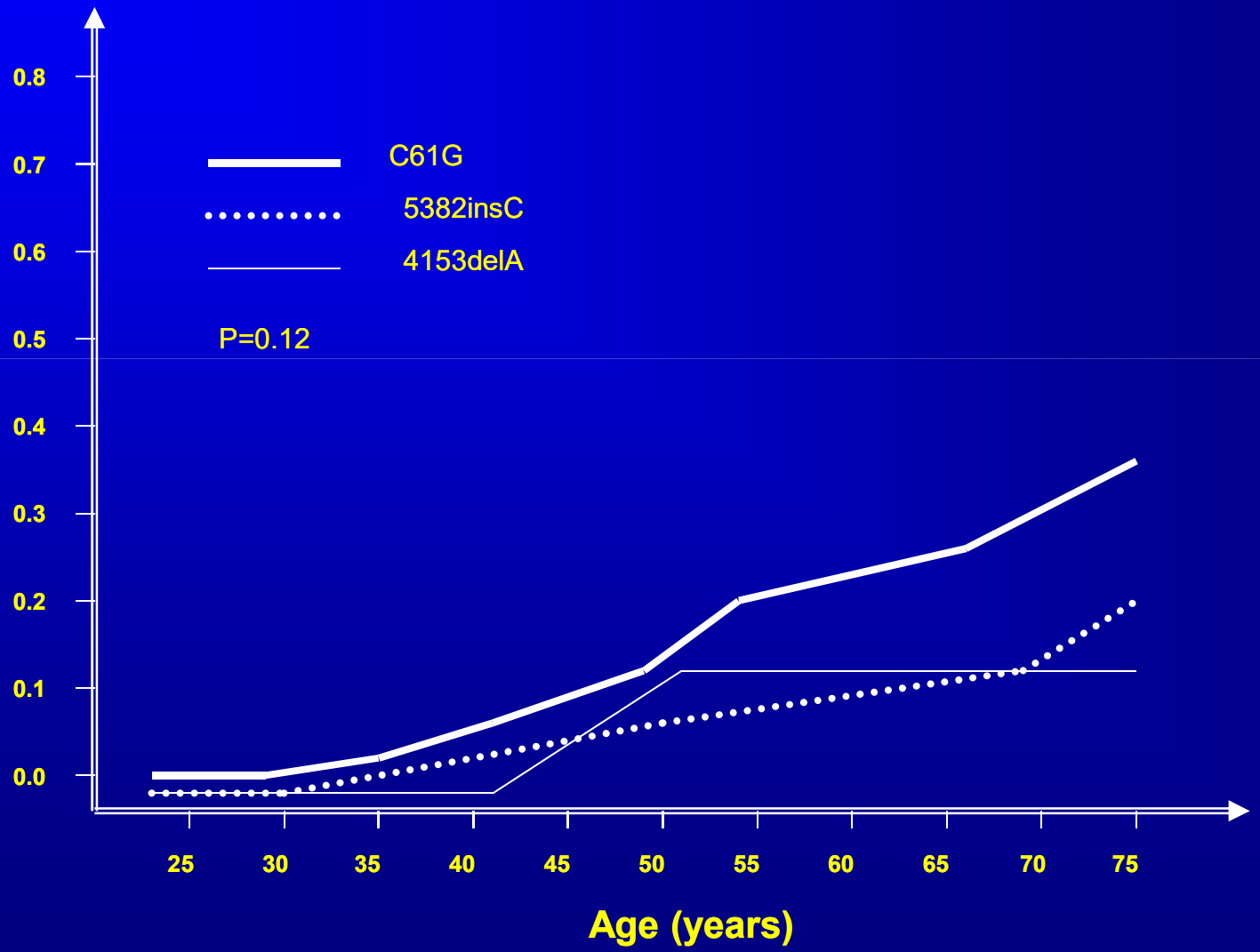
J. Lubiński, Int J Cancer 2012

MUTATION CARRIER PENETRANCE

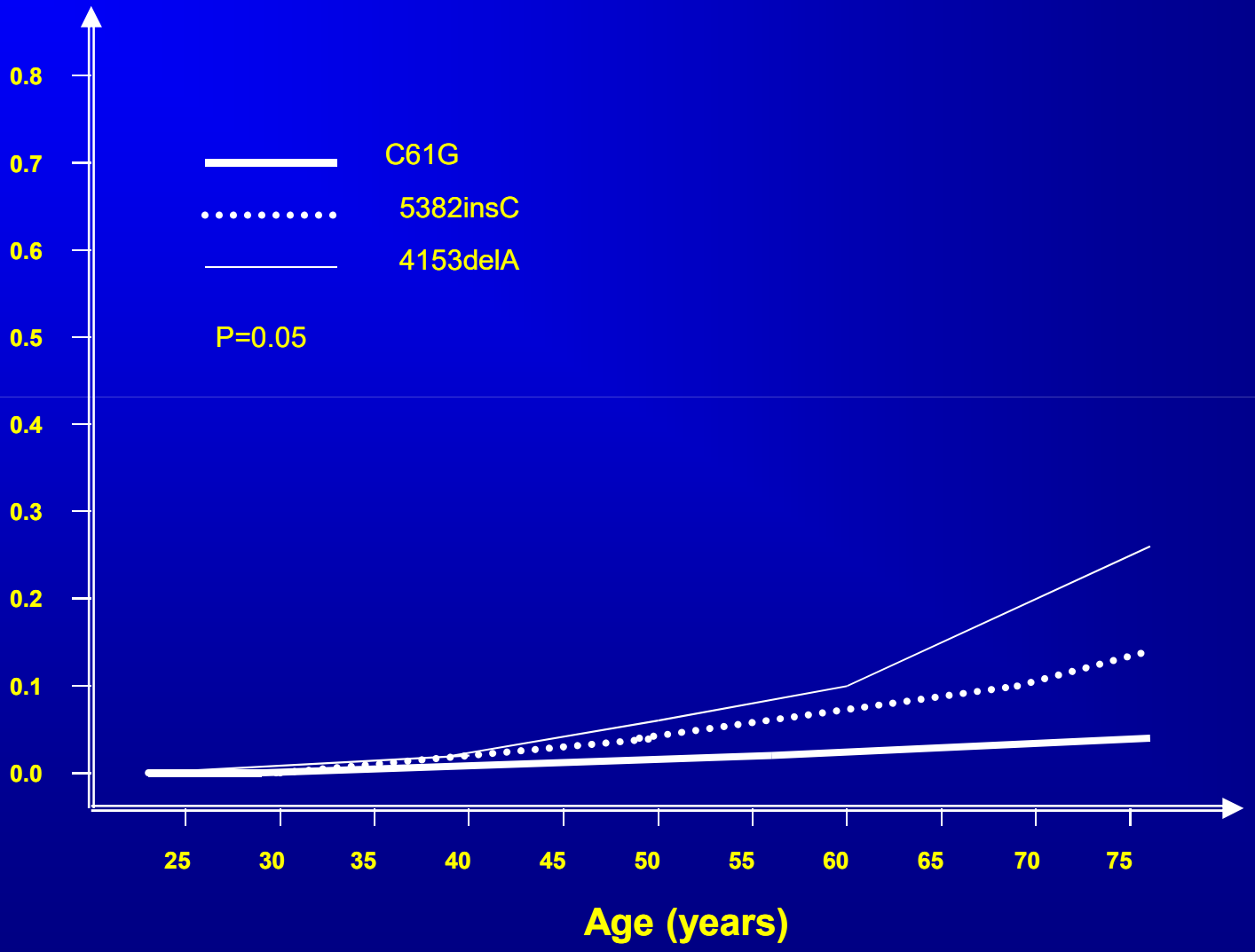
- BRCA1

  - ✓ BREAST CANCER - 60%
  - ✓ OVARIAN CANCER - 30%

Cumulative incidence of breast cancer in first-degree relatives by mutation



Cumulative incidence of ovarian cancer in first-degree relatives by mutation



Surveillance

Organ	Examination	Beginning (yrs)	Interval (months)
Breast	Self-examination	20	1
	Clinician examination	25	6
	MRI	25	12
	Mammography (2 views, 2 readers)	30	12
	USG	25	12 (6 months after X-rays)
Female genital tract	Intravaginal USG (colour Doppler)	25	12
	CA 125	25	12 (6 months after X-rays)

Sensitivity of early breast cancer detection in HBC incl. BRCA1/BRCA2 carriers

USG	MAMMOGR.	MRI
~37.5%	~37.5%	~90%

Riedl CC et al. JCO 2015

DETECTION OF EARLY BREAST CANCERS IN BRCA1 MUTATION CARRIERS

AGE >25

22 cancers detected, 1 interval cancer

CBE	USG	MAM.	MRI
~9	~33%	~36%	~77%

Sensitivity: **4 methods - 95%**
MAM. + CBE - 45%

Warner E. et al. JAMA 2004

BRCA1 MUTATION CARRIERS

INTRAVAGINAL USG

CA125

EARLY CANCERS

ONLY ~10 % CASES

BRCA1 – ADNEXECTOMY

REBBECK T. ET AL. NEJM, 2002

RETROSPECTIVE STUDIES

N=259 CASES AND 292 CONTROLS

- Lenght of follow up - >8 yrs

	BR	OV
cases	21.2%	0.8%
controls	42.3%	19.9%

BRCA1 – ADNEXECTOMY

TORONTO REGISTRY –RETROSPECTIVE ANALYSIS

- Breast cancer risk reduction
  OR – 0.31; p<0.0000006

- Age of adnexectomy — OR

< 40	0.28
40-50	0.34
>50	0.48

JNCI J Natl Cancer Inst (2017) 109(1): djw177

doi: 10.1093/jnci/djw177
First published online September 6, 2016
Article

ARTICLE

Bilateral Oophorectomy and Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers

Joanne Kotsopoulos, Tomasz Huzarski, Jacek Gronwald, Christian F. Singer, Pal Moller, Henry T. Lynch, Susan Armel, Beth Karlan, William D. Foulkes, Susan L. Neuhausen, Leigha Senter, Nadine Tung, Jeffrey N. Weitzel, Andrea Eisen, Kelly Metcalfe, Charis Eng, Tuya Pal, Gareth Evans, Ping Sun, Jan Lubinski, Steven A. Narod, and the Hereditary Breast Cancer Clinical Study Group

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ARTICLE

Abstract

Background: Whether oophorectomy reduces breast cancer risk among *BRCA* mutation carriers is a matter of debate. We undertook a prospective analysis of bilateral oophorectomy and breast cancer risk in *BRCA* mutation carriers.

Methods: Subjects had no history of cancer, had both breasts intact, and had information on oophorectomy status (n = 3722). Women were followed until breast cancer diagnosis, prophylactic bilateral mastectomy, or death. A Cox regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer associated with oophorectomy (coded as a time-dependent variable). All statistical tests were two-sided.

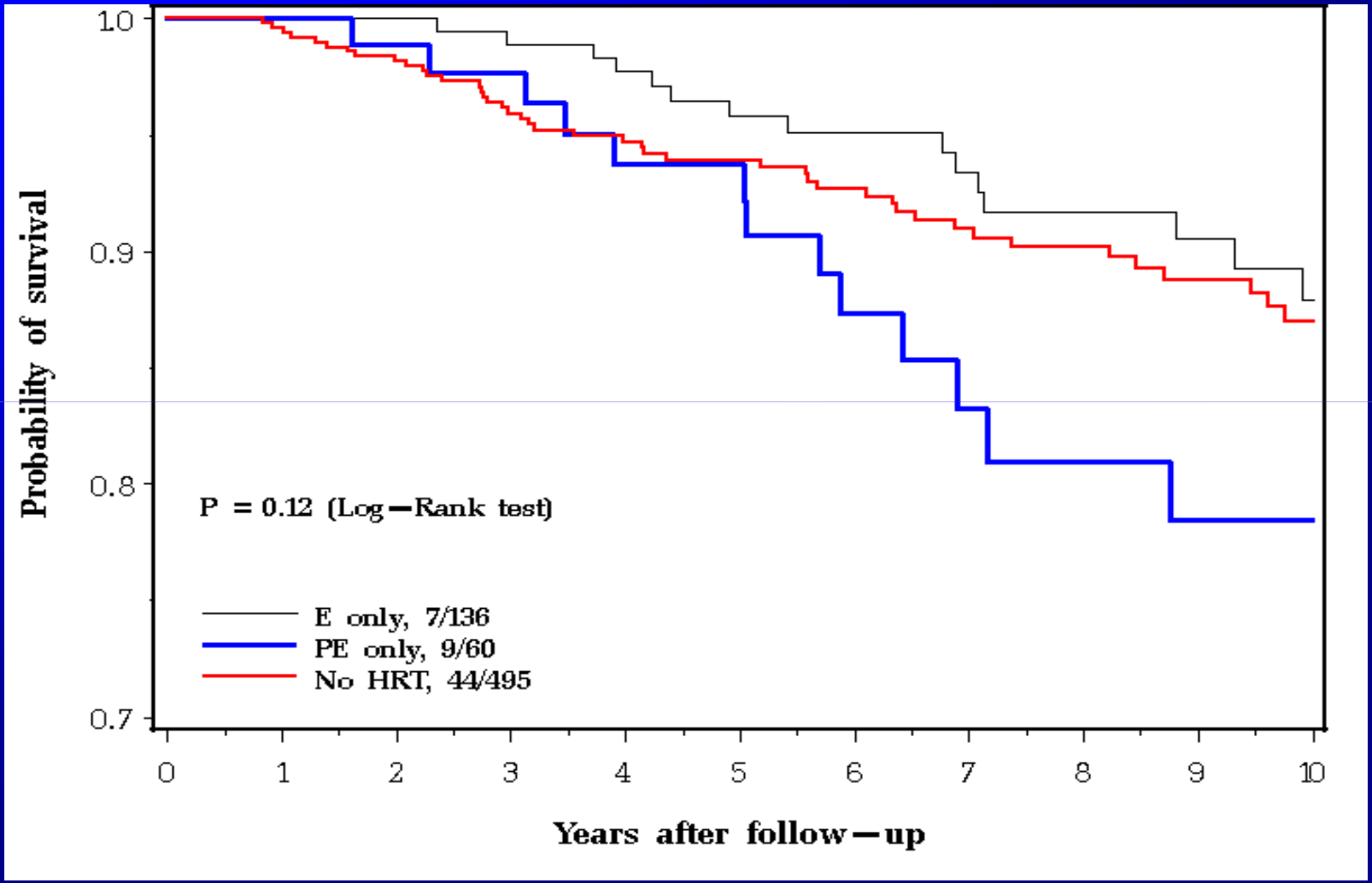
Results: Over a mean follow-up of 5.6 years, 350 new breast cancers were diagnosed. Among women with a *BRCA1* or *BRCA2* mutation, oophorectomy was not associated with breast cancer risk compared with women who did not undergo an oophorectomy. The age-adjusted hazard ratio associated with oophorectomy was 0.96 (95% CI = 0.73 to 1.26, P = .76) for *BRCA1* and was 0.65 (95% CI = 0.37 to 1.16, P = .14) for *BRCA2* mutation carriers. In stratified analyses, the effect of oophorectomy was statistically significant for breast cancer in *BRCA2* mutation carriers diagnosed prior to age 50 years (age-adjusted HR = 0.18, 95% CI = 0.05 to 0.63, P = .007). Oophorectomy was not associated with risk of breast cancer prior to age 50 years among *BRCA1* mutation carriers (age-adjusted HR = 0.79, 95% CI = 0.55 to 1.13, P = .51).

Conclusions: Findings from this large prospective study support a role of oophorectomy for the prevention of premenopausal breast cancer in *BRCA2*, but not *BRCA1* mutation carriers. These findings warrant further evaluation.

Received: January 27, 2016; **Revised:** March 23, 2016; **Accepted:** June 17, 2016

Does HRT after Oophorectomy increase breast cancer risk?

Risk of breast cancer in subjects after oophorectomy by use of HRT



What is the preferable?

MRI Screening

or

Mastectomy

MRI vs Preventive Mastectomy International Cohort Study

	N	New BC	Death by BC	%
MRI	2828	322	15	0.53
No MRI	1850	131	21	1.14
HR = 0.39 (0.17 – 0.90)	p = 0.03		0.31 (0.13 – 0.75)	0.01
Mastectomy	749	3	2	0.4
No Mastectomy	2806	368	29	1.0
HR = 0.26 (0.06 – 1.08)	p = 0.06		0.30 (0.07 – 1.26)	0.10

Mastectomy!

1841 of 2806 (65.6%) women in no mastectomy group had an MRI

BRCA1 – Breast feeding

RISK
BREAST

- **Breast feeding – 1 year: ↓ 0.5**

Jarenstrom H., Lubiński J., Lynch HT. et al. JNCI 2004

BRCA1 – Oral Contraceptives

BREAST CANCER RISK -1311 CASES AND CONTROLS

	OR	p
☞ Ever	1.2	0.15
☞ Use duration		
0-5 y.	1.1	0.47
5-10 y.	1.38	0.03
☞ Age when started		
15-20 y.	1.38	0.04
20-25 y.	1.37	0.04
30-60 y.	0.62	0.06

Narod S., Dube M-R, Klijn J., Lubiński J. et al. JNCI 2002
Kotsopoulos J, Lubiński J, Moller P. et al. Br Cancer Res Treat 2014

BRCA1 – Caffee

			RISK BREAST
Coffee	>	4-5 caps	↓0.5

Nkondjock A et al 2004

BRCA1 – Chest X-ray . (age<30)

N=142 Cases AND 159 Controls

- Breast cancer risk

OR – 1.66; p<0.03

Gronwald J. et al. Breast Cancer Res Treat 2008

Association between Tamoxifen and the risk of contralateral breast cancer

	Univariate analysis Odds ratio [95%CI) p-value	Multivariate analysis Odds ratio [95%CI) p-value
All subjects Tamoxifen any use, Never Ever	 1,00 0,45 [0,29-070] 0,0004	 1,00 0,47 [0,30-0,74] 0,001
BRCA1 carriers Tamoxifen any use, Never Ever	 1,00 0,48 [0,29-079] 0,004	 1,00 0,50 [0,30-0,85] 0,01
BRCA2 carriers Tamoxifen any use, Never Ever	 1,00 0,39 [0,16-0,94] 0,03	 1,00 0,42 [0,17-1,02] 0,05

Gronwald J. et al. Int J Can 2005

A. BRCA1/2 PROPHYLACTICS

		RISK	
		BR	OV
☞ Oral contraceptives	< 30yrs	↑1.3	
	≥ 30yrs		↓0.5
☞ Breast feeding	> 1 yrs	↓0.5	
☞ Later menarche	per yr	↓0.9	
☞ Tubal ligation			↓0.5
☞ Adnexectomy		↓0.5	↓0.05
☞ Tamoxifen		↓0.5	
☞ Mastectomy		↓0.01	

Narod S. et al. 2002 and 2002, Eisen et al.. 2005, Gronwald J. et al. 2005, McLaughlin

Results of prophylactics - OVARY

Number of women >45 r.ż	2001	2010
✓ Poland	7 946 170	8 657 419
✓ Westpomerania	347 255	385 497

No of ovarian cancers diagnosed / year	1999-2001	2008-2010	2011-2013
✓ Poland	3167	3262	3570
✓ Westpomerania	157	124	128

% of BRCA1 carriers with ovarian cancer Westpomerania	12.5%	6.7%	6.9%

Results of prophylactics - BREAST

BRCA1 carrirs

	found program	included into prophylactic program at the moment of breast cancer diagnosis	BRCA1 mutation prophylactic
N		23	17
Tumor diameter		1,7 cm ± 0,69	3,4 cm ± 1,72
Lymph nodes		13,04% (3/23)	58,8% (10/17)
Age of onset		46,5	43,4

Treatment

Ten-Year Survival in BRCA1 Positive Breast Cancer Patients

T. Huzarski et al. JCO 2012

HRs for Selected Variables for BRCA1-Positive Patients (n=233)

Variable	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Oophorectomy*						
No	1			1		
Yes	0.31	0.13 to 0.77	.01	0.30	0.12 to 0.75	.01
Chemotherapy						
No	1			1		
Yes	0.79	0.28 to 2.23	.66	0.42	0.12 to 1.50	.18

Cisplatin In Breast Cancer Treatment In BRCA1-Carriers

Tomasz Byrski, Jan Lubiński, Steven Narod, Jacek Gronwald

INTERNATIONAL HEREDITARY CANCER CENTER
POMERANIAN MEDICAL UNIVERSITY, SZCZECIN, POLAND
Szczecin, 14.10.2013

Breast cancers with BRCA1 Treatment – Neoadjuvant therapy

Type of chemotherapy	No of patients	Complete Response	Partial Response	No Response
BRCA1 – 44				
AT	15	0	**6**	**9**
Other types	29	**4**	**25**	0
Total	44	4	31	9
Non-BRCA1 – 41				
AT	12	0	12	0
Other types	29	2	25	2
Total	41	2	37	2

Byrski T et al.: Breast Cancer Res Treat 2007

PRECLINICAL STUDIES

- BRCA1 breast cancer cell lines
  - resistance to taxanes
  - sensitivity to cis-platinum

Breast Cancer Res Treat
DOI 10.1007/s10549-008-0128-9

CLINICAL TRIAL

Response to neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients

T. Byrski · T. Huzarski · R. Dent · J. Gronwald · D. Zuziak · C. Cybulski · J. Kladny · B. Gorski · J. Lubinski · S. A. Narod

Received: 20 June 2008 / Accepted: 20 June 2008

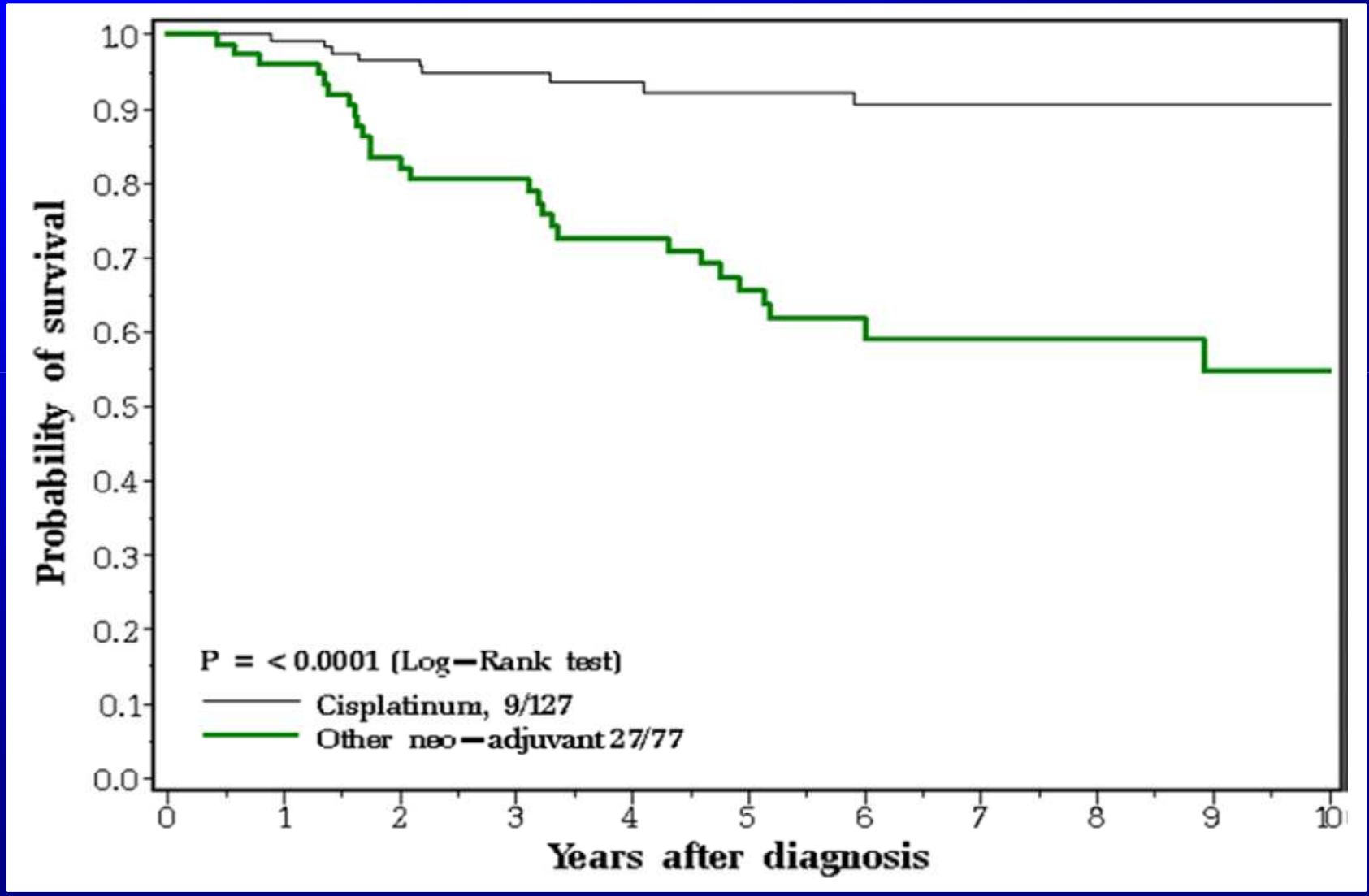
PILOT STUDY

Responses	N (%) (N=10)
Complete Clinical Response	9 (90)
Partial Clinical Response	1 (10)
Stable Clinical Disease	0
Progressive Clinical Disease	0
Pathologic Complete Response	9 (90)

Results

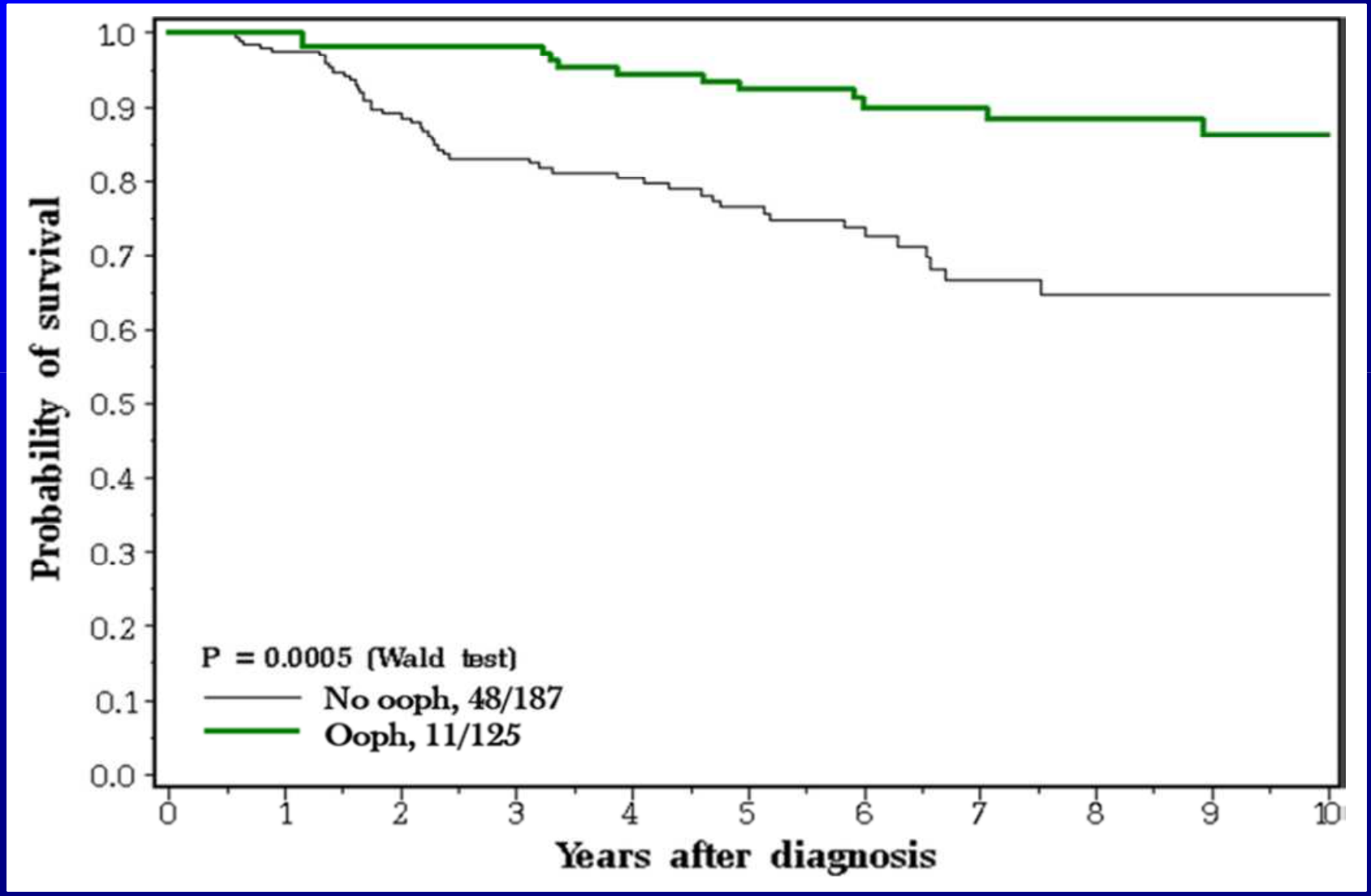
Effects	Groups	
	Cisplatinum	Controls
Pathological complete remission	48% (11/23)	10% (3/29)
Partial remission	52% (12/23)	69% (20/29)
No response	0% (0/23)	21% (6/29)

Breast cancer survival among BRCA1 carriers; Neoadjuvant cisplatinum chemotherapy versus other neoadjuvant chemotherapy



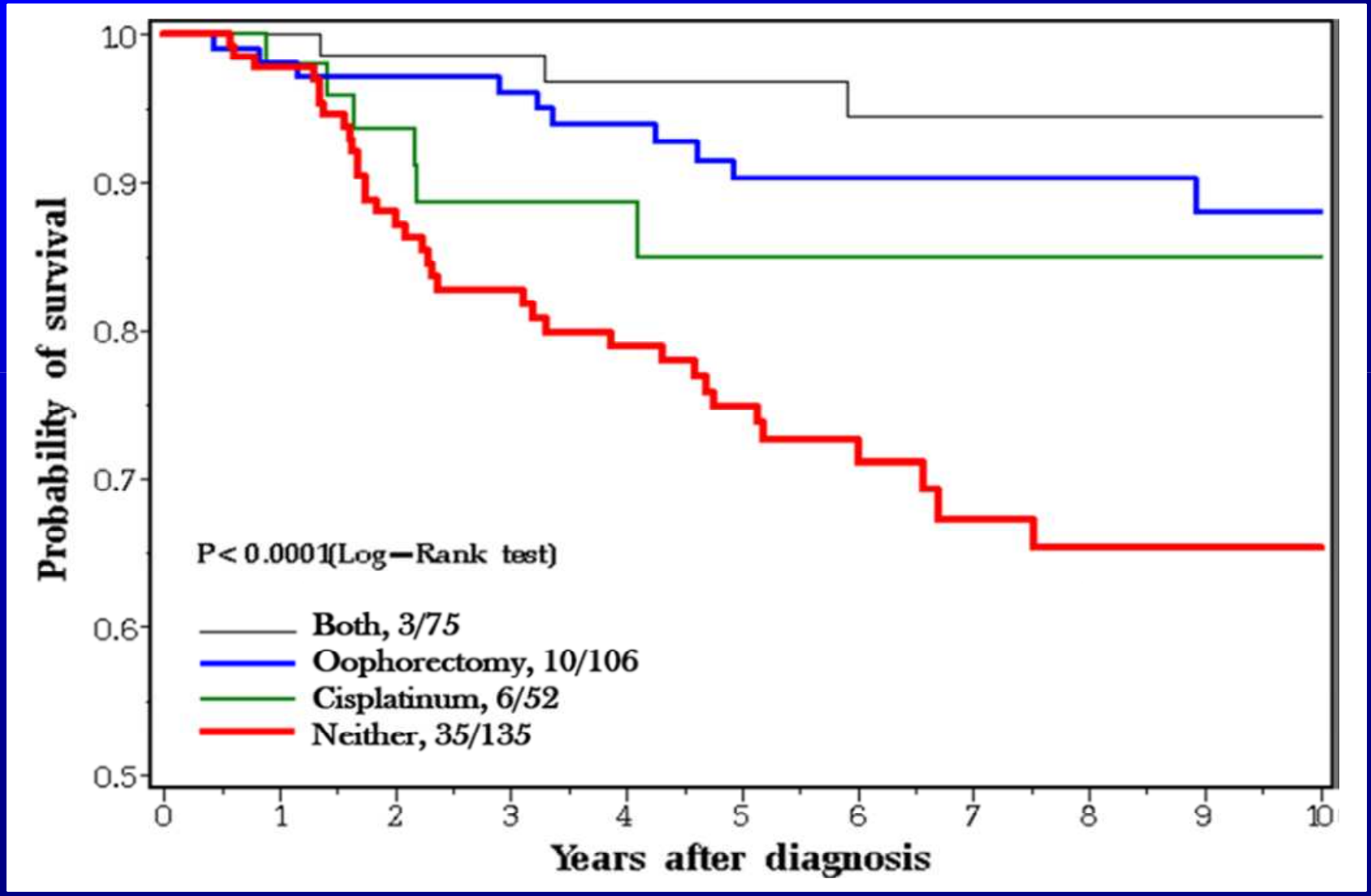
Narod SA, Huzarski T, Gronwald J, Breast Cancer Research and Treatment, 2017

Breast cancer survival among BRCA1 carriers; Oophorectomy versus no oophorectomy.
Adjusted by age at diagnoses, left censored at oophorectomy



Narod SA, Huzarski T, Gronwald J, Breast Cancer Research and Treatment, 2017

Breast cancer survival among BRCA1 carriers; Cisplatinum/ oophorectomy



Narod SA, Huzarski T, Gronwald J, Breast Cancer Research and Treatment, 2017

DZIENNIK URZĘDOWY
MINISTRA ZDROWIA

Warszawa, dnia 3 lipca 2018 r.

Poz. 53

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Marcin Ciężki
Data: 03.07.2018 11:08:08

OBWIESZCZENIE
MINISTRA ZDROWIA[1)]

z dnia 2 lipca 2018 r.

w sprawie zaleceń postępowania dotyczących diagnostyki i leczenia raka piersi

Na podstawie art. 11 ust. 3 ustawy z dnia 27 sierpnia 2004 r. o świadczeniach opieki zdrowotnej finansowanych ze środków publicznych (Dz. U. z 2017 r. poz. 1938, z późn. zm.[2)]) ogłasza się zalecenia postępowania dotyczące diagnostyki i leczenia raka piersi, stanowiące załącznik do obwieszczenia.

MINISTER ZDROWIA
Łukasz Szumowski

Chemioterapia (CHT)

Okołooperacyjną CHT należy stosować przez 3–6 miesięcy (4-8 cykli) (I, A).

U większości chorych w przedoperacyjnej i pooperacyjnej CHT zaleca się sekwencyjne stosowanie wielolekowych schematów opartych na antracyklinach i taksoidach (I, A).

U chorych z grup niższego ryzyka (ER+, N0) wystarczające może być podanie 4 cykli CHT (AC lub EC) (I, B).

Alternatywą dla schematu 4xAC/EC jest schemat zawierający taksoid bez antracyklin (np. 4xTC) (II, B).

Nie zaleca się jednoczasowego stosowania antracyklin i taksoidów (np. AT, TAC) (III, B).

Po podaniu 4 cykli AC, paklitaksel należy stosować w dawce 80 mg/m2 co tydzień (12 razy), a docetaksel w dawce 100 mg/m2 co 3 tygodnie (4 razy) (I, A).

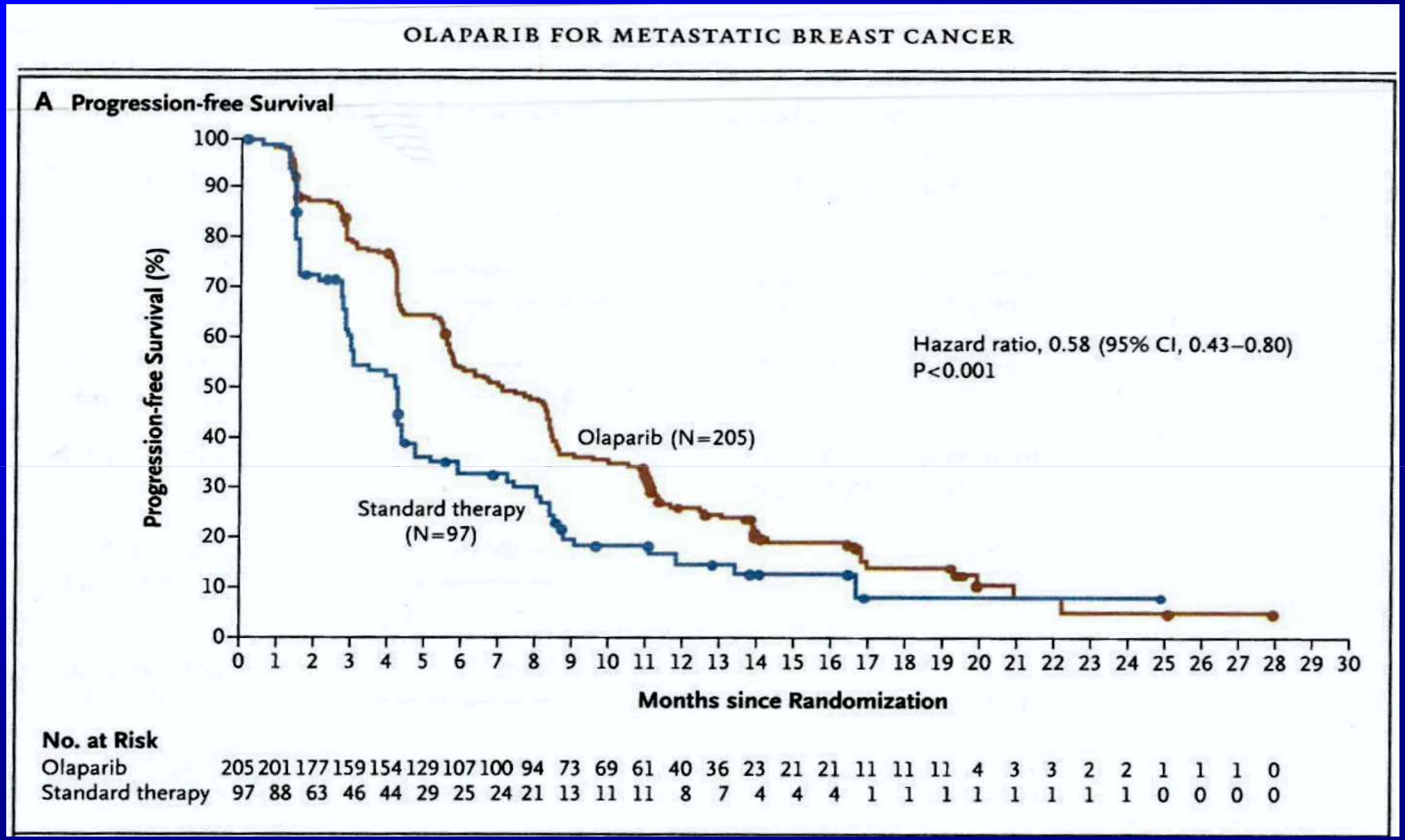
W okołooperacyjnym leczeniu nieuzasadnione jest stosowanie schematów zawierających fluorouracyl (np. FAC czy FEC) (II, B).

U chorych ER- z cechą N+, zwłaszcza w młodym wieku, można rozważyć zastosowanie schematów typu dose-dense" (I, B).

U nosicielek mutacji BRCA1/2 należy rozważyć zastosowanie przedoperacyjnej CHT z udziałem pochodnych platyny (I, B).

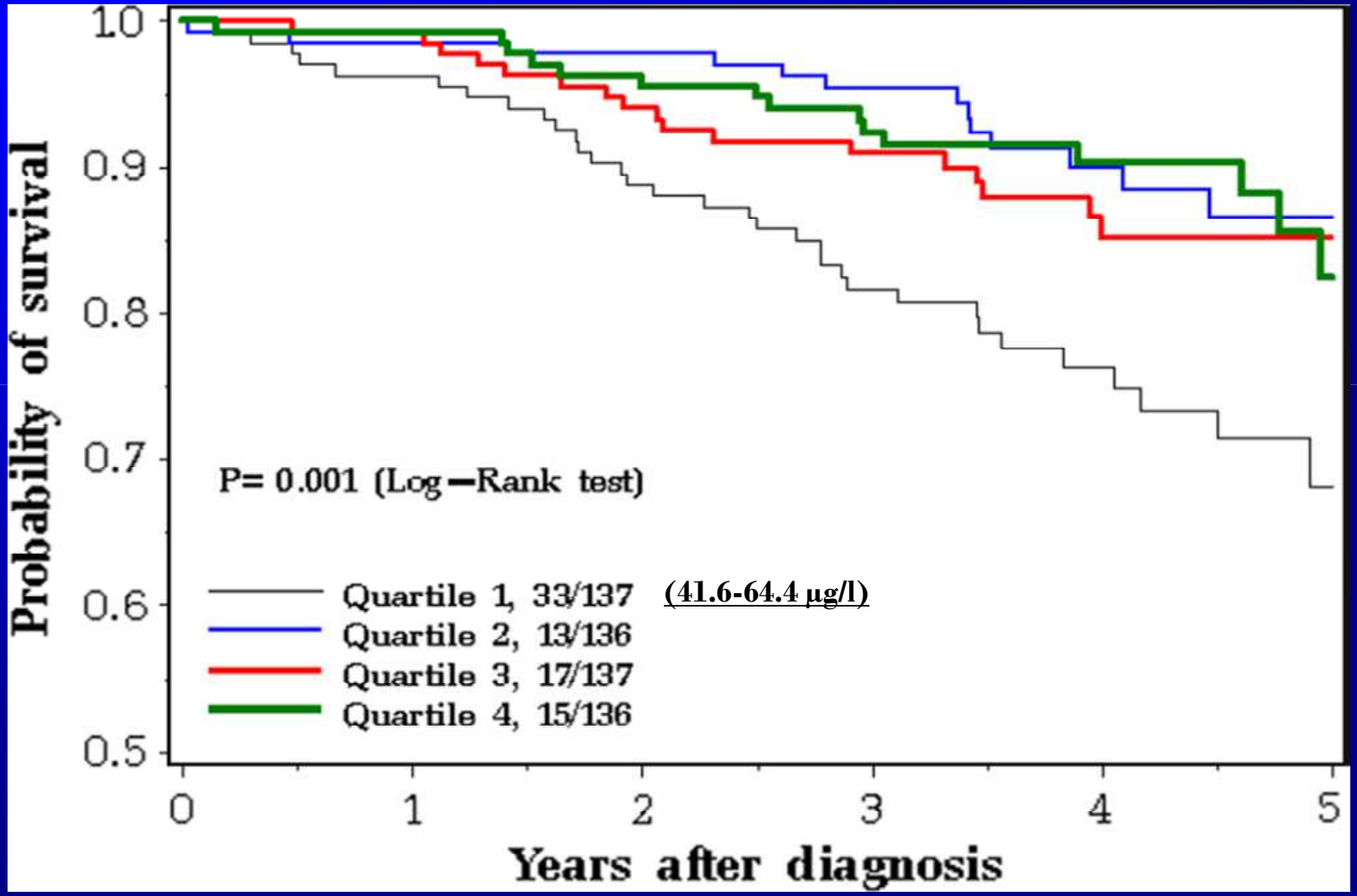
W pooperacyjnym leczeniu nosicielek mutacji BRCA1/2 nie zaleca się rutynowego stosowania pochodnych platyny, natomiast chore te, oprócz antracyklin i taksoidów, powinny otrzymać cyklofosfamid w ramach schematów 4xAC/EC 12xPXL/4xDXL (II, C).

Zaplanowaną przedoperacyjną CHT, niezależnie od stopnia regresji guza, należy podać w całości przed zabiegiem, tj. nie należy jej dzielić na okres przed i po zabiegu (III, B).



Robson M. et al. N Engl J Med. 2017, 377, 523-33

Five-year all-cause mortality by quartile of serum selenium levels, all women (n=546)



Lubiński J. et al. Br Can Res Treat Sept 2017, DOI 10.1007/s10549-017-4525-9

Conclusion

- Cisplatinum is extremely effective in preoperative treatment of breast cancers in BRCA1 mutation carriers
- Further improvements can be expected by adding PARP inhibitors
- Platins + PARP inhibitors probably will be efficient also for breast cancer with BRCAness

✓ **Mutations in BRCA1/2 genes are responsible for about 50% of HBC families**

ADDITIONAL GENES !!!

Am. J. Hum. Genet. 75:1131–1135, 2004

Report

CHEK2 Is a Multiorgan Cancer Susceptibility Gene

C. Cybulski,[1] B. Górski,[1] T. Huzarski,[1] B. Masojć,[1] M. Mierzejewski,[1] T. Dębniak,[1] U. Teodorczyk,[1] T. Byrski,[1] J. Gronwald,[1] J. Matyjasik[1] E. Złowocka,[1] M. Lenner,[2] E. Grabowska,[2] K. Nej,[2] J. Castaneda,[1] K. Mędrek,[1] A. Szymańska,[1] J. Szymańska,[1] G. Kurzawski,[1] J. Suchy,[1] O. Oszurek,[1] A. Witek,[3] S. A. Narod,[4] and J. Lubiński[1]

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A single founder allele of the *CHEK2* gene has been associated with predisposition to breast and prostate cancer in North America and Europe. The CHEK2 protein participates in the DNA damage response in many cell types and is therefore a good candidate for a multisite cancer susceptibility gene. Three founder alleles are present in Poland. Two of these result in a truncated CHEK2 protein, and the other is a missense substitution of an isoleucine

Table 1

Association between CHEK2 Variants and Selected Types of Cancer

Subject Group and Type of Cancer	No. of Subjects Tested	No. of Subjects with Mutation (Frequency in %)				Odds Ratio				*P*			
		IVS2+1G→A	1100delC	Any Truncating Mutation	I157T	IVS2+1G→A	1100delC	Any Truncating Mutation	I157T	IVS2+1G→A	1100delC	Any Truncating Mutation	I157T
Cases:													
Bladder	172	1 (.6)	0	1 (.6)	12 (7.0)	1.2	0	.8	1.5	.7	0	.8	.3
Breast	1,017	11 (1.1)	5 (.5)	16 (1.6)	68 (6.7)	2.3	2.0	2.2	1.4	.04	.3	.02	.02
Colon	300	1 (.3)	2 (.7)	3 (1)	28 (9.3)	.7	2.7	1.4	2.0	.9	.4	.8	.001
Kidney	264	0	2 (.8)	2 (.8)	26 (9.8)	0	2.7	1.0	2.1	0	.5	.8	.0006
Larynx	245	0	0	0	10 (4.1)	0	0	0	.8	0	0	0	.7
Lung	272	0	0	0	7 (2.6)	0	0	0	.5	0	0	0	.1
Melanoma	129	2 (1.5)	1 (.8)	3 (2.3)	6 (4.6)	3.3	3.1	3.2	1.0	.3	.8	.1	.9
Non-Hodgkin lymphoma	120	1 (.8)	0	1 (.8)	11 (9.2)	1.8	0	1.1	2.0	.9	0	.7	.05
Ovary	292	0	0	0	14 (4.8)	0	0	0	1.0	0	0	0	.9
Pancreas	93	0	0	0	6 (6.4)	0	0	0	1.4	0	0	0	.6
Prostate	690	8 (1.2)	3 (.4)	11 (1.6)	54 (7.8)	2.5	1.7	2.2	1.7	.05	.2	.04	.002
Stomach	241	4 (1.7)	0	4 (2.1)	13 (5.4)	3.5	0	2.3	1.1	.05	0	.2	.8
Thyroid	173	5 (2.9)	1 (.6)	6 (3.5)	15 (8.7)	6.2	2.3	4.9	1.9	.0003	.9	.0006	.04
Controls	4,000	19 (.48)	10 (.25)	29 (.73)	193 (4.8)	...	...	...	...	...	...	...	...

Published Ahead of Print on August 29, 2011 as 10.1200/JCO.2010.34.0778
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2010.34.0778

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Risk of Breast Cancer in Women With a *CHEK2* Mutation With and Without a Family History of Breast Cancer

Cezary Cybulski, Dominika Wokołorczyk, Anna Jakubowska, Tomasz Huzarski, Tomasz Byrski, Jacek Gronwald, Bartłomiej Masojć, Tadeusz Dębniak, Bohdan Górski, Paweł Blecharz, Steven A. Narod, and Jan Lubiński

See accompanying article doi:10.1200/JCO.2011.37.1476

Table 2. ORs Associated With a Truncating *CHEK2* Mutation by Family History

Group	Total No.	IVS2+1G>A		1100delC		del5395		Truncating Mutation*		OR	
		No.	%	No.	%	No.	%	No.	%	Point Estimate	95% CI
All patients with breast cancer	7,496	93	1.2	49	0.6	86	1.1	227†	3.0	3.6	2.6 to 5.1
Age ≤ 50 years at diagnosis	5,152	58	1.1	35	0.7	60	1.2	152†	2.9	3.5	2.5 to 5.1
Age > 50 years at diagnosis	2,344	35	1.5	14	0.6	26	1.1	75	3.2	3.8	2.6 to 5.7
History of breast cancer in first- and/or second-degree relative											
Negative	6,045	73	1.2	32	0.5	62	1.0	167	2.8	3.3	2.3 to 4.7
Positive	1,451	20	1.4	17	1.2	24	1.6	60†	4.1	5.0	3.3 to 7.6
First-degree relative with breast cancer	746	14	1.9	9	1.2	12	1.6	35	4.7	5.7	3.6 to 9.2
Mother affected	400	8	2	4	1	8	2	20	5	6.1	3.5 to 10.7
Sister affected	334	6	1.8	5	1.5	5	1.5	16	4.8	5.9	3.2 to 10.6
Mother and sister affected	23	0	0	0	0	1	4.3	1	4.3	5.3	0.7 to 40.3
Second-degree relative with breast cancer	823	8	1	9	1.1	16	1.9	32†	3.9	4.7	2.9 to 7.6
Father's side	378	6	1.6	2	0.5	5	1.3	13	3.4	4.1	2.2 to 7.9
Mother's side	459	2	0.4	7	1.5	11	2.4	19†	4.1	5.0	2.9 to 8.8
First- and second-degree relative with breast cancer	118	2	1.7	1	0.8	4	3.4	7	5.9	7.3	3.2 to 16.8
Controls‡	4,346							37	0.8	Reference	

Abbreviation: OR, odds ratio.

*Truncating mutation indicates any *CHEK2* truncating mutation (del5395, IVS2+1G>A, or 1100delC).

†The total for truncating mutation does not equal the sum of the component parts (del5395, IVS2+1G>A, or 1100delC) because one woman with breast cancer carried two truncating mutations (del5395 and 1100delC).

‡The frequency of the truncating mutations in controls is a reference for OR calculations.

PALB2 and breast cancer risk

8% baseline risk of BC in Poland

OR = 4.5; p<0,0001

36% lifetime risk

OR = 8.5; p<0,0001

68% familal cases of breast cancer

Cybulski C et al. Lancet Oncology 2015

nature genetics

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NATURE GENETICS | LETTER

Germline *RECQL* mutations are associated with breast cancer susceptibility

Cezary Cybulski, Jian Carrot-Zhang, Wojciech Kluźniak, Barbara Rivera, Aniruddh Kashyap, Dominika Wokołorczyk, Sylvie Giroux, Javad Nadaf, Nancy Hamel, Shiyu Zhang, Tomasz Huzarski, Jacek Gronwald, Tomasz Byrski, Marek Szwiec, Anna Jakubowska, Helena Rudnicka, Marcin Lener, Bartłomiej Masojć, Patrica N Tonin, Francois Rousseau, Bohdan Górski, Tadeusz Dębniak, Jacek Majewski, Jan Lubiński, William D Foulkes, Steven A Narod & Mohammad R Akbari

Affiliations | Contributions | Corresponding author

Nature Genetics (2015) | doi:10.1038/ng.3284

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RECQL

Validation phase 2 ~ 26 000 subjects

of the 2 founder mutations

In Polish population:

c.1667_1667+3delAGTA

32/13611 **unselected** cases *vs* 2/4702 controls

OR = 5.5; p = 0.005

In FC population:

c.634C>T

7/1013 higher risk cases *vs* 1/7000 controls

OR = 16; p = 0.00004

Frequency of founders associated with high risk of breast cancer – Poland

BRCA1	3	100 000
CHEK2 (PTM)	3	200 000
PALB2	2	50 000
RECQL	1	10 000
Total	**9**	**360 000**

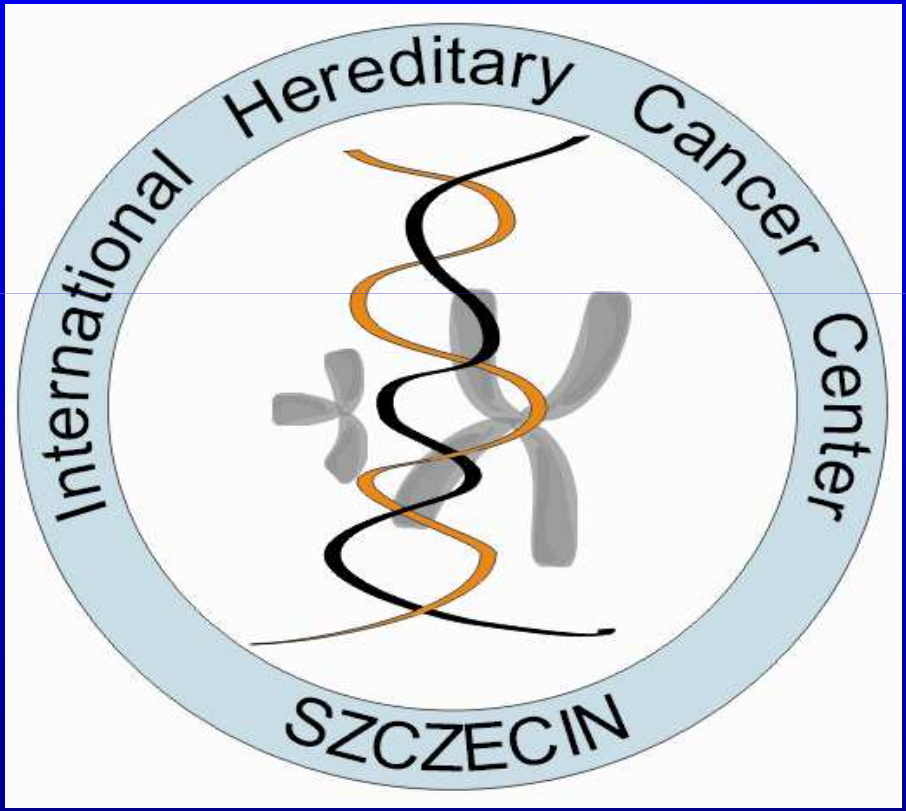
Conclussions

Genetic testing is a critical in optimalisation of prophylactics and treatment of patients with breast - ovarian cancer syndrome

Time for population screening?

Welcome for collaboration

More information:



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