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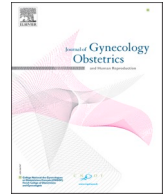
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Original Article

## Prognostic value of BRCA1 promoter methylation for patients with epithelial ovarian cancer

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### ABSTRACT

**Objective:** BRCA1 promoter methylation (BRCA1 $pm$ ) is suspected to alter prognosis of patients with epithelial ovarian cancer (EOC). We aimed to evaluate the prognostic impact of this epigenetic modification.

**Methods:** We conducted a retrospective, monocentric study from 11/2006 to 08/2018. Patients with EOC and available status concerning somatic BRCA1/2 mutation and BRCA1 $pm$  were included. Three groups were defined: patients without BRCA1/2 mutation or BRCA1 $pm$ , patients with BRCA1/2 mutation and patients with BRCA1 $pm$ . BRCA1/2 mutations were analyzed in current care settings by next-generation sequencing (NGS). BRCA1 $pm$  analysis was assessed and quantified from bisulfite converted DNAs using fluorescent methylation specific polymerase chain reaction (PCR) and fragment analysis. All patients signed a consent form and the study was authorized by a Personal Protection Committee. Descriptive statistics were used to describe groups. Multivariate analysis was performed using the logistic regression model and including the variables that could be known at the time of diagnosis and that were significant at univariate analysis. Survival was compared between the groups. Kaplan-Mayer curves were used to express the differences in survival that were compared using log rank tests.

**Results:** 145 patients were included: 95 (65.5 %) patients without BRCA1/2 mutation or BRCA1 $pm$ , 32 (22.1 %) patients with BRCA1/2 mutation, 18 (12.4 %) patients with BRCA1 $pm$ . Median survival was decreased in patients with BRCA1 $pm$ . Comparison of survival revealed a significant difference in overall survival ( $p = 0.0078$ ) with a worse prognosis for patients with a BRCA1 $pm$ .

**Conclusion:** BRCA1 $pm$  in patients with EOC is an independent factor associated with a decreased overall survival.  
**Synopsis:** BRCA1 promoter methylation in patients with epithelial ovarian cancer is an independent factor associated with a decreased overall survival.

### Introduction

With an incidence of approximately 65,000 cases per year, epithelial ovarian cancer (EOC) is the 7th most common cancer in women in Europe, and the 5th leading cause of cancer mortality [1]. All stages combined, EOC has a poor prognosis with a 5-year survival of 43 % [2] since it is often diagnosed at an advanced stage, defined by the presence

of peritoneal carcinomatosis [3]. First-line treatment is based on a combination of platinum-based chemotherapy and cytoreductive surgery (CRS), followed by maintenance treatment with bevacizumab and/or Poly (ADP-ribose) polymerase inhibitors (PARPi). A major prognostic factor is the absence of macroscopic residual disease after CRS [4–8].

Early identification of a BRCA 1 or 2 mutation in EOC patients, as

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well as characterization of genomic instability status (GIS) in non-mutated patients, is a new determinant factor in defining patient prognosis, particularly as these factors are associated with PARPi effectiveness.

The Cancer Genome Atlas (TCGA) integrated genomic study of 489 high-grade serous ovarian carcinomas found approximately 61 mutations per exome. *TP53* mutations were the most frequently somatic event (96 %) and 17 % of patients had germline mutations in *BRCA1/2*. In sporadic forms, a BRCA loss profile is observed with inactivation of the *BRCA1/2* genes by genetic (somatic mutations in 6 % of cases) or epigenetic (methylation of the *BRCA1* promoter in 11 % of cases) phenomena, resulting in chromosomal instability. In the TCGA study, recurrent genomic alterations outside of *TP53* and *BRCA* are rare, but an homologous recombination deficiency was found in approximately 50 % of cases [9].

Methylation of the *BRCA1* promoter is an epigenetic modification suspected to inactivate *BRCA1* gene and thus alter patient prognosis, but its clinical value remains uncertain. The objective of this study was to evaluate the prognostic impact of this *BRCA1* promoter methylation in a monocentric cohort of patients followed prospectively.

## Material and method

### Population

We conducted a retrospective, monocentric, study from 01/11/2006 to 31/08/2018 in the department of Gynecological Oncological and Breast Surgery in collaboration with the Unit of Pharmacogenetics and Molecular Oncology, at the Georges Pompidou European Hospital in Paris, France. Our department is certified for the surgical management of advanced EOC by the European Society of Gynecologic Oncology (ESGO) and the laboratory is certified by an independent organism for somatic oncogenetics (Cofrac 15,189).

Patients with histologically confirmed EOC and with information available concerning somatic *BRCA1/2* mutation and *BRCA1* promoter methylation status were included. Three groups of patients were defined in order to compare prognosis according to observed molecular profile at diagnosis:

- Patients without *BRCA1/2* mutation or *BRCA1* promoter methylation
- Patients with *BRCA1/2* mutation
- Patients with *BRCA1* promoter methylation

### Data collected

The following data was collected, clinical characteristics (age, body mass index (BMI), American Society of anesthesia (ASA) score, notable medical and surgical history, pre-disposing genetic mutations, menopausal status), tumor characteristics (histological type, CA 125, International Federation of Gynecology and Obstetrics (FIGO) stage), oncological treatment (adjuvant chemotherapy, associated targeted therapies), surgical parameters (peritoneal carcinomatosis score (PCI), extent of surgery, possible tumor residue) and oncological outcomes (progression-free survival (PFS) and overall survival (OS)).

### Objective

Our primary objective was to evaluate the prognostic impact of methylation of *BRCA1* promoter in a monocentric cohort of patients followed prospectively.

### Patient management

Therapeutic management was decided for each patient during multidisciplinary tumor boards that included surgeons, oncologists,

radiologists, pathologists, and nuclear medicine physicians. All patients had an initial evaluation (computed tomography (CT) and laparoscopy) with histological confirmation of EOC. Surgery generally included a hysterectomy with bilateral adnexectomy, removal of all visible peritoneal lesions, omentectomy and lymphadenectomy if indicated according to the conclusion of the LION study [10] and the French guidelines [11].

After surgery, patients had platinum-based adjuvant chemotherapy and targeted therapies (bevacizumab, PARP inhibitors) if indicated by the tumor board.

### Molecular biology protocol

Tumor samples were stored at the Biological Resources center and Tumor Bank Platform (PRB-HEGP BB-0033–00,063) before nucleic acids extraction.

### Nucleic acid extraction/quantification from tumor

DNAs were extracted on a Maxwell® RSC Instrument (Promega, France) using Maxwell® RSC DNA FFPE Kit (Promega, France) for FFPE samples, quantified by Qubit Fluorometric Quantitation using the Qubit dsDNA BR Assay Kit (Life Technologies–Thermo Fisher Scientific, Saint Aubin, France) and stored at  $-20^{\circ}\text{C}$  before testing.

### Next-generation DNA sequencing (NGS)

BRCA mutations were analyzed in current care settings by NGS using the OncoPrint™ BRCA Research Assay, Chef Ready procedure (Thermo Fisher Scientific). Sequences were run on Ion PI Chips Kit v3 on the Ion Proton System. FASTQ were first processed and aligned to the human genome (hg19) using the Ion-Torrent Suite v5.0.4; variant call files were loaded on a galaxy platform and annotated using the Safir2report tool (<https://github.com/OvoiDs/IonTorrentReport>). Coverage depth data were used to detect gene deletion.

*BRCA1* methylation analysis was assessed and quantified from bisulfite converted DNAs using fluorescent methylation specific PCR and fragment analysis. For a specific CpG site, 2 couples were designed with a reverse primer localized on CpG site and a forward outside of any CpG site. R primers were HEX tagged for methylated fragments and FAM tagged for non-methylated fragments. Migration was performed on ABI3730xl sequencer data were analyzed with Genemapper software (ThermoFisher diagnostics).

For *BRCA1*, CpG regions described to be implicated in transcriptional regulation were selected on promoter (Table 1). Sensibility and specificity were assessed by serial dilutions of methylated DNA using commercially available 100 % and 0 % methylated DNA (Fig. 1). *BRCA1* promoter methylation was defined by at least one positive region.

### Ethics

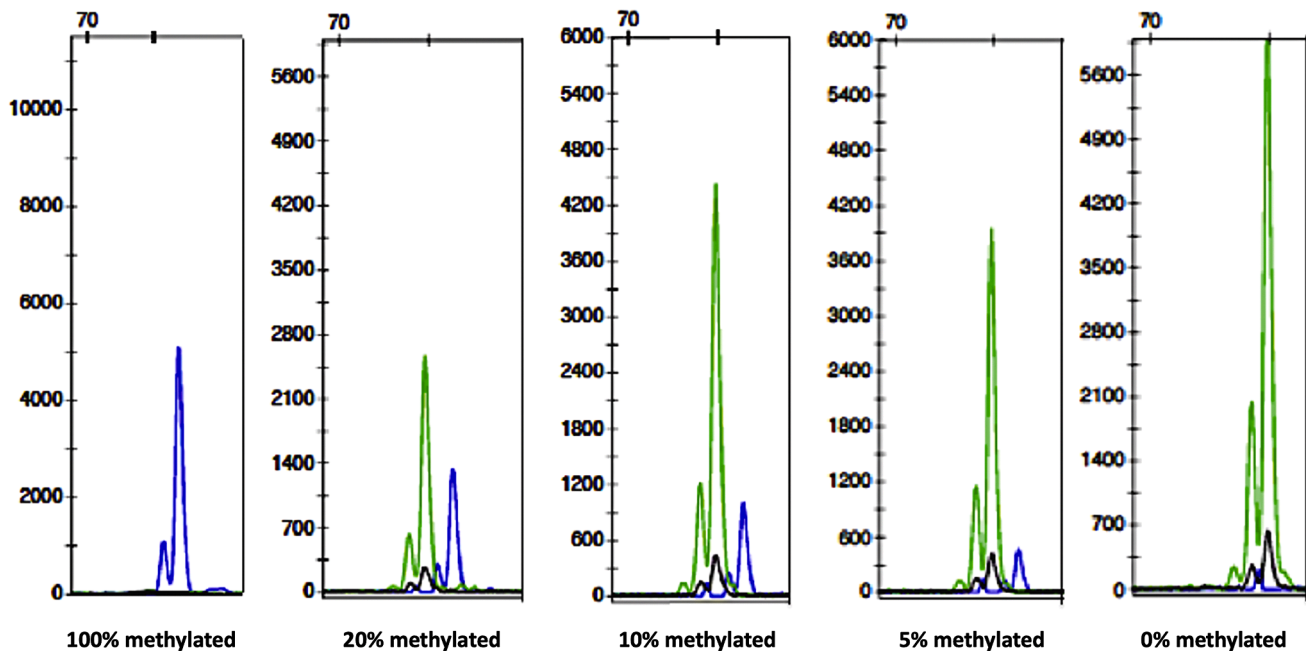
All patients included in the study signed a consent form to collect data used in routine care for the research. The use of this consent form was authorized by a Personal Protection Committee (“OncoHEGP” CPP :2012–08–09 MS4). Anonymized data were collected on a secure server and the database was declared to the competent French authorities (ChirGyn\_BaseOvaire\_HEGP, CNIL id :1,922,081).

### Statistical analysis

Basic descriptive statistics were used to describe groups. Categorical variables were reported as frequencies and percentages. Continuous variables were reported as mean and standard deviation (SD) or median and range. A Student-t-test and chi2 test were used to compare the continuous and categorical values, respectively. To compare the variables across groups, the Student’s t-test and ANOVA were used for normally distributed data, the Mann–Whitney U test for non-parametric data, and the Chi-Square test for categorical data. Statistical significance

**Table 1**  
Primers used for BRCA1 promoter methylation detection.

Gene	Mix Primer	Orientation	Specificity	Oligonucleotides	CpG in amplicon	Amplicon size (base pairs)
BRCA1	1	Forward	Methylated	CGATTGCGCGCGGTGAGTTCG	8	152
		Forward	Unmethylated	TGATTGTGTGGTGTGAGTTTGT		151
		Reverse	Universal	CACTTAAACCCCTATCCCT		
	2	Forward	Methylated	TTTTGGTTTTCGTGGTAAC	8	120
		Forward	Unmethylated	TTTTTTGGTTTTTGTGGTAAT		122
		Reverse	Universal	TATCTAAAAAACCCACAACCTATC		
	3	Forward	Methylated	TTAATTTAGAGTTTCGAGAGAC	3	93
		Forward	Unmethylated	AATTTAGAGTTTTGAGAGAT		91
		Reverse	Universal	CTAAACAACAACCTCTCAAAATA		



**Fig. 1.** Sensibility and specificity. Example of results showing serial dilution of 100 % methylated DNA in unmethylated DNA for BRCA1 mix « 3 » assessed by fragment analysis and migration in an ABI 3730xl genetic analyzer (Thermo Fisher Scientific). Methylated pic (blue), unmethylated (green).

was set at  $p < 0.05$  for a bilateral test.

Multivariate analysis was performed using the logistic regression model and including the variables that could be known at the time of diagnosis and that were significant at univariate analysis. A P-value of 0.05 was considered significant.

The RFS and OS were compared between the groups of patients. RFS and OS were respectively defined as the time from the date of the initial diagnosis to tumor recurrence or death, of any cause. A cox survival model was used to search variables associated with RFS and OS. A Kaplan Mayer curve was used to graphically express the differences in RFS and OS. A log rank test compared the two curves.

Analysis was carried out using an Excel database and the R software (The CRAN Project, Version 3.0).

## Results

### Patient characteristics

One hundred and forty-five patients with EOC and for whom we had information regarding BRCA mutation status and BRCA1 promoter methylation status were included with the following repartition in the three groups:

- Patients without BRCA 1/2 mutation or BRCA1 promoter methylation ( $n = 95$ )
- Patients with BRCA 1/2 mutation ( $n = 32$ )
- Patients with BRCA 1 promoter methylation ( $n = 18$ )

Main characteristics of the population are detailed in Table 2. There was no difference between the three groups concerning patient characteristics. Briefly, mean age ranged from 60 to 64 years, depending on the group, and body mass index from 24 to 25.5. The most frequent histological type was high-grade serous carcinoma (87.5 % to 100 %). The disease was most often diagnosed at an advanced stage (stage 3–4 of the FIGO classification in 77.8 % to 93.8 %). The majority of patients underwent cytoreductive surgery with no macroscopic residual disease (72.6 % to 87.5 %). Almost all patients received chemotherapy (93.8 % to 100 %).

### Survival in case of BRCA1 promoter methylation

Follow-up was similar in the three groups (median 44 +/- 30.6, 31.5 +/- 28.1 and 41 +/- 26.7 months for BRCA mutation, BRCA methylation and no mutation respectively). During this follow-up period, the median times from diagnosis to recurrence were 26 (10–114), 16 (5–39), 21 (0–106) months for BRCA mutation, BRCA methylation and no mutation respectively with no significant difference between the groups ( $p$

**Table 2**  
Patient's characteristics.

	BRCA 1/2 mutation n = 32	BRCA1 promoter methylation n = 18	No mutation or methylation n = 95	P-value	P-value (ANOVA)
<b>Age (years)</b>				* 0.38	0.11
Mean ± SD	60.0 ± 10.8	62.2 ± 7.0	64.2 ± 13.0	\$ 0.08	
Median (range)	61.0 (32.0 - 81.0)	62.0 (50.0 - 76.0)	67.0 (26.0 - 87.0)	# 0.34	
<b>BMI (kg/m<sup>2</sup>)</b>				* 0.43	0.21
Mean ± SD	25.5 ± 5.7	24.2 ± 5.3	24.0 ± 5.4	\$ 0.23	
Median (range)	23.5 (16.3 - 39.4)	24.0 (18.4 - 39.0)	22.5 (15.6 - 41.1)	# 0.92	
<b>Menopause</b>				* 1	0.57
n (%)	26 (81.3)	16 (88.9)	70 (73.7)	\$ 0.63	
				# 0.61	
<b>ASA score</b>					0.95
n (%)	3 (9.4)	1 (5.6)	7 (7.4)	* 0.76	
1	10 (31.3)	7 (38.9)	27 (28.4)	\$ 0.86	
2	3 (9.4)	1 (5.6)	5 (5.3)	# 0.91	
3	1 (3.1)	0 (0)	1 (1.1)		
4	15 (46.9)	9 (50)	56 (58.9)		
NA					
<b>Tumor histological type</b>					0.51
n (%)	28 (87.5)	18 (100.0)	83 (87.4)	* 1	
High-grade Serous	1 (3.1)	0 (0)	8 (8.4)	\$ 0.15	
Low-grade Serous	0 (0)	0 (0)	2 (2.1)	# 1	
Low-grade Endometrioid	1 (3.1)	0 (0)	0 (0)		
Undifferentiated	2 (6.2)	0 (0)	2 (2.1)		
NA					
<b>CA125</b>				* 0.33	0.92
Mean ± SD	1475.1 ± 2006.0	2195.8 ± 2623.5	1387.0 ± 2411.9	\$ 0.84	
Median (range)	700.0 (6.0 - 8557.0)	847.0 (23.0 - 8609.0)	553.0 (8.0 - 16,230.0)	# 0.25	
<b>Initial FIGO</b>					0.09
n (%)	1 (3.1)	1 (5.6)	2 (2.1)	* 0.31	
1	0 (0)	2 (11.1)	4 (4.2)	\$ 0.49	
2	19 (59.4)	10 (55.6)	69 (72.6)	# 0.06	
3	11 (34.4)	4 (22.2)	17 (17.9)		
4	1 (3.1)	1 (5.6)	3 (3.2)		
NA					
<b>Initial PCI</b>				* 0.83	0.23
Mean ± SD	13.2 ± 11.5	14.0 ± 9.8	16.3 ± 9.1	\$ 0.23	
Median (range)	10.5 (0.0 - 34.0)	13.0 (0.0 - 30.0)	16.0 (0.0 - 34.0)	# 0.47	
<b>CC score</b>					0.34
n (%)	28 (87.5)	15 (83.3)	69 (72.6)	* 0.15	
CC0	2 (6.3)	0 (0)	8 (8.4)	\$ 0.53	
CC1	1 (3.1)	3 (16.7)	7 (7.4)	# 0.25	
CC2	0 (0)	0 (0)	0 (0)		
CC3	1 (3.1)	0 (0)	11 (11.6)		
NA					
<b>Chemotherapy</b>				* 1	0.58
n (%)	30 (93.8)	18 (100)	92 (96.8)	\$ 1	
				# 1	
<b>Peroperative complication</b>				* 0.11	0.39
	4 (12.5)	3 (16.7)	6 (6.3)	\$ 0.52	
				# 0.44	

\*: p-value for comparison « BRCA1/2 mutation » versus « BRCA1 promoter methylation ».

#: p-value for comparison « BRCA1/2 mutation » versus « No mutation or methylation ».

\$: p-value for comparison « BRCA1 promoter methylation » versus « No mutation or methylation ».

BMI: Body Mass Index. ASA: American Society of Anesthesiologists.

PCI: Peritoneal Carcinomatosis Index. CC score: Completeness of Cytoreduction score.

= 0.66). The median times from diagnosis to death was higher in the mutation group in comparison with the methylation group, with 44 (1–114) months versus 31.5 (5–134) months respectively ( $p = 0.04$ ), and it was also higher in the group without mutation or methylation in comparison with the methylation group, with 41 (0–149) months versus 31.5 (5–134) months respectively ( $p = 0.04$ ).

The comparison of survival between the “BRCA1 promoter methylation” group, the “BRCA 1/2 mutation” group and the “No mutation or methylation” group by the Log rank test revealed a significant difference in OS with a worse prognosis for patients with a BRCA1 promoter

methylation ( $p = 0.0078$ ). The comparison is in favor of a worse PFS for this group with a p value at the limit of significance ( $p = 0.05$ ) (Fig. 2).

To determine the prognostic value of BRCA1 promoter methylation, we compared it in a multivariate Cox model to other presumed prognostic factors ( $p < 0.05$  in univariate analysis). Stage according to the FIGO classification and age were not associated with OS in univariate analysis. There was a prognostic impact of BRCA1 promoter methylation while this factor was found to be the only factor associated with a decrease in OS in multivariate analysis ( $p = 0.02$ ) (Table 3).

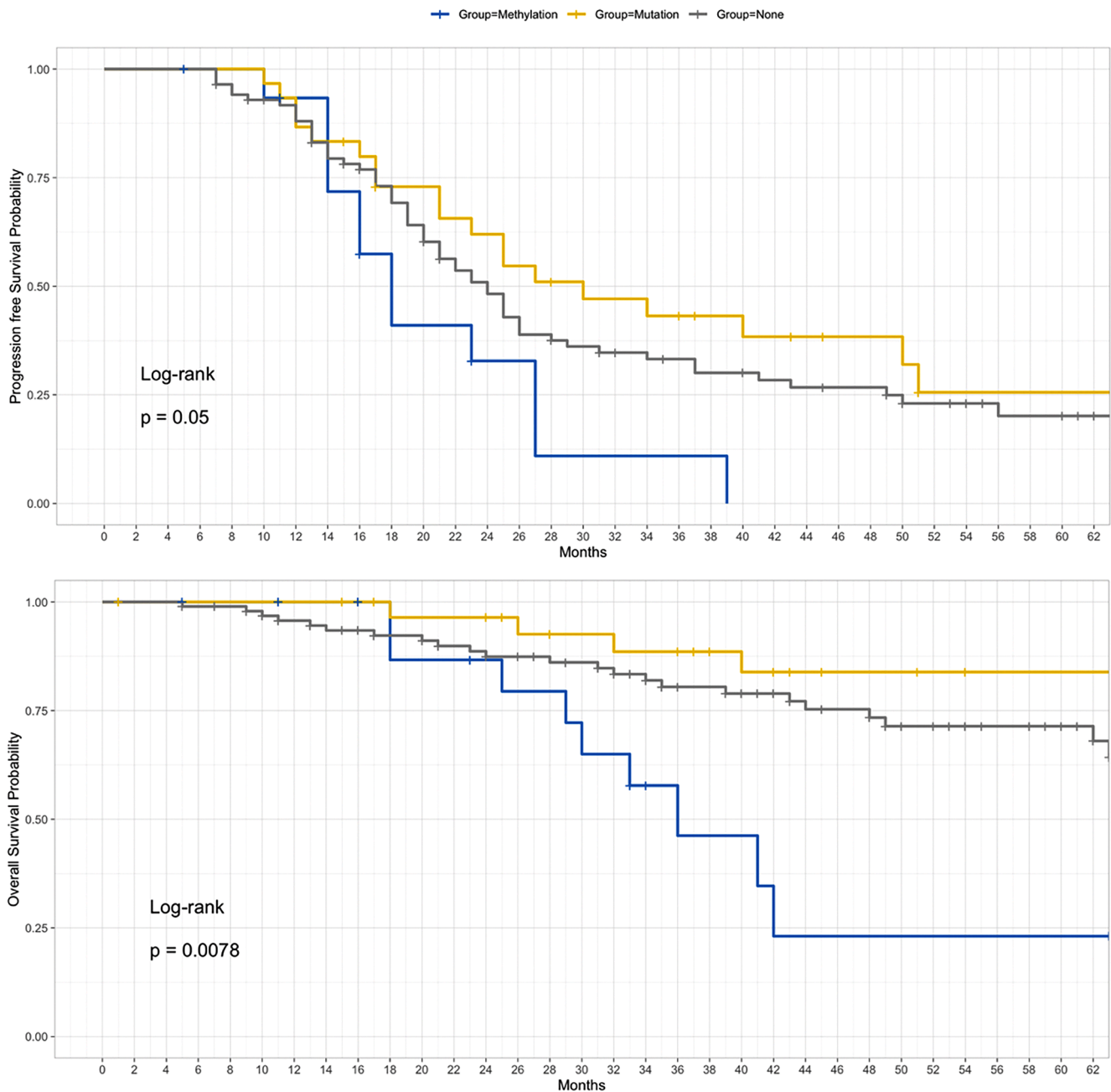


Fig. 2. Survival according to status regarding BRCA1/2 mutation and BRCA1 promoter methylation.

**Discussion**

In this study, we observed that BRCA1 promoter methylation in patients with EOC is an independent factor associated with a decreased overall survival.

In the TCGA study on 489 high-grade serous EOC, an inactivation of the BRCA1/2 genes by methylation of the BRCA1 promoter was found in 11 % of cases [9]. In another study on 332 patients with EOC conducted by Bernards et al., BRCA1 promoter methylation was detected in 22 carcinomas (6.6 %). The authors stated that patients with BRCA1 promoter methylated carcinomas shared clinical characteristics with patients with BRCA1-mutated carcinomas including younger age and predominantly high-grade serous histology. However, they observed that, unlike mutation, RAD51C and BRCA1 promoter methylation were not associated with improved survival or greater sensitivity to platinum

chemotherapy [12]. This is consistent with our experience. On 145 patients studied in this study, BRCA1 promoter methylation was detected in 18 carcinomas (12.4 %) and the prognosis of this subgroup was poorer. The TCGA study also revealed EMSY amplification (8 % of cases), PTEN deletion (7 % of cases), RAD51C hypermethylation (3 % of cases), ATM/ATR mutation (2 %) or other mechanisms leading to a defect in homologous recombination [9]. We do not routinely look for these mutations in our center, as they are rare and the evidence for their therapeutic impact is currently limited.

Nevertheless, the data in the literature remain contradictory regarding the prognostic role of BRCA1 promoter methylation, probably because of heterogeneity regarding the impact of this epigenetic event, particularly on genomic instability. Thus, in the meta-analysis of Kalachand et al., among 2636 tumors, 430 (16.3 %) were BRCA1-methylated. BRCA1 methylation was associated with younger age and

**Table 3**

Multivariate analysis to determine prognostic value of BRCA1 promoter methylation concerning overall survival.

Overall survival		Univariate			Multivariate		
		Hazard ratio	95 % confidence interval	p-value	Hazard ratio	95 % confidence interval	p-value
Mutation or methylation status	-None	Reference			Ref		
	-Methylation	2.61	1.23–5.56	<b>0.01</b>	4.07	1.25–13.3	<b>0.02</b>
	-Mutation	0.66	0.28–1.54	0.3	0.91	0.26–3.18	0.9
CC score	-CC0	Ref			Ref		
	-CC1	2	0.68–5.85	0.2	1.66	0.18–15.3	0.6
	-CC2	4.06	1.50–11	<b>0.006</b>	1.06	0.21–5.42	0.9
Type of surgery	-Initial	Reference					
	-Interval	1.52	0.71–3.28	0.3	0.73	0.18–2.93	0.7
	-None	4.20	1.52–11.6	<b>0.006</b>	4.5	0.9–10	0.65
PCI		1.07	1.03–1.12	<b>0.002</b>	1.05	0.98–1.13	0.2
CA 125		1.01	1–1.02	<b>0.01</b>	1	1–1	0.4

PCI: Peritoneal Carcinomatosis Index. CC score: Completeness of Cytoreduction score.

advanced-stage, high-grade serous EOC, but there were no survival differences between BRCA1-methylated and non-BRCA1-methylated patients (median PFS = 20.0 vs 18.5 months, hazard ratio [HR] = 1.01, 95 % CI = 0.87 to 1.16;  $P = 0.98$ ; median OS = 46.6 vs 48.0 months, HR = 1.02, 95 % CI = 0.87 to 1.18;  $P = 0.96$ ). Authors stated that BRCA1 promoter methylation displayed no survival advantage over BRCA1/2 wild-type (BRCAwt) non-BRCA1-methylated EOC, and that method used to define BRCA1 promoter methylation may impact the observed prognosis, suggesting that refining these assays may allow better identification of cases with silenced BRCA1 function and improved patient outcomes [13]. We agree that the technique used to define BRCA1 promoter methylation should be discussed because it impacts the functional effect of the methylation, the allocation of patients to a given group and thus the prognostic analysis. In our series, we considered that BRCA1 promoter methylation was significant for a methylation ratio higher than 5 %, but this ratio was higher than 25 % in 75 % of patients. It is also important to specify the timing of the test in the therapeutic sequence as this may impact the result and its interpretation, depending on whether the BRCA1 promoter methylation test was performed at diagnosis, after neoadjuvant chemotherapy or after surgery, or their possible relapse.

Although the prognostic impact of BRCA1 promoter methylation is debated, this status is associated with greater genomic instability and homologous recombination deficiency making patients eligible for PARPi. In the study by Hodgson et al. about the long-term outcome of candidate biomarkers of sensitivity to olaparib in BRCAwt tumors, authors observed that a higher median Myriad MyChoice® HRD score was observed in BRCA mutated and BRCAwt tumors with BRCA1 methylation. They concluded that these patients may constitute molecularly identifiable and clinically relevant population who derive treatment benefit from olaparib similar to patients with BRCA mutation [14].

These results are consistent with those presented in the publication by Blanc-Durand et al. about 100 patients among which 11 % harbored a deleterious BRCA1/2 mutation, and 19 % of BRCA1/2 wild-type patients had BRCA1 promoter methylation. All of the methylated tumors were classified deficient for homologous recombination (HRD) with the genomic-instability score (GIS) by MyChoice CDx (Myriad Genetics). Mean GIS was 61.5 for BRCA mutated patients 66.4 for BRCA1 promoter high-methylated patients, 58.9 for BRCA1 promoter low-methylated patients and 33.3 for BRCA1/2 wild-type unmethylated patients. Low methylation levels detected in samples previously exposed to chemotherapy appeared to be associated with poor outcome. Authors concluded that patients with high levels of BRCA1 promoter methylation were very likely to have high GIS and therefore represent good candidates for PARPi treatment [15].

In the PAOLA-1/ENGOT-ov25 trial [16], promoter methylation was identified in 67 (12.9 %) samples for BRCA1 and 25 (4.8 %) for RAD51C

(4 were methylated on both genes). Methylation and BRCA mutation were mutually exclusive except for 3 samples. Mean GIS scores were 62.5 [59.6–65.5]; 59.4 [57.2–61.5]; 54.2 [50.5–57.8]; 23.4 [21.6–25.2] for BRCA1 or RAD51C methylation group, BRCA mutation group, no-mutation/no-methylation HRD+ group, and HRP (proficient) tumors respectively. Among tumors with promotor methylation, 92 % (66/72) were GIS positive (>42). The mean GIS score of tumors with promotor methylation were significantly higher than that of no-mutation/no-methylation HRD+ samples ( $p = 0.009$ ). Authors reported that methylated BRCA1/RAD51 tumors are HRD+ and provide to ovarian cancer patients a similar clinical benefit of olaparib/bevacizumab association as patients with HRD+ and no-mutation/no-methylation tumors. They concluded that methylation assessment may represent a rapid and cost-effective tool, which coupled with BRCA1–2 somatic testing allows the identification of the majority (81 %) of HRD+ patients.

It is possible that the poor prognosis observed in our study for the group of patients with BRCA1 promoter methylation is linked to the fact that this is a relatively old cohort and patients have not been routinely exposed to PARPi. Maintenance treatment with PARPi could improve the prognosis of this subgroup of patients. Thus, while the indications for PARPi are expanding, our results provide information on the prognosis in the absence of PARPi maintenance treatment of this patient population, which is often HRD+ but whose prognosis appears to be worse than that of other patients with homologous recombination deficiency.

Further research is needed to refine the criteria for defining BRCA1 promoter methylation in order to homogenize the definitions and functional interpretations of this observation according to the natural history of the disease.

## Conclusion

In this study, we observed that BRCA1 promoter methylation is an epigenetic phenomenon of interest because it is associated with a worse prognosis but could be an indication for the prescription of targeted therapy, in particular PARP inhibitors, given its inactivating action on the BRCA1 gene. This epigenetic modification, not systematically sought in conventional panels, may result in higher genomic instability scores than in the population of non-mutated, non-methylated patients. This is an additional argument for systematically defining the genomic instability score for all patients managed for ovarian cancer, and thus guiding the prescription of maintenance treatments.

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None.

### CRedit authorship contribution statement

**Henri Azais:** Conceptualization, Visualization, Methodology, Data curation, Formal analysis, Writing – review & editing. **Simon Garinet:** Formal analysis, Writing – review & editing. **Louise Benoit:** Formal analysis, Writing – review & editing. **Julie de Jesus:** Data curation. **Mohamed Zizi:** Data curation. **Samuel Landman:** Data curation. **Anne-Sophie Bats:** Formal analysis. **Valérie Taly:** . **Pierre Laurent-Puig:** Formal analysis. **Hélène Blons:** Conceptualization, Visualization, Methodology, Formal analysis, Writing – review & editing, Supervision.

### Declaration of competing interest

No conflicts of interest were disclosed by the authors.

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