Comunicazione orale:

METACHRONOUS AND SYNCHRONOUS BREAST AND OVARIAN CANCER: A MULTICENTRIC EXPERIENCE

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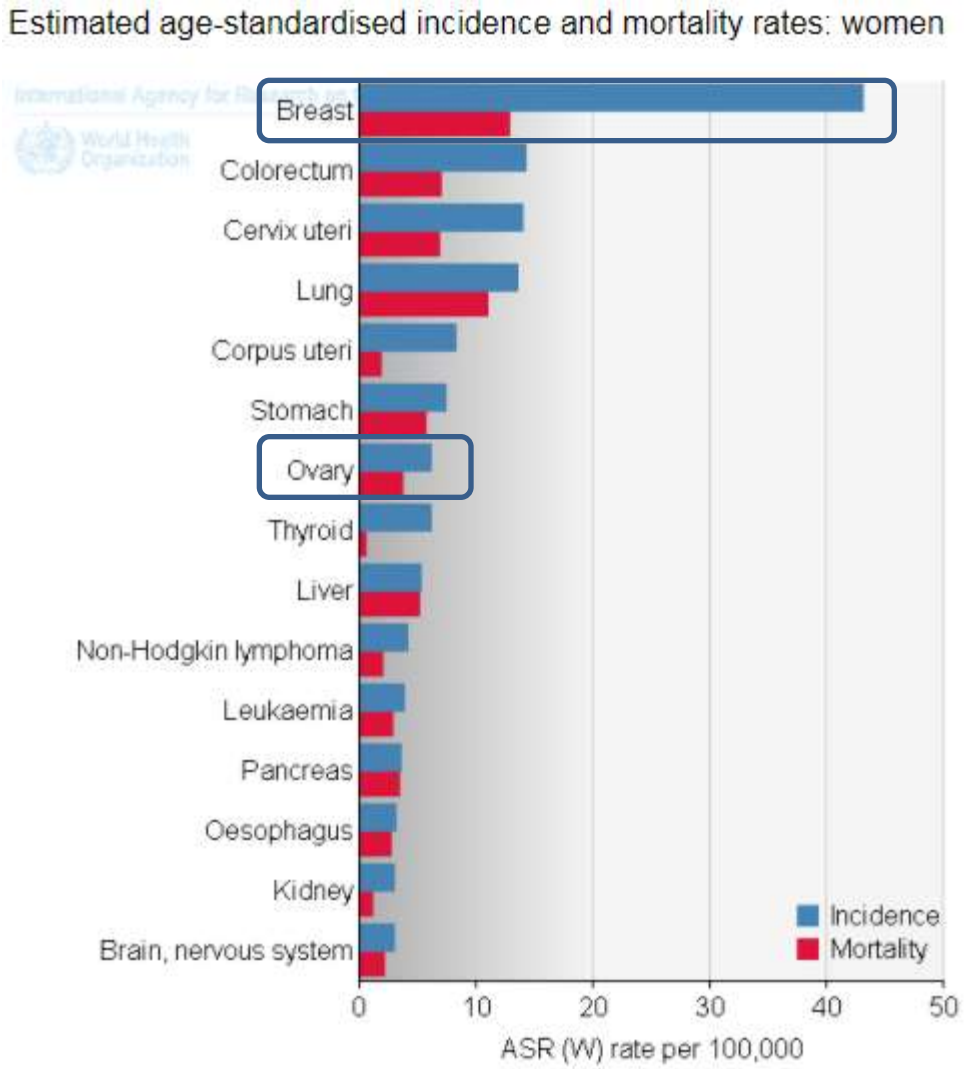
EPIDEMIOLOGY OF BREAST AND OVARIAN CANCER



BREAST CANCER

1,671,149 (25,1%)
521,907 (14,7%)

OVARIAN CANCER

238,719 (3,6%)
151,917 (4,3%)

WORLD GLOBOCAN 2012 data

METACHRONOUS AND SYNCHRONOUS BREAST AND OVARIAN CANCER

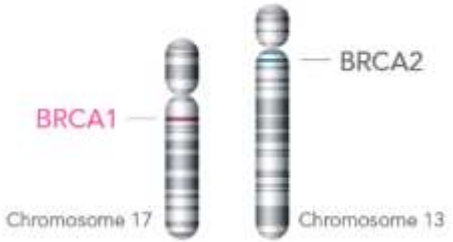
From literature…

- When compared with the general population, cancer survivors have generally an increased risk of developing a second primary cancer;
- Women with a history of BC have a higher risk of developing a subsequent OC and *vice versa*;
- Hereditary breast and ovarian cancer syndrome (HBOC) is due to BRCA1 and BRCA2 genes mutations;
- Metachronous or synchronous tumors of the breast/ovary regardless of BRCA mutations→ common etiologic factors or other susceptibility genes mutations;
- According to limited evidence, BC is diagnosed first in 75% of cases and patients with BC first had a worse outcome on comparison to patients with first OC.

Lynch HT et al. JAMA 1972
Liou WS et al. Gynecol Oncol 2006

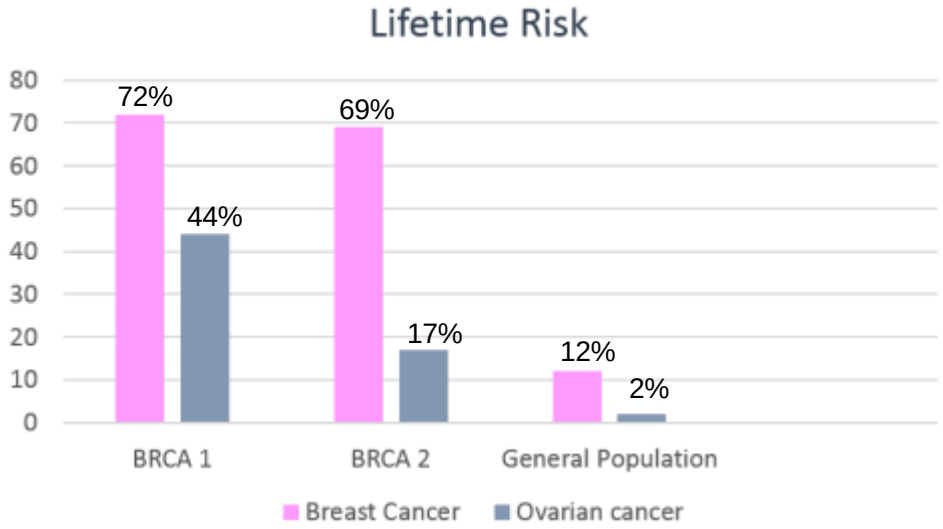
BRCA1 AND BRCA2 GENES

- Involved in repairing DNA double-strand break through homologous recombination and in cell cycle control points;



- Germinal mutations occur in about 1 in 300-800 individuals in the general population (the prevalence varies between ethnic groups and geographic areas - "founder effect");

- 10-15% of OCs and 5-10% of BCs are due to BRCA1/2 mutations;

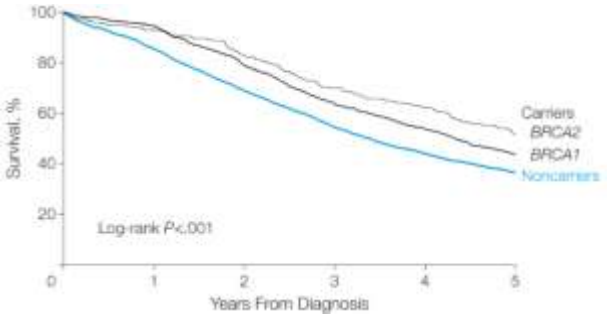


Kuchenbaecker KB et al. JAMA 2017

MAIN FEATURES OF BRCA1/2 ASSOCIATED BREAST AND OVARIAN CANCER

BRCA Genes and Ovarian Cancer

- Serous histology
- High grade
- Stage III/IV
- Visceral metastases
- Better prognosis (platinum sensitivity)



BRCA Genes and Breast Cancer

- Triple Negative histotype
- 30 – 40 yy

BRCA1

- HR positive and 15% HER2 positive
- 40-70 yy

BRCA2

Bolton KL et al. JAMA 2012
Christinat A et al. Breast 2013

AIMS OF THE STUDY

- To evaluate clinico-pathological characteristics of patients according to the sequence of BC and OC diagnoses and BRCA mutational status;
- To evaluate the time interval between diagnoses according to the sequence of BC and OC diagnoses and BRCA mutational status;
- To evaluate the global survival according to the sequence of BC and OC diagnoses, BRCA mutational status and other major prognostic factors.

MATERIALS AND METHODS

- 270 patients treated at Istituto Oncologico Veneto (PD) and Istituto Europeo di Oncologia (MI) from 1981 to 2016;
- 182 patients with mutational status available;
- Age at diagnoses, tumor stage, histotype, grade, lymph nodal status and hormonal/HER2 receptors status (BC only), surgical and medical treatment and survival status/death causes.

BC First Group

OC First Group

Synchronous Group

BRCA mutated Group

BRCA wild type Group

RESULTS 1: CLINICO-PATHOLOGICAL CHARACTERISTICS ACCORDING TO DIAGNOSIS SEQUENCE

	BC First n° (%)	*OC First* n° (%)	p
BRCA status			.006
Wild Type	42 (31.6%)	19 (59.4%)	
Mutated	**91 (68.4%)**	13 (40.6%)	
Total	133	32	
OC Histolgy			.002
Serous	**146 (75.3%)**	24 (49.0%)	
Endometrioid	18 (9.3%)	16 (32.7%)	
Indifferent.	12 (6.2%)	3 (6.1%)	
Other	18 (9.3%)	6 (12.2%)	
Total	194	49	
OC Stage			.039
I - II	52 (26.9%)	22 (45.8%)	
III - IV	**141 (73.1%)**	26 (45.8%)	
Total	193	48	
OC Grade			<.001
1 - 2	22 (11.5%)	20 (42.6%)	
3	**169 (88.5%)**	27 (57.4%)	
Total	191	47	
Mean age at 1st diagn.	**48** (28 - 83)	54 (30 - 76)	<.001
Mean age at 2nd diagn.	57 (38 - 84)	61 (36 - 79)	<.001

	BC First n° (%)	*OC First* n° (%)	p
BC Histology			.038
Ductal	**154 (85.1%)**	35 (70.0%)	
Lobular	9 (5.0%)	8 (16.0%)	
Other	18 (9.9%)	7 (14.0%)	
Total	181	50	
BC Stage			.022
≤ I	72 (45.9%)	30 (60.0%)	
≥ II Total	**85 (54.1%)**	20 (40.0%)	
	157	50	
BC HR			.051
Negative	**73 (42.4%)**	14 (27.5%)	
Positive	99 (57.6%)	37 (72.5%)	
Total	172	51	

BC first group:

- 72% of patients cohort;
- More frequently BRCA1/2 mutated;
- Lower age at 1st diagnosis;
- More frequently high grade, advanced stage, serous OC;
- High percentage of HR negative BC.

RESULTS 1: CLINICO-PATHOLOGICAL CHARACTERISTICS ACCORDING TO DIAGNOSIS SEQUENCE

	Synchronous n° (%)	p
BRCA status		.006
Wild Type	9 (52.9%)	
Mutated	8 (47.1%)	
Total	17	
OC Histolgy		.002
Serous	**18 (72.0%)**	
Endometrioid	5 (20.0%)	
Indifferent.	1 (4.0%)	
Other	1 (4.0%)	
Total	25	
OC Grade		<.001
1 - 2	4 (16.0%)	
3	**21 (84.0%)**	
Total	25	
BC Stage		.022
≤ I	**18 (72.0%)**	
≥ II Total	7 (28.0%)	
	25	

***Synchronous* group:**

- 9% of patients cohort;
- More frequently high grade serous OC;
- More frequently low stage BC.

RESULTS 2: CLINICO-PATHOLOGICAL CHARACTERISTICS ACCORDING TO BRCA MUTATIONAL STATUS

	BRCA Wild Type n° (%)	BRCA Mutated n° (%)	p
OC Histolgy			.006
Serous	33 (55.0%)	**79 (76.0%)**	
Endometrioid	12 (20.0%)	11 (10.6%)	
Indifferent.	3 (5.0%)	8 (7.7%)	
Other	12 (20.0%)	6 (5.8%)	
Total	60	104	
OC Stage			.002
I - II	28 (47.5%)	25 (24.3%)	
III - IV	31 (52.5%)	**78 (75.7%)**	
Total	59	103	
OC Grade			<.001
1 - 2	23 (39.0%)	8 (7.8%)	
3	36 (61.0%)	**95 (92.2%)**	
Total	59	103	
BC Grade			<.001
1 - 2	35 (70.0%)	31 (36.5%)	
3	15 (30.0%)	**54 (63.5%)**	
Total	50	85	
TNBC			.001
No TN	45 (86.5%)	51 (58.6%)	
TN	7 (13.5%)	**36 (41.4%)**	
Total	52	87	
Mean age at 1st diagn.	54 (34 - 85)	**47** (28 - 80)	.001
Mean age at 2nd diagn.	62 (42 - 85)	**55** (36 - 81)	.001

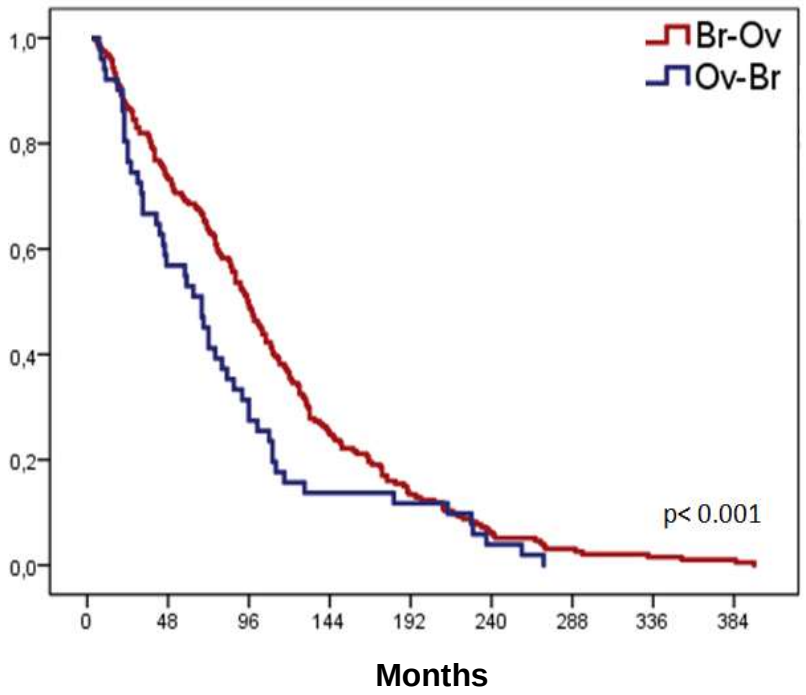
BRCA mutated group:

- 62% of patients;
- Lower age at both diagnoses;
- More frequently high grade, advanced stage, serous OC;
- High percentage of TNBC.

RESULTS 3: TIME TO SECOND DIAGNOSIS ACCORDING TO DIAGNOSIS SEQUENCE

BC First Group

OC First Group



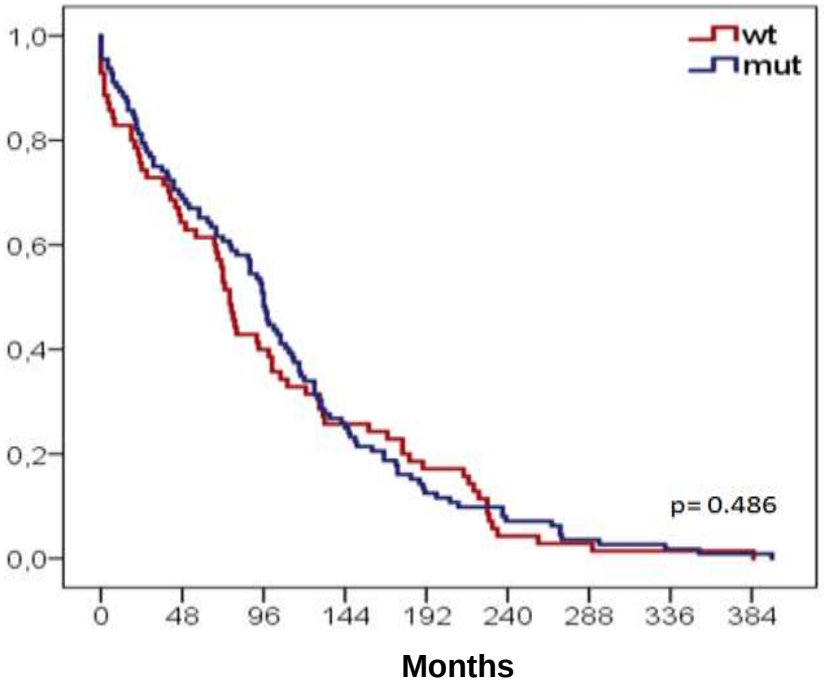
	Median (95% CI)	HR (95% CI)	p value
BC First	95 (84 – 106)	Ref.	
OC First	68 (46.7 – 89.8)	1.435 (1.05 – 1.95)	.023

Median time interval from first to second diagnosis in overall cohort:
78 months (95%CI 67.6 – 88.4)

RESULTS 4: TIME TO SECOND DIAGNOSIS ACCORDING TO BRCA MUTATIONAL STATUS

BRCA mutated Group

BRCA wild type Group



	Median (95% CI)	HR (95% CI)	p value
BRCA wild type	76 (67.8 – 84.2)	Ref.	
BRCA mutated	96 (87.1 – 104.9)	0.920 (0.68 – 1.24)	.588

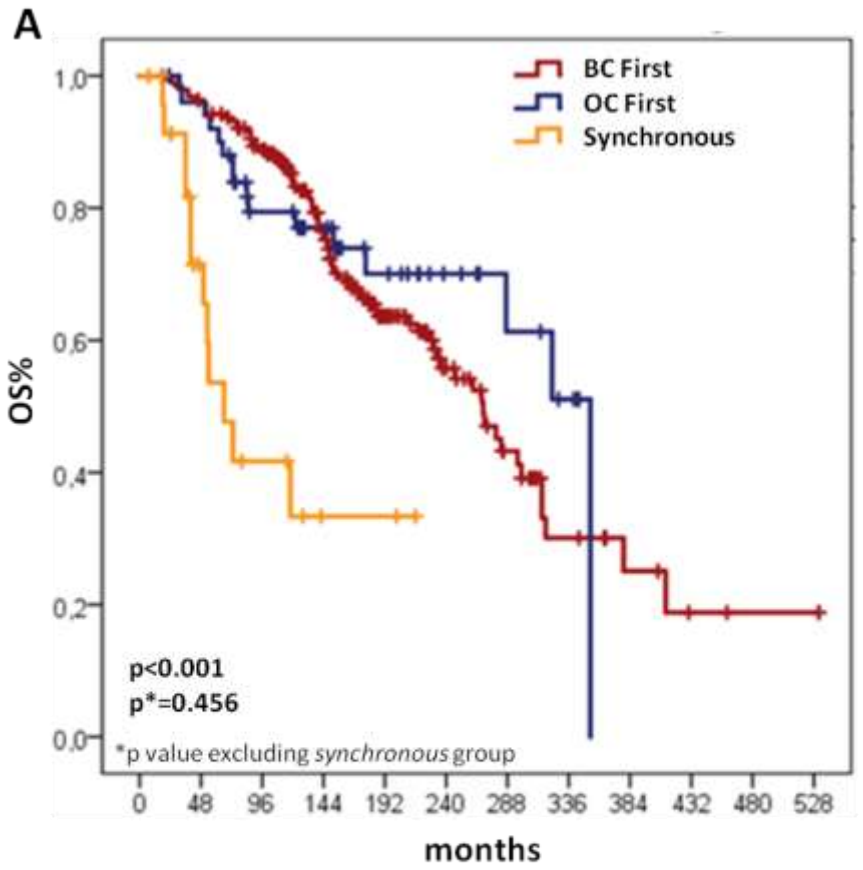
Median time interval from first to second diagnosis in overall cohort:
96 months (95%CI 46.7 – 89.8)

RESULTS 5: OVERALL SURVIVAL FROM 1ST DIAGNOSIS ACCORDING TO DIAGNOSIS SEQUENCE

BC First Group

OC First Group

Synchronous Group

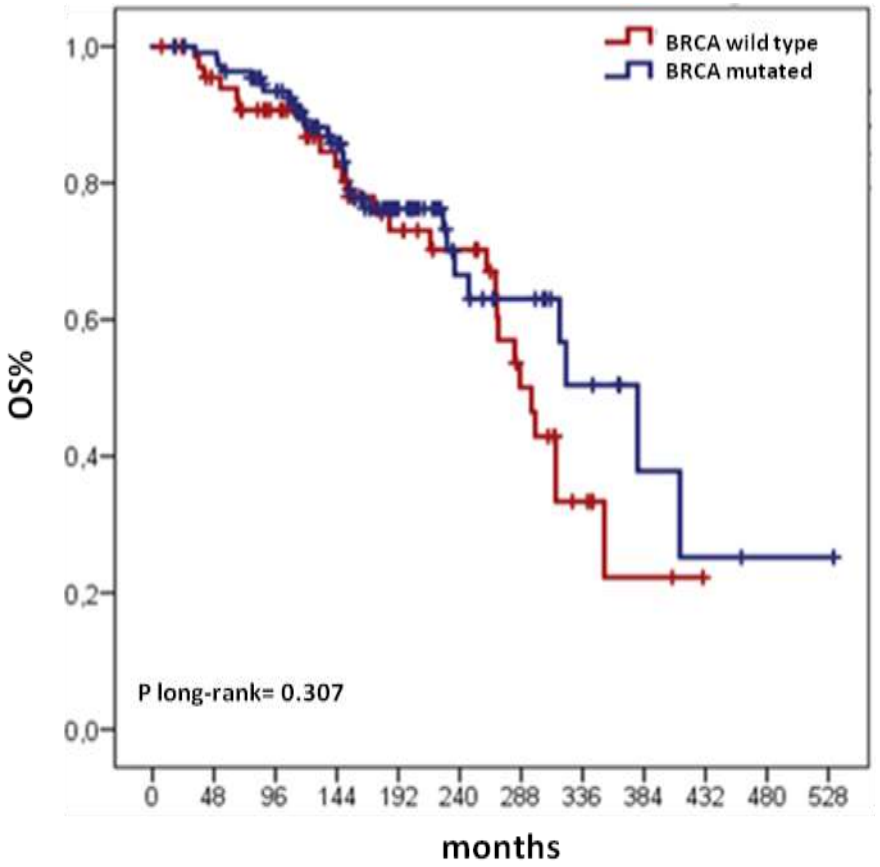


	OS from 1st diagnosis		
	10-years OS%	HR (95% CI)	p
OC first	79.4	Ref.	
BC first	83.3	1.229 (0.715–2.113)	.456
Synchronous	33.4	5.674 (2.627–12.258)	<.001

RESULTS 6: OVERALL SURVIVAL FROM 1ST DIAGNOSIS ACCORDING TO BRCA MUTATIONAL STATUS

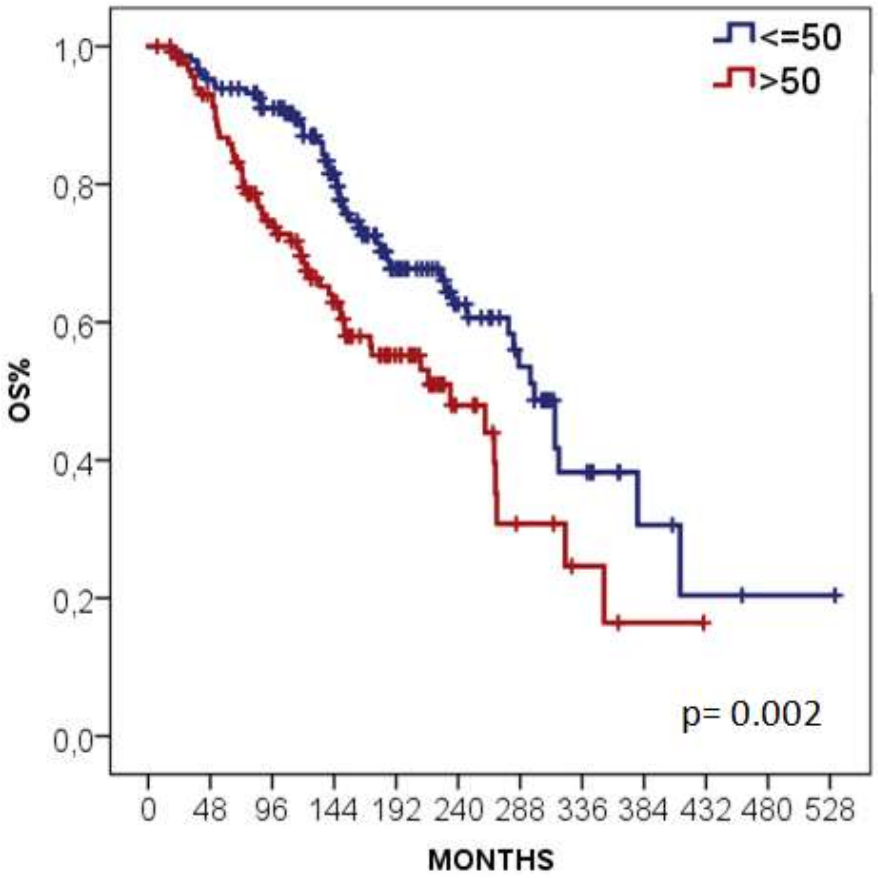
BRCA mutated Group

BRCA wild type Group



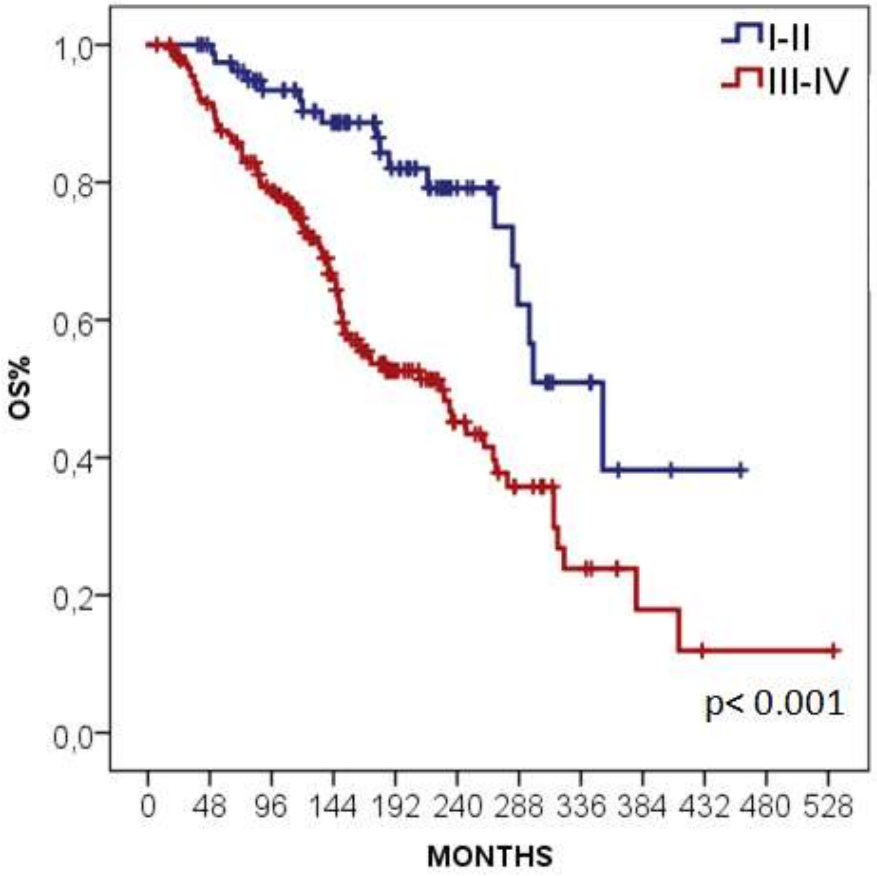
	OS from 1st diagnosis		
	10-yeasr OS %	HR (95% CI)	p
BRCA wild type	86.7	Ref.	
BRCA mutated	88.2	0.757 (0.443 – 1.295)	.310

RESULTS 7: OVERALL SURVIVAL FROM 1ST DIAGNOSIS ACCORDING TO OTHER PROGNOSTIC FACTORS



	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Age at 1st diagnosis 50≤ vs >50 yy	1.817	1.235 – 2.674	.002	1.843	1.251 – 2.714	.002

RESULTS 7: OVERALL SURVIVAL FROM 1ST DIAGNOSIS ACCORDING TO OTHER PROGNOSTIC FACTORS



	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
OC Stage						
<III vs ≥III	2.991	1.720 – 5.203	<.001	2.687	1.615 – 4.469	<.001

TO SUMMARIZE 1

- This is the second largest cohort, following that reported by *Liou et al.* in 2006;
- The prevalence of BRCA mutated patients, especially BRCA1 mutated, in *BC first* group may account for some of the differences between the groups, with *BC first* patients showing younger age at 1st and 2nd diagnosis, more aggressive OC features and a higher prevalence of TNBC;
- Patients characteristics according to BRCA mutational status was consistent with previous studies;
- Longer interval to 2nd diagnosis in *BC first* group than in *OC first* group→ younger age at 1st diagnosis in *BC first* group;
- No difference in OS from 1st diagnosis according to diagnosis sequence→ the potential favorable effect of a long time interval between diagnoses was somehow neutralized by the poor prognosis that these patients experienced after OC diagnosis (poor characteristics of OC);

TO SUMMARIZE 2

- No difference in OS from 1st diagnosis according to BRCA mutational status→better prognosis of BRCA mutated patients with OC might not be confirmed in cases with a metachronous BC (also in Zaaijer LH et al.);
- Age at 1st diagnosis> 50 years and OC≥ III FIGO stage are independent poor prognostic factors;
- 70.5% of patients died for OC related causes → survival is dominated by OC prognosis;
- 87.5% of patients underwent genetic test after the 2nd diagnosis of cancer → importance to recognize high risk BRCA1/2 mutated women.

TAKE HOME MESSAGES

- Our data may be useful in order to plan and carry out adequate and timely surveillance programs and preventive measures;

- In BRCA mutated patients, especially after the first diagnosis, if preventive surgical interventions is deemed appropriate, our study add evidence that might suggest timing of intervention;

- Appropriate surveillance and prophylactic salpingo-oophorectomy are recommended for BC survivors with *BRCA* mutation;

- Genetic counselling in patients with *BRCA*-associated OC is more complex: it should address not only the subsequent risk of BC but also the consideration of this risk against the OC prognosis;

- The risk of BC in view of the mortality rates after advanced OC call into question the necessity of risk-reducing prophylactic mastectomy **for all** BRCA1/2 carriers with OC (The benefits of more aggressive preventive measures are expected to be small in terms of lives saved).

GRAZIE!