

CLINICOPATHOLOGICAL PROFILE OF BREAST CANCER IN TWO ALBANIAN HOSPITALS, TIRANA AND FIER, AND A FAMILY CARRYING A *BRCA1* EXON 11 DELETION

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ABSTRACT

Clinicopathological and genetic data on breast cancer in Albania are scarce. The aim of this study is to compare data from breast cancer patients of two Albanian hospitals, in Tirana and Fier, and describe a family in which multiplex ligation-dependent probe amplification detected a deletion in *BRCA1* exon 11. A total of 417 patients, 252 from Tirana and 165 from Fier, were compared for age, family history, histology, stage, hormone receptor, HER2, Ki-67 and triple-negative status, with false discovery rate correction. Most characteristics were similar: ductal carcinoma accounted for 85.1 and 89.3% of tumors, a Ki-67 index $\geq 25\%$ for 50.4 and 48.7%, and a family history of breast cancer for 17.5 and 19.7% of patients in Tirana and Fier, respectively. Estrogen receptor-negative tumors were less frequent in Fier (4.2 vs 13.9%; $q = 0.032$) and the stage distribution was shifted toward earlier disease (stage III-IV 12.7 vs 22.9%; $q = 0.049$); however, these differences should be interpreted with caution, because receptor data were missing for 26-29% and stage data for 19% of Fier patients. In the pooled sample, 6.7% of patients were diagnosed before age 45, 9.5% of tumors were triple-negative and 19.3% were diagnosed at stage III-IV. In the familial case, a heterozygous 40-nucleotide deletion in *BRCA1* exon 11 was detected in all six women tested: a 68-year-old woman with early-onset breast cancer, her 58-year-old sister with breast cancer, two first-degree relatives aged 28 and 33 years with breast cancer, and the two daughters of the 68-year-old woman, aged 32 and 35 years, without breast cancer. The exact variant could not be defined by this method and requires confirmation by sequencing. These data provide a comparative clinicopathological profile from two Albanian hospitals and suggest that *BRCA1*-associated hereditary breast cancer occurs in Albania.

KEYWORDS: Breast cancer; *BRCA1*; Hereditary breast cancer; Clinicopathological characteristics; Founder mutation; Albania

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women worldwide, with about 2.3 million new cases and 666,000 deaths in 2022 (Bray et al., 2024). In the Balkans, the burden of breast cancer varies considerably between countries; in Albania it is the lowest in the region, but it more than doubled between 1990 and 2019 and is forecast to increase further by 2030 (Todorovic et al., 2023).

Clinicopathological characteristics, including histological type, stage at diagnosis, hormone receptor and HER2 status and proliferation, guide treatment and reflect the effectiveness of early detection. In Albania, such data are limited to single-center series from Tirana (Pajenga et al., 2016; Hasa et al., 2026), and no comparison between hospitals or regions of the country has been reported.

Pathogenic germline variants in *BRCA1* and *BRCA2* confer a cumulative breast cancer risk to age 80 of about 70% (Kuchenbaecker et al., 2017), and tumors in *BRCA1* carriers are predominantly estrogen receptor-negative and triple-negative, particularly at younger ages (Mavaddat et al., 2012). The spectrum of pathogenic variants is strongly population-specific because of founder effects (Rebbeck et al., 2018). In Greece, six recurrent *BRCA1* variants account for more than half of all mutations detected in breast/ovarian cancer families (Konstantopoulou et al., 2014). Among ethnic Albanians, *BRCA1* c.3700_3704del was detected in 3 of 55 Albanian breast cancer patients from North Macedonia (Jakimovska et al., 2018) and in 6% of breast cancer patients from Kosovo, the highest frequency of this variant reported worldwide and probable evidence of an Albanian founder mutation (Maleva Kostovska et al., 2022). No comparable data exist from Albania, where germline testing is not covered by the public health system (Mati et al., 2023).

The aims of this study were: (i) to compare the clinicopathological characteristics of breast cancer patients treated at the national referral hospital in Tirana and at the regional hospital in Fier; and (ii) to describe a family from Tirana in which multiplex ligation-dependent probe amplification detected a *BRCA1* exon 11 deletion,

previously presented by our group in abstract form (Xhetani et al., 2024), and to identify the most likely candidate variant.

MATERIAL AND METHODS

Study design and patients

This retrospective, hospital-based study included 165 breast cancer patients treated at the Department of Oncology, Regional Hospital of Fier, between 2022 and early 2025, and 252 patients from the Oncology Department of Mother Teresa University Hospital, Tirana, between 2021 and 2024. The Tirana cohort has been described previously (Hasa et al., 2026).

Clinicopathological variables

Variables were coded identically in both cohorts: age at diagnosis (<45 vs ≥45 years); family history of breast cancer; laterality; histological type; stage according to the American Joint Committee on Cancer (AJCC) 8th edition prognostic staging system (Giuliano et al., 2017); estrogen receptor (ER) and progesterone receptor (PR) expression (<1%, 1-9%, ≥10%), with ≥1% considered positive (Allison et al., 2020); HER2 immunohistochemistry score (0-1+, 2+, 3+); Ki-67 index (<14%, 14-24%, ≥25%); and triple-negative status. Data were available as de-identified category counts.

Familial case and molecular testing

The familial case, from the Tirana cohort, was investigated because of breast cancer in two generations. Genomic DNA was isolated from peripheral whole blood of all six women in the family and screened for deletions and duplications by multiplex ligation-dependent probe amplification (MLPA; Schouten et al., 2002) with the SALSA P002 *BRCA1* probemix; findings were confirmed with the P087 *BRCA1* confirmation probemix (MRC Holland, Amsterdam, the Netherlands). Fragment analysis and copy number calculation were performed with Coffalyser.Net (MRC Holland). In our earlier report (Xhetani et al., 2024), a reduced signal of the exon 11 probe(s) was interpreted as a heterozygous 40-nucleotide deletion in exon 11 (legacy numbering); because MLPA does not define the size or the breakpoints of a deletion, this interpretation is provisional and no variant name is assigned.

To identify the most likely candidate, all *BRCA1* variants in gnomAD v4 (Karczewski et al., 2020) were screened for 30-50-nucleotide deletions, consistent with this interpretation, in exon 11 (exon 10 in the MANE Select transcript NM_007294.4; c.671-c.4096), and their ClinVar classifications were recorded (Landrum et al., 2018).

Statistical analysis

Distributions were compared with Pearson's chi-square test with Monte Carlo P values (200,000 replicates) and Cramér's V, and with the Mann-Whitney U test for stage and Ki-67. Binary contrasts were tested with Fisher's exact test and summarized as odds ratios (OR, Fier vs Tirana) with Woolf 95% confidence intervals (95%CI). P values of the 10 overall comparisons in Table 1 were adjusted with the Benjamini-Hochberg false discovery rate (FDR) procedure (Benjamini and Hochberg, 1995) and are reported as q; binary contrasts (Table 2) were exploratory and are reported without adjustment. Percentages were calculated among evaluable cases. Analyses were performed in R 4.3.3 (R Core Team, 2024).

Ethical considerations

This retrospective study used de-identified data. Access to the records of the Fier cohort was authorized by the Regional Hospital of Fier; the Tirana data have been published previously by co-authors of this study (Hasa et al., 2026). The family data were previously reported by our group (Xhetani et al., 2024), for which the family members had given informed consent, and are presented here in de-identified form.

RESULTS

Clinicopathological characteristics

The characteristics of the 417 patients are given in Table 1. Receptor, HER2 and Ki-67 data were missing for at most 2.8% of Tirana patients but for 26-29% of Fier patients, and stage for 1.2 and 18.8%, respectively.

Table 1. Clinicopathological characteristics of breast cancer patients in the Tirana and Fier cohorts.

Characteristic	Tirana (N = 252) N (%)	Fier (N = 165) N (%)	P	q	V
Age at diagnosis (years)			0.433	0.659	0.04
<45	19 (7.5)	9 (5.5)			
≥45	233 (92.5)	156 (94.5)			
Family history of breast cancer			0.659	0.659	0.03
Yes	35 (17.5)	24 (19.7)			
No	165 (82.5)	98 (80.3)			
Not recorded*	52	43			
Laterality			0.575	0.659	0.05
Right	106 (42.1)	77 (46.7)			
Left	144 (57.1)	86 (52.1)			

Bilateral	2 (0.8)	2 (1.2)	0.329	0.658	0.08
Histological type					
Ductal	205 (85.1)	134 (89.3)			
Lobular	21 (8.7)	7 (4.7)			
Other	15 (6.2)	9 (6.0)			
Not recorded*	11	15	0.010 (0.003)	0.049	0.17
AJCC stage					
I	16 (6.4)	18 (13.4)			
II	176 (70.7)	99 (73.9)			
III	55 (22.1)	15 (11.2)			
IV	2 (0.8)	2 (1.5)	0.003	0.032	0.17
Not recorded*	3	31			
Estrogen receptor					
<1%	35 (13.9)	5 (4.2)			
1-9%	6 (2.4)	0 (0.0)			
≥10%	211 (83.7)	114 (95.8)	0.235	0.587	0.09
Not recorded*	0	46			
Progesterone receptor					
<1%	46 (18.3)	15 (12.3)			
1-9%	4 (1.6)	4 (3.3)			
≥10%	202 (80.2)	103 (84.4)	0.492	0.659	0.06
Not recorded*	0	43			
HER2 (IHC)					
0-1+	210 (85.7)	103 (88.0)			
2+	12 (4.9)	7 (6.0)			
3+	23 (9.4)	7 (6.0)	0.657 (0.998)	0.659	0.05
Not recorded*	7	48			
Ki-67 index					
<14%	54 (21.4)	22 (18.8)			
14-24%	71 (28.2)	38 (32.5)			
≥25%	127 (50.4)	57 (48.7)	0.131	0.436	0.08
Not recorded*	0	48			
Triple-negative					
Yes	28 (11.1)	7 (6.0)			
No	224 (88.9)	110 (94.0)			
Not recorded*	0	48			

Percentages refer to evaluable cases. *Not recorded; excluded from denominators. P = chi-square test with Monte Carlo P value (Mann-Whitney U test in parentheses for ordinal variables); q = Benjamini-Hochberg-adjusted P across the 10 variables; V = Cramér's V. Other histological types: Tirana, mucinous (5), papillary (4), Paget disease (3), mixed (2), medullary (1); Fier, papillary (7), invasive metaplastic (2). AJCC = American Joint Committee on Cancer; IHC = immunohistochemistry.

Most characteristics were similar between cohorts (Cramér's $V \leq 0.09$). Patients aged <45 years accounted for 7.5 and 5.5% ($P = 0.43$), a positive family history for 17.5 and 19.7% ($P = 0.66$), ductal carcinoma for 85.1 and 89.3%, a Ki-67 index $\geq 25\%$ for 50.4 and 48.7%, and triple-negative tumors for 11.1 and 6.0% ($P = 0.13$) in Tirana and Fier, respectively. Two variables differed ($V = 0.17$), both significant after FDR correction; given the missing data in Fier, these differences should be regarded as exploratory. ER-negative tumors were less frequent in Fier (4.2 vs 13.9%; $OR = 0.27$, 95%CI = 0.10-0.71; $P = 0.004$; q for the ER distribution = 0.032), and stage was shifted toward earlier disease (overall q = 0.049), with more stage I (13.4 vs 6.4%; $OR = 2.26$, 95%CI = 1.11-4.59) and fewer stage III-IV tumors (12.7 vs 22.9%; $OR = 0.49$, 95%CI = 0.27-0.88). None of the other binary contrasts reached nominal significance (Table 2).

Table 2. Binary contrasts between the Fier and Tirana cohorts.

Characteristic	Tirana n/N (%)	Fier n/N (%)	OR (95%CI)	P
Age <45 years	19/252 (7.5)	9/165 (5.5)	0.71 (0.31-1.60)	0.433
Family history of breast cancer	35/200 (17.5)	24/122 (19.7)	1.15 (0.65-2.05)	0.657
Lobular carcinoma	21/241 (8.7)	7/150 (4.7)	0.51 (0.21-1.24)	0.160
Stage I	16/249 (6.4)	18/134 (13.4)	2.26 (1.11-4.59)	0.025
Stage III-IV	57/249 (22.9)	17/134 (12.7)	0.49 (0.27-0.88)	0.021
ER-negative (<1%)	35/252 (13.9)	5/119 (4.2)	0.27 (0.10-0.71)	0.004
PR-negative (<1%)	46/252 (18.3)	15/122 (12.3)	0.63 (0.34-1.18)	0.179
HER2 3+	23/245 (9.4)	7/117 (6.0)	0.61 (0.26-1.48)	0.314
Ki-67 $\geq 25\%$	127/252 (50.4)	57/117 (48.7)	0.94 (0.60-1.45)	0.823
Triple-negative	28/252 (11.1)	7/117 (6.0)	0.51 (0.22-1.20)	0.130

n/N = cases/evaluable patients. OR = odds ratio (Fier vs Tirana) with Woolf 95% confidence interval (95%CI); P = two-sided Fisher exact test, not adjusted for multiple testing. ER = estrogen receptor; PR = progesterone receptor.

In the pooled sample, 6.7% of patients were diagnosed before age 45, 18.3% reported a family history, 19.3% were diagnosed at stage III-IV, 89.2% had ER-positive tumors, 8.3% had HER2 3+ tumors and 9.5% had triple-negative tumors.

Familial case

The family comprised six women, in all of whom MLPA detected the heterozygous 40-nucleotide deletion in *BRCA1* exon 11 (Xhetani et al., 2024). Two sisters, aged 32 and 35 years, had no clinical breast cancer; their mother, aged 68 years, had early-onset breast cancer, and her sister, aged 58 years, was diagnosed with breast cancer and underwent mastectomy. Two other women, aged 28 and 33 years, first-degree relatives, were also diagnosed with breast cancer. The deletion was therefore present in all four affected women and in two unaffected carriers. Among the 7,287 *BRCA1* variants in gnomAD v4, only one 40-nucleotide deletion was located in exon 11: c.1175_1214del (p.Leu392GlnfsTer5; 1294del40), classified as pathogenic by the ENIGMA expert panel in ClinVar, observed in 12 of 1,614,088 alleles and described as a recurrent mutation in Irish families (Richter and Seth, 1998). For comparison, c.3700_3704del was observed in only 5 of 1,461,882 gnomAD alleles.

DISCUSSION

To our knowledge, this is the first comparison of breast cancer series from two hospitals in Albania. Both cohorts showed a predominantly ductal, stage II, hormone receptor-positive profile. Receptor positivity (89%) was higher than in an earlier Albanian series (Pajenga et al., 2016), possibly reflecting newer methods; the 1% positivity threshold (Allison et al., 2020) contributed little, because only 6 tumors (1.6%) were ER-low (1-9%). The lower frequency of ER-negative tumors and the earlier stage in Fier should be interpreted with caution, because receptor data were missing for 26-29% and stage for 19% of Fier patients; if untested patients mainly had advanced or aggressive disease, the tested subset would be enriched for early, receptor-positive tumors. Moreover, the Tirana cohort came from the national referral hospital, which also treats patients from other regions, including Fier, and the two cohorts covered different periods; the comparison is therefore between hospital-based series rather than regional populations.

The receptor profile was broadly similar to that of population-based series. The triple-negative proportion in Tirana (11.1%) was close to the 12% reported in US registry data, whereas HER2 3+ tumors (8.3% overall) were less frequent than the approximately 15% of HER2-positive tumors in the same data (Howlander et al., 2014). Part of this difference may reflect HER2 2+ tumors (5.2%), some of which may be amplified, but which could not be reclassified because in situ hybridization results were not part of the dataset (Wolff et al., 2018). About half of the tumors had a Ki-67 index $\geq 25\%$ in both cohorts; comparisons with other series should be cautious, because Ki-67 cut-offs and scoring methods are not standardized between laboratories (Nielsen et al., 2021).

One in five tumors was diagnosed at stage III-IV and fewer than one in ten at stage I, a clear target for early detection in Albania (Todorovic et al., 2023). Almost one in five patients reported a family history, a substantial group without a reimbursed testing pathway (Mati et al., 2023). Because only 6.7% of patients were diagnosed before age 45, testing criteria based on young age would identify few potential carriers; in Kosovo, the high frequency of c.3700_3704del led to the proposal of testing strategies that do not depend on family history (Maleva Kostovska et al., 2022).

The familial case suggests that *BRCA1*-associated hereditary breast cancer is present in Albania itself, with breast cancer before the age of 35 years in the younger generation and the deletion present in all four affected women. Because tumors in *BRCA1* carriers are predominantly ER-negative and triple-negative, especially at younger ages (Mavaddat et al., 2012), the receptor status of the tumors of the affected women would provide additional support for the role of the deletion. If the deletion is about 40 nucleotides long, it is distinct from the 5-nucleotide Kosovo variant, and the database search pointed to c.1175_1214del as the most likely candidate; because c.3700_3704del is also located in exon 11, sequencing should first exclude this founder variant. Because MLPA detects small deletions only when they overlap a probe ligation site, PCR with fragment analysis and Sanger sequencing are needed to confirm the breakpoints; medium-sized exon 11 deletions can escape both methods when they lie outside the few exon 11 probes or affect a primer binding site (Herman et al., 2012). Once the breakpoints are known, the variant should be classified according to the ACMG/AMP criteria (Richards et al., 2015).

The rarity of c.3700_3704del in gnomAD despite its 6% frequency in Kosovo shows that global databases do not represent Albanians. Haplotype analysis, interpreted against the Albanian population structure (Xhetani et al., 2026), would show whether the familial deletion is a second founder variant. In Greece and North Macedonia, a limited number of recurrent variants account for a large share of *BRCA1/2* mutations (Konstantopoulou et al., 2014; Jakimovska et al., 2018), a pattern that supports targeted testing strategies; identifying recurrent Albanian variants would make a similar approach possible in Albania.

This study has limitations. Only aggregated counts were available, which precluded multivariable analysis and surrogate molecular subtyping; data were missing for up to 29% of Fier patients; the two cohorts were hospital-

based and covered different periods; and the familial variant has not yet been confirmed by sequencing. Its strengths are the identical coding of variables in both cohorts, correction for multiple testing and the availability of the analysis script, which makes all results reproducible.

CONCLUSION

Breast cancer in Tirana and Fier showed a similar, predominantly stage II, hormone receptor-positive profile, and the familial case suggests the presence of *BRCA1*-associated hereditary breast cancer in Albania. Standardized pathology reporting, early detection and a systematic *BRCA1/2* study of Albanian patients are needed.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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