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► To cite this version:

Mateo Sanchis-Borja, Vincent Fallet, Elisabeth Fabre, Marie Wislez, Stéphane Culine, et al.. Characterization of lung cancers in patients with BRCA germline variants: A multicenter series. *Lung Cancer*, 2022, 173, pp.67-70. <10.1016/j.lungcan.2022.09.002>. <hal-03959753>

HAL Id: hal-03959753

<https://hal.science/hal-03959753v1>

Submitted on 8 Feb 2023

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Characterization of lung cancers in patients with BRCA germline variants: A multicenter series

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ARTICLE INFO

Keywords:

Lung cancer

BRCA1

BRCA2

Germline variants

Genetic susceptibility to cancer

ABSTRACT

Introduction: *BRCA1* and *BRCA2* (Breast Cancer susceptibility genes) are two tumor-suppressor genes associated with the hereditary breast and ovarian cancer susceptibility syndrome. Recent studies also suggest an increased lung adenocarcinoma risk in carriers.

Methods: We conducted a multi-center retrospective study in 18 different French pulmonology and/or oncology departments on medico-administrative and clinical data prospectively collected in the Clinical Data Warehouse (CDW) of Greater Paris University Hospitals (Assistance Publique-Hôpitaux de Paris, AP-HP). Clinical characteristics and outcomes of patients with LC and a previously known *BRCA1/2gl* variant were retrospectively evaluated.

Results: 17 patients with LC and known *BRCA1/2gl* variant were included. Patients were most women, former smokers with localized disease and *BRCA2* variants. All LC were adenocarcinoma. For patients with medical history of cancer, median time from the first cancer in the *BRCA* spectrum and the LC occurrence was 20 years. Median disease-free survival (DFS) and overall survival (OS) in localized tumor (Stage I and II) was not reached and 78.6 months, respectively. In advanced cancer (Stage III and IV) median progression free survival was 9.7 months and median OS was 17.8 months. Univariate OS and DFS/PFS analyses by *BRCA* status did not find significant differences.

Conclusion: Results seem to show particular LC features in carriers of *BRCA2* variants: adenocarcinoma subtype, woman, former or non-smoker.

1. Introduction

A proportion of lung carcinomas (LC) occurs in non-smokers. Along with environmental factors (radon, pollution), genetic factors are a major contributor. There are two established major lung cancer susceptibility syndromes: Li-Fraumeni, in which carriers of germline pathogenic variants (PV) in the *TP53* tumor-suppressor gene have an increased risk of a variety of cancers, often starting at a young age,

including LC [1] and *EGFR*-associated susceptibility syndrome, in which carriers of the *EGFR* T790M activating variant have an increased LC risk during adulthood [2]. The *BRCA1* and *BRCA2* (Breast Cancer susceptibility genes) are two tumor-suppressor genes localized respectively on chromosome 17 and 13 [3]. Both *BRCA1* and *BRCA2* proteins are critical to the repair of double-strand DNA breaks (DSBs) by a process called homologous recombination repair (HRR), a form of DNA repair that uses a homologous DNA sequence to guide repair at the DSB. In HRR

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deficient cells, non-conservative forms of DNA repair predominate, leading to DNA alterations/mutations that can foster cancer initiation or progression [3,4]. *BRCA1/2* germline (GL) pathogenic variants (PV, formerly called mutations) (*BRCA1/2glpv*) are associated with the hereditary breast and ovarian cancer susceptibility syndrome (HBOC) [5]. Other *BRCA* germline variants have been described but are considered either as benign or of unknown significance. *BRCA1/2glpv* carriers are also at increased risk of prostate and pancreatic cancer [6]. As for lung cancer (LC), recent studies hint at an association, especially for *BRCA2*. For example, *BRCA2glpv* were the most commonly observed cancer susceptibility variants among 1794 cases of LC from China [7]. There was an excess of PV in cases compared to controls, resulting in an OR of 5.18 (95 %CI 2.34–11.33). In addition, Reckamp et al observed that LC development was accelerated by 12 years in *BRCA2glpv* women carriers (95 %CI, 2.5–20.6) [8]. The main objective of the present work was to describe clinical and outcome characteristics of a series of LC patients harboring *BRCA1/2gl*.

2. Methods

We conducted a multi-center retrospective study on medico-administrative and clinical data prospectively collected in the Clinical Data Warehouse (CDW) of Greater Paris University Hospitals (Assistance Publique-Hôpitaux de Paris, AP-HP). Patients records from 18 different French pulmonology and/or oncology departments with a diagnosis of LC and a previously known *BRCA1/2gl* variant because of a personal or family history of cancer were anonymously retrieved from the CDW through diagnosis code (C34 for lung cancer) and keywords (*BRCA*, *BRCA1*, *BRCA2*) for the January 2012 to December 2018 period. Each file was anonymously reviewed to ensure the diagnosis of LC and the germline nature of the *BRCA* variants. All data were collected retrospectively from anonymized medical records.

The following clinical information was collected: demographics, smoking history, tumor characteristics, *BRCA* variant, previous treatment lines and clinical outcome.

The study was approved by the ethics committee of the CDW (CSE

project-18–40). The study was purely academic and was not funded by industry.

3. Results

During the study period, a total of 9850 patients with confirmed LC were retrieved, among whom 17 had a known *BRCA1/2gl* variant (Table 1). Median age at diagnosis of LC was 55 years (32–75 years) with most women (12/17, 71 %), former smokers (11/17, 65 %) with an average of 20 pack years. Most patients had localized disease (13/20, 65 %). *BRCA2* and *BRCA1* variants were identified in 12 (71 %) and 5 (29 %) patients, respectively. Two patients (12 %) had first degree family history of LC and 71 % (12/17) had first degree family history of a *BRCA* spectrum cancer (breast, ovarian, prostate, pancreas). For patients with medical history of cancer, median time from the first *BRCA* spectrum cancer and LC was 20 years; a second LC also occurred in 3 patients (delay, 13–114 months). All LC were adenocarcinoma among which a somatic mutation was identified in 8 (42 %) i.e. *KRAS* (n = 6), *EGFR*, *TP53* and *C-Myc*, one each. Fig. 1 illustrates individual efficacy of successive treatments, including platinum-based chemotherapy and PARP-inhibitors. With a median follow-up time of 34 months (2–204), median disease-free survival (DFS) and overall survival (OS) in localized tumor (Stage I and II) was not reached and 78.6 months, respectively. In advanced cancer (Stage III and IV) median progression free survival (PFS) was 9.7 months and median OS was 17.8 months. Univariate OS and DFS/PFS analyses by *BRCA* status did not find significant differences. Precise *BRCA1/2* variant classification according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendation [9] was available in 11/17 patients including 7 known PV, 2 variants of unknown significance and 2 variants classified as benign.

4. Discussion

In our series of *BRCA1/2gl* variant carriers, a particular presentation with young former or non-smokers developing lung adenocarcinoma

Table 1

M/F: male/female; PY: pack year; *BRCA*: BREast CANcer susceptibility genes; NA: not available; PD-L1: programmed cell-death protein-1 ligand; *KRAS*: Kirsten rat sarcoma viral oncogene homolog; *BRAF*: v-Raf murine sarcoma viral oncogene homolog B. PFS: progression free survival; OS: overall survival.

Patient (M/F)	History of cancer	First degree familial history of cancer	Tobacco (PY)	BRCA mutation	Lung Cancer		Somatic molecular alterations	Second localisation	Relapse	Survival
					Age at diagnosis	Stage				
5 (F)	Colon	Ovarian	0	<i>BRCA 1</i>	50	Stage I	0	No	No	PFS (median): not reached OS (median): 78.6 months
7 (F)	Skin	Ovarian x2	20	<i>BRCA 2</i>	75	Stage I	0	No	No	
8 (F)	Breast	0	60	<i>BRCA 1</i>	63	Stage I	0	Yes	No	
9 (M)	Prostate	Breast	35	<i>BRCA 2</i>	72	Stage I	<i>KRAS</i>	No	Yes	
10 (F)	Breast	Breast	45	<i>BRCA 2</i>	55	Stage I	<i>KRAS</i>	No	Yes	
13 (F)	Breast, Pancreas	Breast, Prostate	30	<i>BRCA 1</i>	66	Stage I	0	No	No	
1 (F)	0	Breast, Pancréas	8	<i>BRCA 2</i>	44	Stage II	<i>EGFR</i>	No	Yes	PFS (median): 9.7 months OS (median): 17.8 months
11 (F)	0	Breast, Lung	20	<i>BRCA 2</i>	46	Stage II	0	Yes	No	
12 (F)	Breast	Breast, Lung	20	<i>BRCA 2</i>	45	Stage II	<i>KRAS</i>	No	No	
16 (F)	Breast	Melanoma	3	<i>BRCA 2</i>	67	Stage II	<i>KRAS</i>	No	Yes	
4 (M)	0	Pancreas	25	<i>BRCA 2</i>	44	Stage III	0	No	Yes	
6 (F)	Breast	0	0	<i>BRCA 1</i>	59	Stage III	0	No	NA	
14 (F)	Breast	Breast, Ovarian	0	<i>BRCA 1</i>	56	Stage III	0	Yes ^b	No	PFS (median): 9.7 months OS (median): 17.8 months
2 (M)	0	Colon	30	<i>BRCA 2</i>	40	Stage IV	<i>TP53</i> , <i>C-Myc</i>	No	Yes	
3 (F)	Breast	Breast	0	<i>BRCA 2</i>	66	Stage IV	0	No	Yes	
15 (M)	0	Breast	20	<i>BRCA 2</i>	44	Stage IV ^a	<i>KRAS</i>	No	Yes	
17 (M)	Testicle	0	18	<i>BRCA 2</i>	32	Stage IV	<i>KRAS</i>	No	Yes	

^a Oligo-metastatic patient; ^b Stereotactic radiotherapy on suspicious contralateral nodule > 12 months after first cancer.

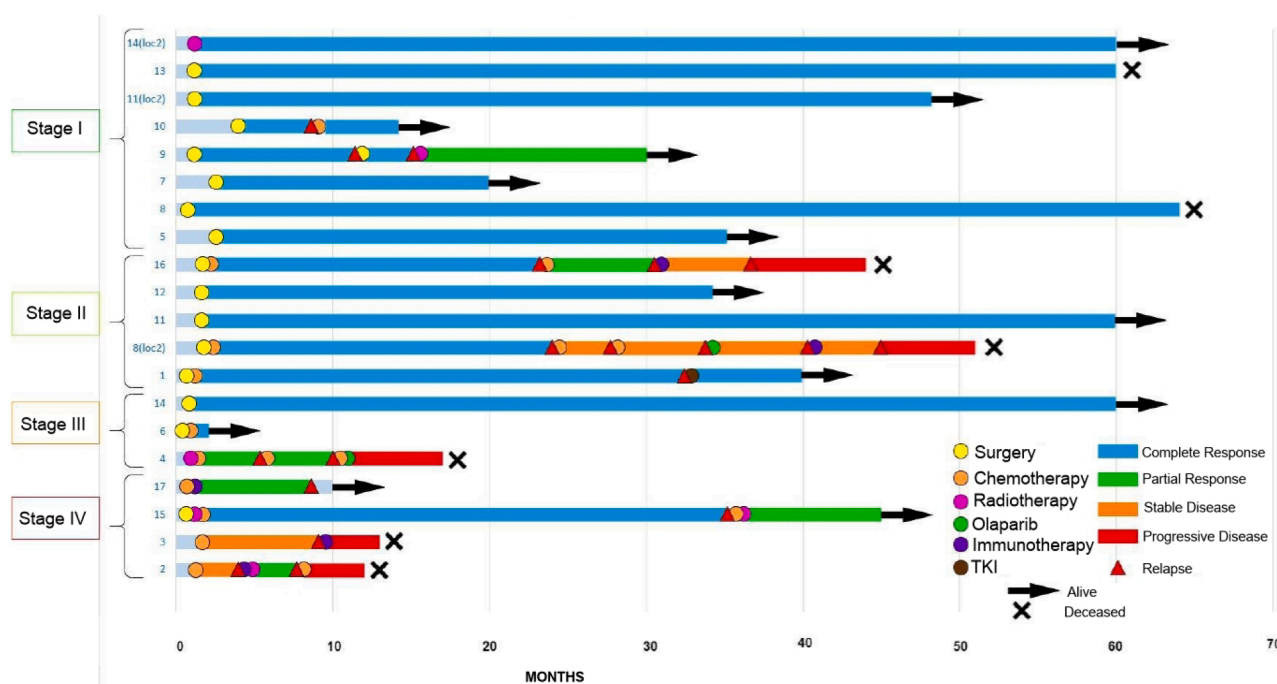


Fig. 1. Representation of treatment modality (colored circles), treatment efficacy (colored bands), disease free survival (for surgically resected patients) or progression-free survival and overall survival for each of the 20 *BRCA1/2gl* variant carrier's patients with lung cancer. Patients 8, 11 and 14 and second locations for which the individual course of treatment are shown separately. Overall survival duration > 65 months are not shown in this figure. TKI: Tyrosine Kinase Inhibitor; Loc 2: second location.

emerges. Frequency of *BRCA1/2gl* variants in our LC cohort was 0.2 %. Our design does not allow for an estimate of the prevalence of *BRCAglp* among LC and there is a selection bias. The population included in our cohort had a *de facto* known *BRCA1/2gl* variant prior to the LC diagnosis. These patients thus had a personal or family history of cancer that triggered germline genetic screening. To obtain a reliable prevalence, germline *BRCA* analysis by next-generation sequencing should have been performed on all LC patients. Regarding the women predominance, it has certainly been caused by ascertainment bias. Indeed, women are more likely to have *BRCA1/2* germline testing since the main cancers associated with these two genes are female cancers.

Studies other than the two presented in the introduction [7,8] have found an unusually high prevalence of *BRCA1/2gl* variants among LC patients. In a national Chinese multicenter retrospective study conducted in advanced stage (stage III-IV) non-small cell lung cancer (NSCLC), Hu et al [10] found a 1.03 % (64 of 6220 participants) prevalence of *BRCA1/2glp* which was higher than the estimated frequency in East Asians (0.2 %) [11]. In a recent cross-sectional study including 7768 LC patients, the prevalence of *BRCA2glp* [12] was 0.66 %. The SAFIRO2-Lung trial [13] is a French multi-center, open-label, randomized, phase II adaptive trial investigating untreated advanced NSCLC wild-type for *EGFR* and *ALK*. In this study, 8 (2.1 %) among the 379 patients evaluated by next generation sequencing had a *BRCA1/2gl* variant including 2 PV and 6 variants of undetermined significance. Sang et al. [14] performed whole exome sequencing in a homogenous population including 1461 LC cases and 1316 controls and found a gene-level association of *BRCA2* with overall LC risk ($P = 0.007$). Finally, in the latest Consortium of Investigators of Modifiers of *BRCA1/2* paper [15], there was a statistically increased LC risk in female *BRCA2* PV carriers with a RR of 2.84 (95 % CI, 1.23 to 6.60), although there was no overall association when both genes and genders were considered together.

Earlier studies, however, warrant caution. Lee et al. [16] conducted a meta-analysis based on epidemiological studies comparing the expected number of cases of LC (derived from the LC incidence rate in the general

population) and the number of cases observed in a population of patients with *BRCAgl* variant. They analyzed the results of 13 studies and found a relative risk of LC for *BRCA2gl* variants carriers of 0.76 (95 % confidence interval (CI) [0.48–1.19]), 0.66 (95 % CI [0.41–1.05]) for *BRCA1gl* variants carriers and an overall relative risk for *BRCA1/2gl* carriers of 0.96 (95 % CI 0.66–1.40). The authors concluded that there was no association with LC and *BRCA1/2*. This meta-analysis, although informative, has several weaknesses: i) there was a strong heterogeneity between studies (with an I^2 of 98.2 %); ii) the certainty of *BRCA1/2glp* in LC patients was confirmed in only 5 studies and iii) similarly, the certainty of LC diagnosis was known in only 4 studies (for several studies, the diagnosis of LC was based on the testimony of a family member).

If we hypothesize, in analogy with the Li Fraumeni syndrome [1], that there is a synergistic association with tobacco i.e., the major confounder is the absence of information concerning the smoking habits. Smoking is thought to increase the risk of all types of cancer in patients with *BRCA1/2glp* [17] but is rarely reported. Consequently an explanation why association between LC and *BRCAgl* is rarely found in epidemiological studies might be the significant decrease in daily smoking among *BRCA1/2glp* carriers observed within 5 years after the genetic results (HR 0.83; CI95%: 0.69–0.99) [18]; it can be hypothesized that by decreasing their own smoking habit *BRCA1/2glp* carriers protect themselves against a low-penetrance predisposing syndrome.

Another major point when discussing lung cancer in *BRCAglp* carriers is whether the gene has a role in the lung cancer development as it might lead to consider using PARP inhibitors, platinum chemotherapy or combinations. In their series Kadouri et al [19] reported interesting response rate to platinum compounds. Additionally, most tumours with genomic scores had high LOH/HRD scores. Diossy et al. also reported mutational signatures typically associated with HRD in *BRCA1/2*-deficient LC [20]. In our series two patients received a PARP inhibitor (Olaparib) in the course of their disease. The first had progressive disease despite receiving a platinum-based-PARP-inhibitor combination therapy. However, the second received olaparib, and disease was stable

under treatment.

The retrospective nature of our study and the anonymization of the data collected imply certain limitations, including missing data on the exact nomenclature of some *BRCA1* variants and the impossibility of knowing the last status of patients beyond the latest data available in the database. Similarly, our study is purely descriptive and does not present a matched control cohort to verify whether the differences observed with respect to the overall lung cancers are significant.

In conclusion, we have reported on the largest French cohort of LC cases with *BRCA1* variants. There seems to be particular features in carriers of *BRCA2* variants: adenocarcinoma subtype, female sex, occurrence in non- or former smokers. Previous large epidemiological studies by design rarely take account the smoking habit of patients with *BRCA1*. Overall, LC risk might be low, and therefore hard to highlight in studies. Smoking might then be the trigger that unmasks the increased risk. Large, prospective studies with a control group would be interesting to investigate this hypothesis. Regardless of the reality of the *BRCA*–LC association, thoracic oncologists should incorporate clinical cancer genetics in the multidisciplinary management of lung cancer patients, given the importance of other established LC susceptibility syndromes [21].

CRediT authorship contribution statement

Mateo Sanchis-Borja: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Vincent Fallet:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Elisabeth Fabre:** Resources. **Marie Wislez:** Resources. **Stéphane Culine:** Resources. **Gérard Zalcman:** Resources. **Jean-Philippe Spano:** Resources. **Nathalie Chabbert Buffet:** Resources. **Florence Coulet:** Resources. **Patrick R. Benusiglio:** Writing – review & editing. **Jacques Cadranet:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J. Cadranet reports fees for participation on boards of experts for the development of cancer drugs from AZ, BMS, Jansen, MSD, Novartis, Lilly, Pfizer, Roche and Takeda. PR Benusiglio has received honoraria from AstraZeneca and MSD, the manufacturers of the PARP-inhibitor olaparib.

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