

○ **The Latest Advances
in Clinical Genetics
Of Breast Cancer
– The Polish Experience**

Jan Lubiński, MD, PhD
International Hereditary Cancer Center
Pomeranian Medical University,
Szczecin, Poland

Question

- **Why are we getting so much in Poland?**

Luck!!!

Poland

- ~38 mil population with high level of genetic homogeneity

Luck!!! Poland

- **If genetic events are present, they are expressed strongly**

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

Polish Families With Strong Aggregation of Breast/Ovarian Cancers (N = 200)

- **BRCA 1** ~65%
- **BRCA2** ~4%

Polish Panel of BRCA1 Mutations

- 5382 ins C
- C 61 G
- 4153 del A

90% of mutations

BRCA1 Founder Mutations in Poland

- **Górski B, et al**
 - Patent No P335917
 - Multiplex Pcr - 50€

High Penetrance/Risk – Breast Ca

1. Family history

2. DNA tests

✓ **BRCA1**

✓ **BRCA2**

✓ **CHEK2** – homozygotes
– htr + FH
– **BRCA2 (5972 C/T)**

✓ **ATM**

Poland – Limited Number of Founder / Recurrent Mutations in Other Cancer-Susceptibility Genes

- NBS1,
- NOD2,
- CHEK2,
- MSH2,
- MLH1,
- APC

Population Screenings In Poland

ROZOWA WSTAZKA

Po raz pierwszy medycyna daje szansę kobietom zagrożonym rakiem piersi
Gen raka można wytropić i zapobiec chorobie

**FUNDUJEMY
BADANIA GENETYCZNE ZA
500 000 ZŁOTYCH
DLA PIĘCIU TYSIĘCY KOBIET
MOŻESZ BYĆ JEDNĄ Z NICH**

NIGDY DOTĄD W POLSCE TYLKO KOBIECI NIE MIAŁO TAKIEJ SZANSY

Twoi **STYL**
Dodatek Specjalny
Październik 2001

- 4% (~200) of BRCA1 carriers among 5000 relatives of women with breast cancer dx < 50 yrs or ovarian cancer dx at any age
- Thanks to geneticists - oncologists from 20 Polish centers!

Population Screenings In Poland

West-Pomerania Region
January 2001 – May 2002

- **1258 mil questionnaires
out of 1.45 mil inhabitants**
- **The first worldwide large screening
for hereditary cancers**

27 marca 2005 | NR 12 | Cena 4,50 zł (w tym 7% VAT)

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Cancer Biobank – IHCC

- **~2,000,000 cancer family histories**
- **>250,000 biological samples and clinical data from cancer patients, their relatives, and controls**

**BRCA1 Registry:
Szczecin, Poland**

>5000 Carriers

**The Largest Registry In The
World**

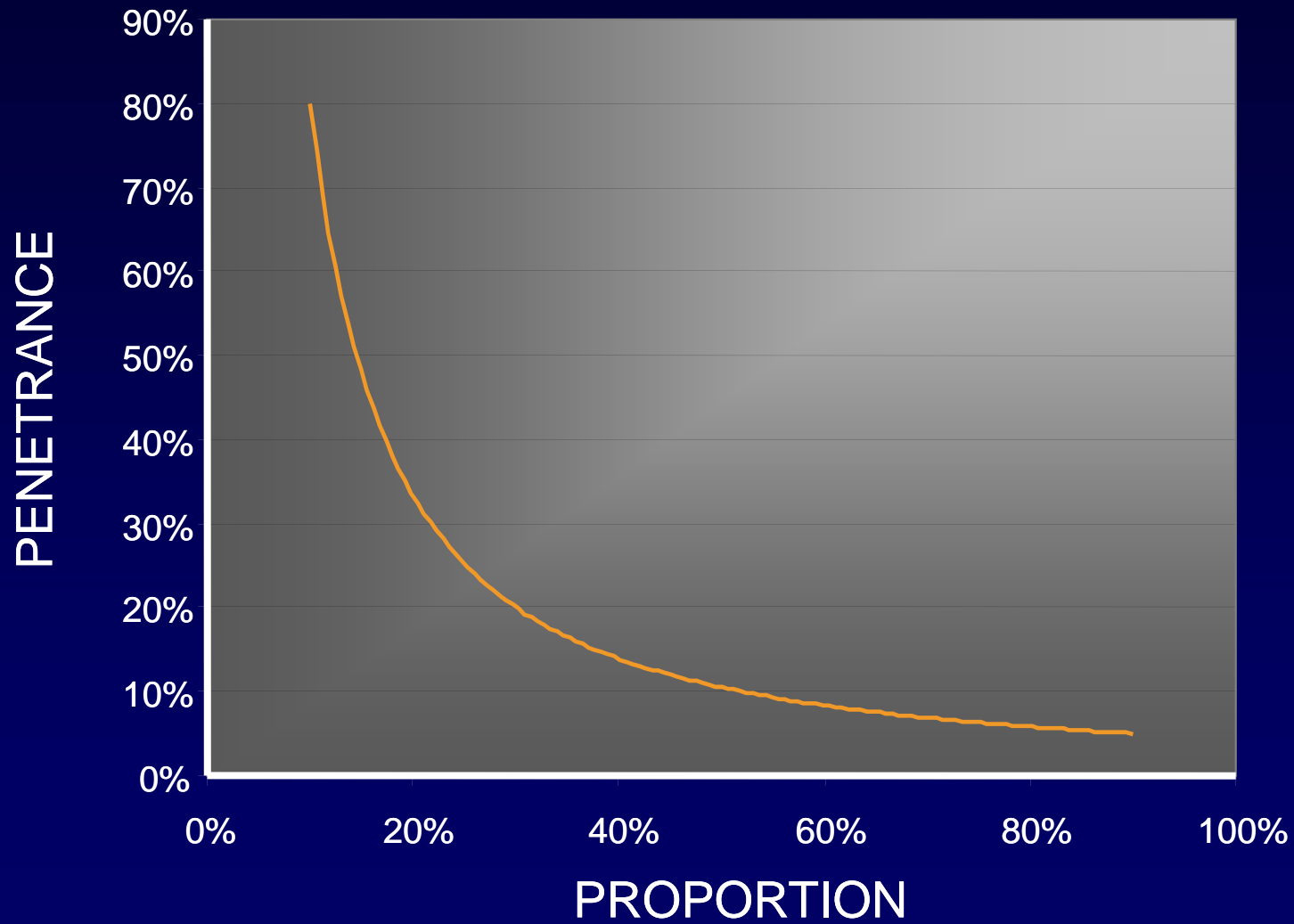
Milestone Discoveries

1. Genetic contribution to all cancers

Hypothesis

> 90%
of cancers have
genetic constitutional
background

Penetrance and Proportion of Cancers



Serrano-Fernandez P, et al. *Hered Cancer Clin Pract.* 2006;15(4):25-27.



Impossible



Risky statement



Perhaps

**Genetic Contribution to All Cancers:
The First Demonstration Using the
Model of Breast Cancers From Poland
Stratified by Age at Diagnosis
and Tumour Pathology**

Lubiński J, et al. *Breast Cancer Res Treat.* 2009, 114(1):121-126.
Patent US61/069,403 31.03.2009

Frequency of Identified Panel of Markers in all Consecutive Cancers and Controls

Gene/Marker	Cases (%)	Controls (%)
BRCA1	2.7% (26/977)	0% (0/977)
CKEK 2	11.9% (113/951)	6% (59/977)
p 53	10.1% (85/838)	5.7% (52/918)
TNR	55.6% (419/753)	45.8% (397/866)
FGFR - GG	18.3% (61/334)	13.9% (65/469)
CDKN2A	7% (19/273)	5.4% (22/404)
XPD - GG	41% (104/254)	36.4% (139/382)
XPD - CC/AA	17.3% (26/150)	14% (34/243)
BRCA2	7.3% (9/124)	4.8% (10/209)
XPD - AA	20% (23/115)	18.6% (37/199)
Any marker	90.6% (885/977)	83.4% (815/977)
Statistical significance	$P = 3 \times 10^{-6}$	

Conclusion

- 1. At present, the major significance of the current findings is the proof of principle that there is no cancer without a genetic component.**
- 2. DNA analysis will be the initial starting point for prevention, surveillance, and treatment schemes for all adults.**

Milestone Discoveries

2. Complete remission of BRCA1– dependant breast cancers using cisplatinium

Breast Cancers With BRCA1 Response to Neoadjuvant Therapy

Type of CHTH	No of patients	CR	PR	No response
<i>BRCA1 – 44</i>				
AT	15	0	6	9
Other types	29	4	25	0
Total	44	4	31	9
<i>Non-BRCA1 – 41</i>				
AT	12	0	12	0
Other types	29	2	25	2
Total	41	2	37	2

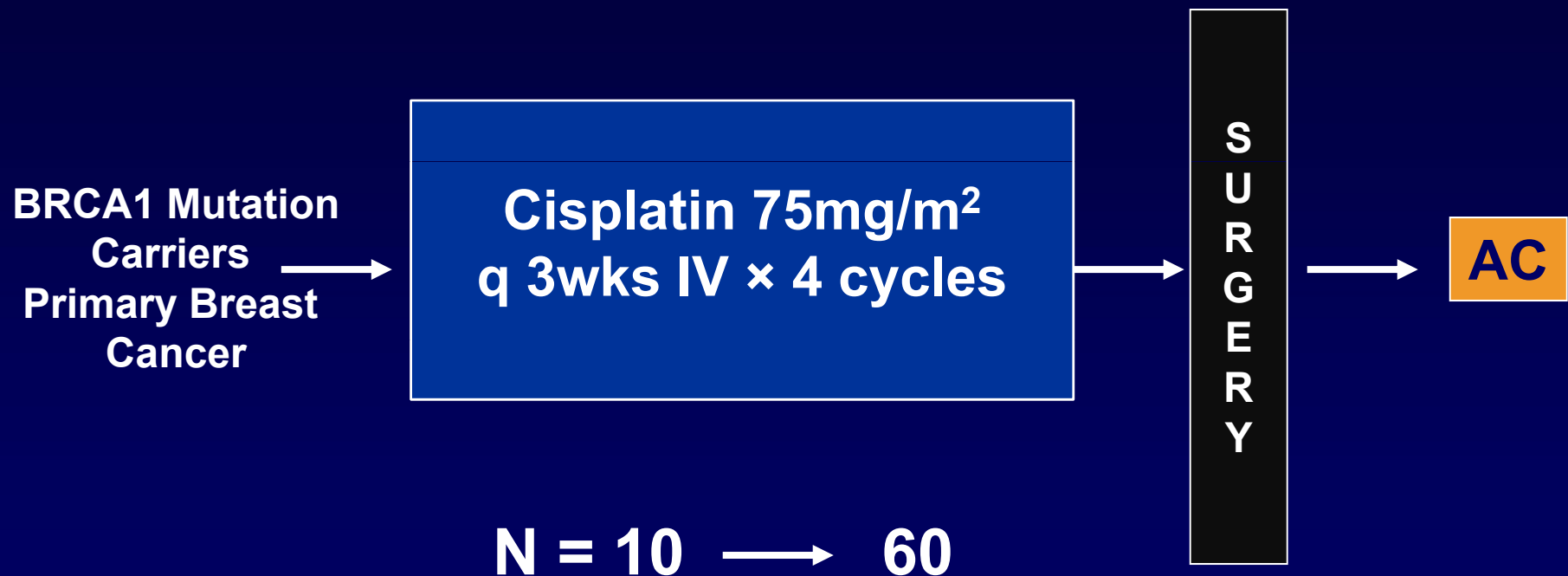
Preclinical Studies

- 👉 **BRCA1 breast cancer cell lines**
 - **resistance to taxanes**
 - **sensitivity to cisplatin**

BRCA1–Dependent BC

- **Neoadjuvant Study**

Current Study Design



Primary Endpoint: pCR (in breast and axilla, DCIS permitted)

Pilot Study

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
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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)

Pathologic Complete Response Rates in Young Women With *BRCA1*-Positive Breast Cancers After Neoadjuvant Chemotherapy

Tomasz Byrski, Jacek Gronwald, Tomasz Huzarski, Ewa Grzybowska, Magdalena Budryk, Małgorzata Stawicka, Tomasz Mierzwa, Marek Szwiec, Rafał Wiśniowski, Monika Siolek, Rebecca Dent, Jan Lubinski, and Steven Narod

See accompanying editorial on page 361

From the Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin; Department of Tumor Biology, Centre of Oncology, Maria Skłodowska-Curie Memorial Institute, Gliwice; Prophylactic and Epidemiology Center, Poznań; Regional Oncology Hospital, Bydgoszcz; Regional Oncology Center, Opole; Regional Oncology Hospital, Bielsko Biala; Holy Cross Oncology Center, Kielce, Poland; Odette Cancer Centre, Sunnybrook Regional Cancer Centre; and Womens College Research Institute, University of Toronto, Toronto, Ontario, Canada.

Written on behalf of the Polish Hereditary Breast Cancer Consortium.

Submitted October 22, 2008; accepted June 24, 2009; published online ahead of print at www.jco.org on December 14, 2009.

Supported by the Polish Ministry of Science Grant No. PBZ-KBN-122/po5/

A B S T R A C T

Purpose

To estimate the rate of pathologic complete response (pCR) to neoadjuvant chemotherapy in *BRCA1* mutation carriers according to chemotherapy regimen.

Patients and Methods

From a registry of 6,903 patients, we identified 102 women who carried a *BRCA1* founder mutation and who had been treated for breast cancer with neoadjuvant chemotherapy. Pathologic complete response was evaluated using standard criteria.

Results

Twenty-four (24%) of the 102 *BRCA1* mutation carriers experienced a pCR. The response rate varied widely with treatment: a pCR was observed in one (7%) of 14 women treated with cyclophosphamide, methotrexate, and fluorouracil (CMF); in two (8%) of 25 women treated with doxorubicin and docetaxel (AT); in 11 (22%) of 51 women treated with doxorubicin and cyclophosphamide (AC) or fluorouracil, doxorubicin, and cyclophosphamide (FAC), and in 10 (83%) of 12 women treated with cisplatin.

Conclusion

A low rate of pCR was observed in women with breast cancer and a *BRCA1* mutation who were treated with AT or CMF. A high rate of pCR was seen after treatment with cisplatin. An intermediate rate of PCR was associated with AC or FAC. The relative benefits of AC and platinum therapy need to be confirmed through follow-up of this and other cohorts.

Retrospective Analysis: Neoadjuvant Treatment of 141 Consecutive BRCA1 Mutation Carriers With Diagnosis of Breast Cancer < 51 Yrs (N = 7000)

Regimen	Number treated	Number of pCR	% pCR
<i>CMF</i>	15	1	7%
AC	24	4	17%
FAC	28	5	18%
AT	24	1	4%
Cisplatin	50	34	68%

C: cyclophosphamide
M: methotrexate
F: 5-flourouracil
A: adriamycin
T: docetaxel

Chemotherapy

- **Neoadjuvant treatment of breast cancer – complete pathologic remission**



- **> 95% five-year survival !**

BRCA1–Dependent Cancers

- **Cancers Of Other Sites**

Conclusions

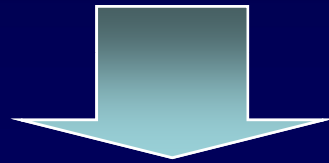
- 1. Platinum-based chemotherapy is effective in a high proportion of patients with BRCA1-associated breast cancers**
- 2. BRCA1 testing is a critical issue for choice of breast cancer treatment**
- 3. Validating studies needed**

Milestone Discoveries

3. Genotypes associated with sensitivity to cancer chemoprevention using selenium

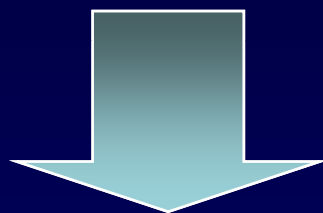
Great Dream

- Chemoprevention for individuals of high genetic risk



BRCA1?

Selenium – Proven Cancer-Risk Reduction in Animals



Rats – BR CA – DMBA

WHO Recommendation

- **Cancer risk persons**



- **Diet supplementation
with selenium 250 – 300 μg daily**

Selenium – Breast / Ovarian Cancers – BRCA1 IHCC - Poland

- Sodium selenite – pilot study

BRCA1 CARRIERS

N = 130 Se



3 Br/Ov Ca

N = 130 (-)



9 Br/Ov Ca

Selenium – Breast / Ovarian Cancers – BRCA1 IHCC, Poland

- **Clinical trial 2004 – 2008**
- **1344 BRCA1 carriers**
- **Unaffected or after treatment of unilateral breast cancer**
- **Double-blind studies**
- **677 Placebo**
- **666 Selenium**
- **Follow-up ~2,9 yrs**
- **Dose ~300 μ g per day (WHO recommendations)**

New Cases of Cancer in the Study

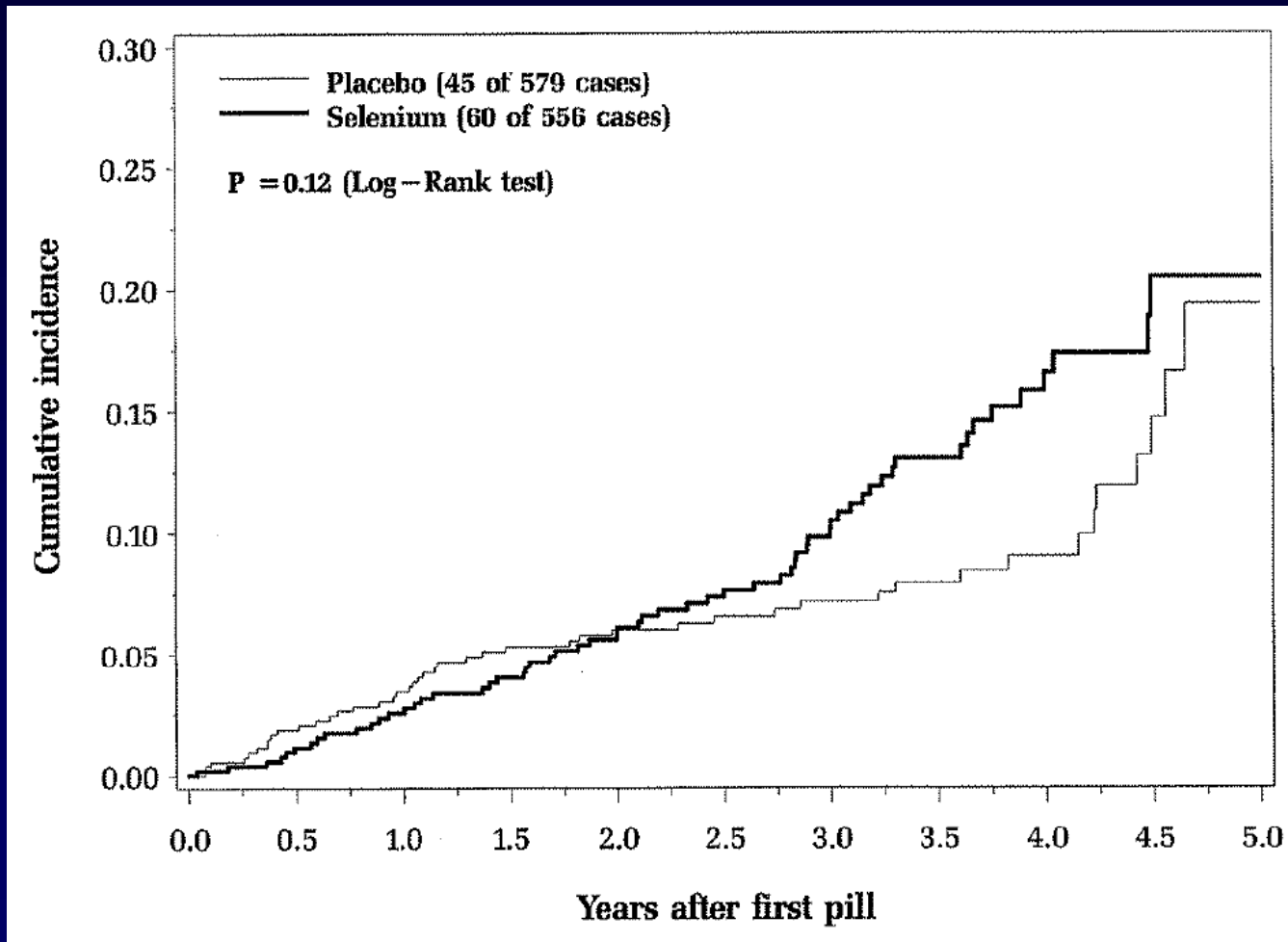
	Placebo	Selenium	Total
Breast	29	41	70
Ovary	11	14	25
Fallopian	1	2	3
Peritoneal	0	1	1
Endometrial	3	3	6
Lung	1	0	1
Brain	1	0	1
Total	46	61	107

Two individuals had two cancers

Hazard Ratios Associated With Selenium Supplementation for Various Cancers

Type of cancer	Hazard ratio	95% confidence interval	P-value
Primary breast cancer	1.35	0.72 - 2.51	0.35
Contralateral breast cancer	1.53	0.73 - 3.21	0.26
Ovarian/fallopian cancer	1.26	0.59 - 2.70	0.55
Any cancer	1.36	0.93 - 2.01	0.12

Cumulative Risk of Cancer (All Types) Among Women Randomised To Selenium or Placebo



Lubiński J, et al. Presented at: 4th Familial Cancer Conference; June 7-8, 2010: Madrid, Spain. Abstract.

Hypothesis

- **Cancer risk is correlated with selenium serum level**

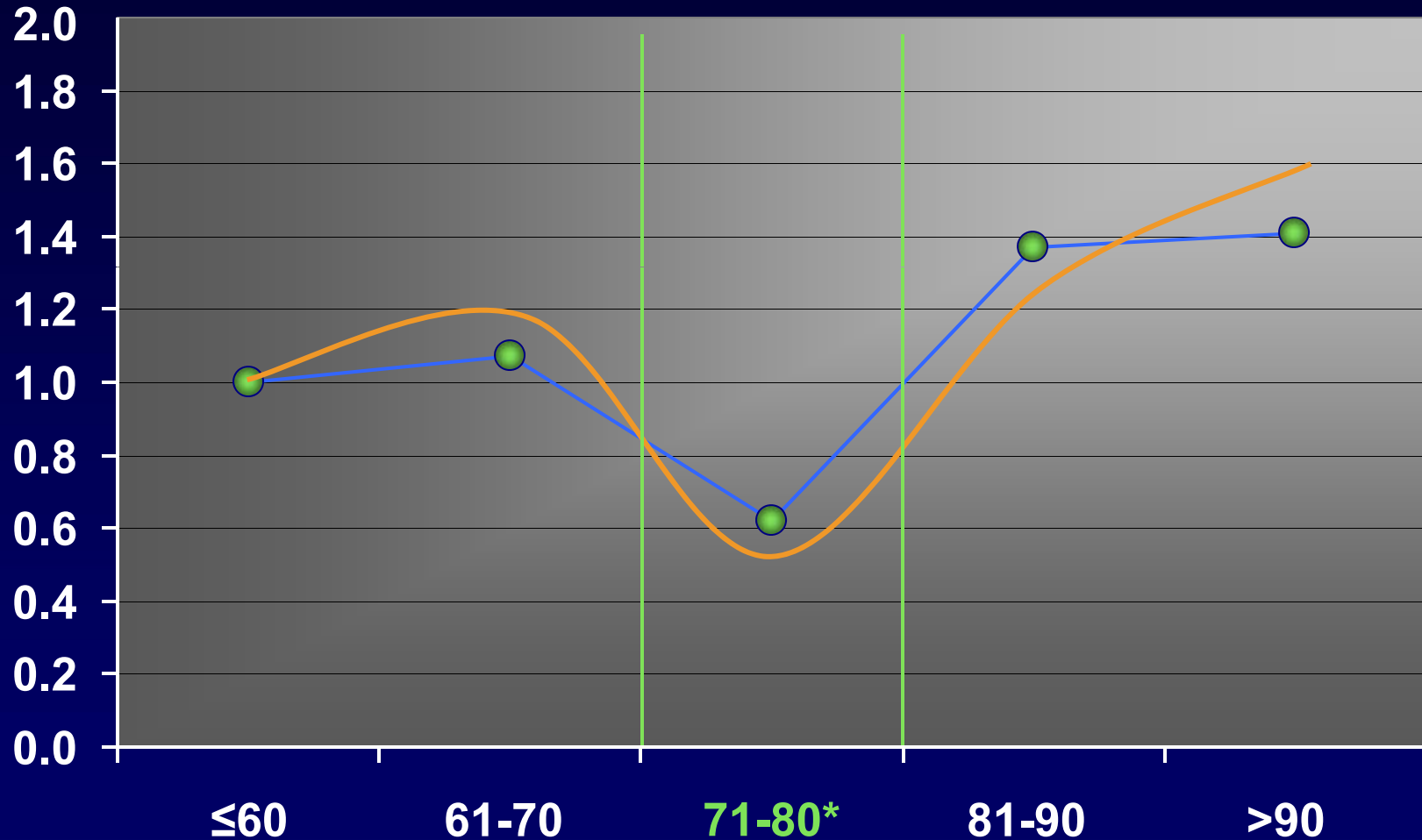
Br/Ov Cancer Risk in BRCA1 Carriers Depending on Selenium Level

Selenium Concentration	RR (aff/unaff)	
≤60	1.00	7/14
61–70	1.07	22/41
71–80*	0.62	23/74
81–90	1.37	24/35
91–100	1.41	12/17
>100	0.92	6/13

* $P = 0.0173$; OR-0.5040; CI = 0.0907-0.8740

- N = 291 cases/controls 1:2; matched for age at dx; adnexectomy; previous cancers; Se or placebo group in clinical trial

Relative Risk of Breast/Ovarian Cancers in BRCA1 Carriers Depending on Selenium Concentration



* $P = 0.0173$; OR-0.5040; CI = 0.907–0.8740

Lubinski J, et al. Presented at 2010 ESHG Gothenburg.

**Genotypes Associated
With Correlation Between
Cancer Risk and Selenium Level**

Gene Candidates

- **11 changes preselected by sequencing**
- **Association studies**
 - **case / control n = 255**

Br/Ov Cancer Risk in BRCA1 Carriers Depending on Selenium Level and Genotypes

Genotype		Se level	OR	<i>P</i>	CI
X1	nTT	60–80	0.32	0.0009	0.16–0.63
X2	GG	60–80	0.33	0.005	0.15–0.71
X3	nTT	60–80	0.4	0.007	0.24–0.78
X1	TT	>80	0.1	0.047	0.01–0.93

**Clinical Status and Cancer Risk
Dependance on Selenium Level**

Br/Ov Cancer Risk in BRCA1 Carriers Depending on Selenium Level in Sub-Group of Pts Initially Unaffected After Adnexectomy

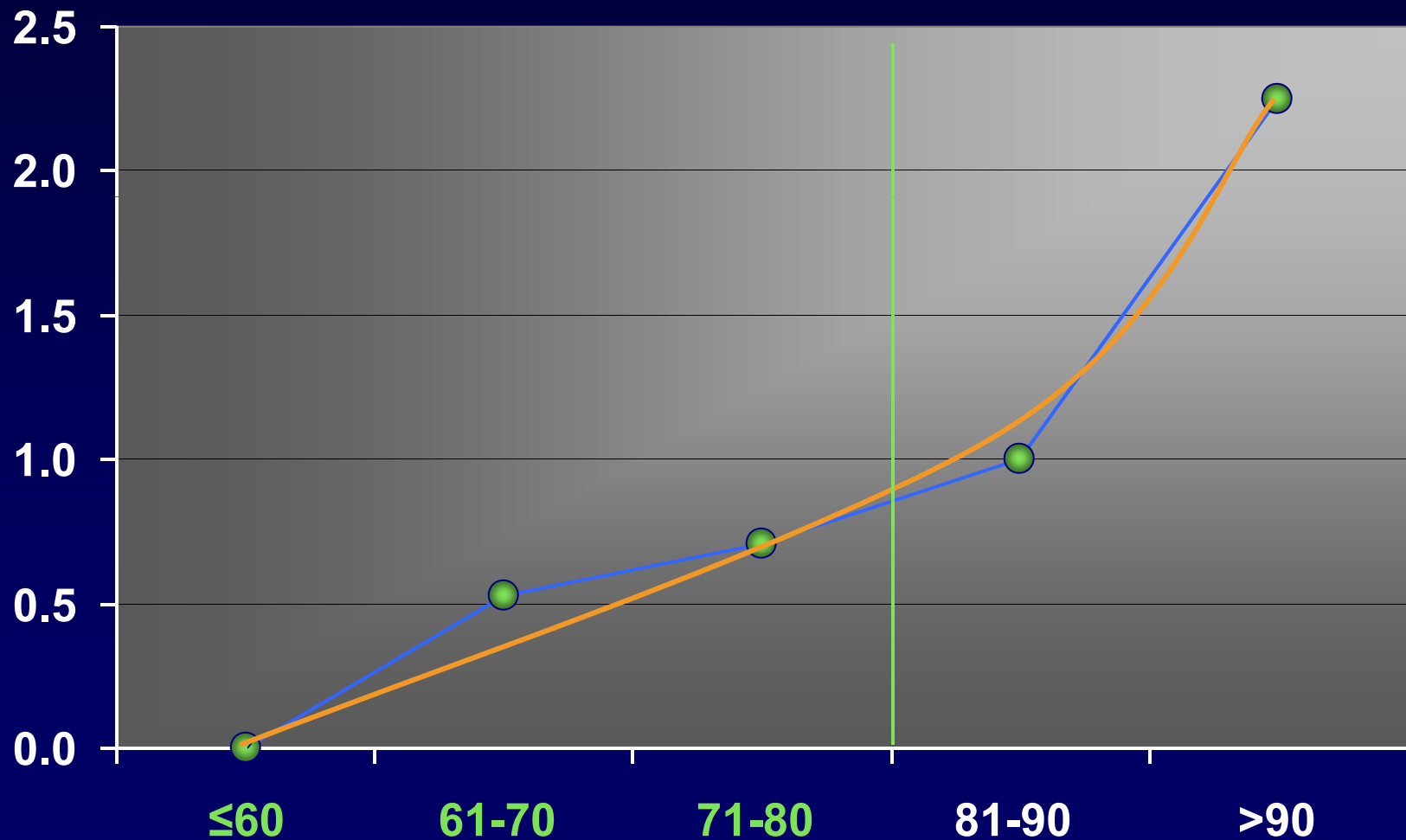
Selenium Concentration	RR (aff/unaff)	
≤60	0,00	0/1
61–70	0,53	4/15
71–80	0,71	6/17
81–90	1,00	6/12
>90	2,25	9/8

*10/33 vs 9/8; $P = 0.034$; OR-0.26; CI = 0.08-0.88

- **N = 78 cases/controls 1:2; matched for age at dx; adnexectomy; previous cancers; Se or placebo group in clinical trial**

Relative Risk Breast/Ovarian Cancers BRCA1 Carriers Depending on Selenium Concentration

Patients Initially Unaffected After Adnexectomy



Genotypes, Selenium Level, and Cancer Risk in Initially Unaffected BRCA1 Carriers

A. Without Adnexectomy

Genotype		Se level	OR	p	CI	%
X1	TT	>80	0.038	0.014	0.00-0.54	19%
X2	GG	60-80	0.20	0.014	0.06-0.70	54%
X3	CC	60-80	0.23	0.014	0.07-0.70	61%

- Any of above combination genotype – Se level ~86% (90/105)
11/51 vs 13/11;
OR – 0.18; P = 0.0013; CI = 0.064 – 0.51

Genotypes, Selenium Level and Cancer Risk in Initially Unaffected BRCA1 Carriers

B. After Adnexectomy

Genotype	Se level	OR	p	CI	%
X4 CC	<80	0.04	0.034	0.00-0.62	26%
X2 nGG	<80	0.10	0.045	0.01-0.98	47%
X8 GG	<80	0.11	0.015	0.02-0.62	61%

- Any of above combination genotype – Se level ~81% (54/66)
2/22 vs 14/16;
OR – 0.10; P = 0.0026; CI = 0.021 – 0.52

Conclusions for BRCA1 Carriers

- **Most likely:**
 - 1. Selenium can cause cancer and prevent it as well**
 - 2. Selenium serum level is a cancer risk marker; optimal ranges depend on clinical status and genotypes**
 - 3. Diet with controlled amount of selenium is an attractive option for lowering cancer risk**



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Hereditary Cancer in Clinical Practice 2009, 7:6 (31 March 2009)

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Evgeny N Suspitsin, Nathalia Yu Sherina, Daria N Ponomariova, Anna P Sokolenko, Aglaya G Iyevleva, Tatyana V Gorodnova, Olga A Zaitseva, Olga S Yatsuk, Alexandr V Togo, Nathalia N Tkachenko, Grigory A Shiyanov, Oksana S Lobeiko, Nadezhda Yu Krylova, Dmitry E Matsko, Sergey Ya Maximov, Adel F Urmancheyeva, Nathalia V Porhanova, Evgeny N Imyanitov

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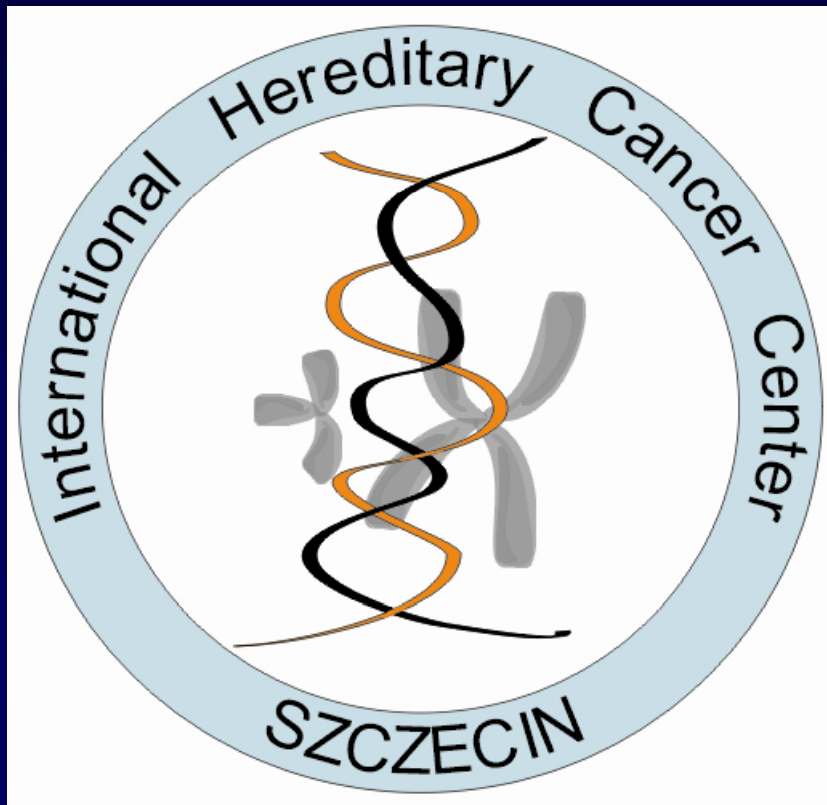
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