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Retrospective Study

A biomarker study in Peruvian males with breast cancer

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Abstract

BACKGROUND

Breast cancer (BC) frequency in males is extremely low and tumor features vary from its female counterpart. Breast cancer clinical and pathological features differ by race in women. Tumor infiltrating lymphocyte (TIL) levels, mismatch repair (MMR) protein loss, androgen receptor (AR) expression, and PIK3CA gene mutations are predictive biomarkers of response to biological therapy in female BC. There is limited information about clinical and pathological features as well as predictive biomarkers in males of non-Caucasian races with BC.

AIM

To investigate clinicopathological features and biomarkers of BC tumors in males and their prognostic value in Peruvian population.

METHODS

This study looked at a single-institution series of 54 Peruvian males with invasive BC who were diagnosed from Jan 2004 to June 2018. Standard pathological features, TIL levels, MMR proteins, AR immunohistochemistry staining, and PIK3CA gene mutations were prospectively evaluated in cases with available

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Institutional review board

statement: This study was reviewed and approved by the Instituto Nacional de Enfermedades Neoplasicas Institutional Review Board. Personal and filiation data including identity of every patient was protected with an added code in the excel table. It is a retrospective case series that does not have any not activity or contact with the patients.

Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

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paraffin material. Percentage of AR and estrogen receptor (ER) positive cells was additionally calculated by software after slide scanning. Statistical analyses included association tests, intraclass correlation test and Kaplan Meier overall survival curves.

RESULTS

The median age was 63 years and most cases were ER-positive (85.7%), HER2 negative (87.2%), Luminal-A phenotype (60%) and clinical stage II (41.5%) among our male breast tumors. Median TIL was 10% and higher levels tended to be associated with Luminal-B phenotype and higher grade. AR-positive was found in 85.3% and was correlated with ER (intraclass index of 0.835, $P < 0.001$). Loss of MMR proteins was found in 15.4% and PIK3CA mutation (H1047R) in 14.3% (belonged to the Luminal-A phenotype). Loss of MMR proteins was associated with AR-negative ($P = 0.018$) but not with ER ($P = 0.43$) or TIL ($P = 0.84$). Early stages ($P < 0.001$) and lower grade ($P = 0.006$) were associated with longer overall survival. ER status, phenotype, AR status, TIL level, MMR protein loss nor PIK3CA mutation was not associated with survival ($P > 0.05$).

CONCLUSION

Male BC is usually ER and AR positive, and Luminal-A. MMR loss and PIK3CA mutations are infrequent. Stage and grade predicted overall survival in our South American country population.

Key Words: Male breast neoplasm; Androgen receptor; Tumor-infiltrating lymphocyte; Mismatch repair protein; PIK3CA mutation

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Core Tip: Most male breast cancers were estrogen receptor-positive, HER2-negative, androgen receptor (AR)-positive, and Luminal A phenotype. Loss of mismatch repair (MMR) and PIK3CA mutations was found in around 15% of the cases. AR was correlated with ER expression and without loss of MMR proteins. Stage and grade are prognostic features in Peruvian male breast cancer.

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INTRODUCTION

Male breast cancer (BC) represents less than 1% of mammary carcinomas. Male BC has a higher expression rate of estrogen receptor (ER), higher proliferative activity, and generally more aggressive behavior than in females. The etiological attribution of inheritance for BC is more prevalent among males than females, but only a small fraction is attributed to BRCA2 mutation, and even less to BRCA1[1-5].

Combination of immunohistochemical biomarkers predicts response to therapy and allows us to classify molecular subtypes in female BC[6]. Molecular subtypes distribution and clinical features differ regarding racial populations, for instance, high triple negative breast cancer (TNBC) prevalence and young age at diagnosis are described in Latin-American women[6]. However, only a few small reports have evaluated frequency of molecular BC subtypes in Latin-American males [7,8].

Androgen-receptor (AR) expression[9], tumor-infiltrating-lymphocytes (TIL)[10], loss of mismatch-repair (MMR) proteins (biomarker of the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome)[11] and PI3K mutations[12] have been associated with response to target therapy in female BC. There is a need to develop epidemiological and therapeutic information in the male counterpart. This work aims

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to evaluate the prevalence of clinical and molecular biomarkers of BC tumors in Peruvian males, as well as their impact on survival.

MATERIALS AND METHODS

Study design and Patients

Fifty-four male BC cases who were histologically diagnosed at the Instituto Nacional de Enfermedades Neoplásicas between 2004 and 2018 were included. Clinical information was obtained from the patients' medical records. Live status of patients with not accurate follow-up was obtained from the Peruvian national registry (<https://www.reniec.gob.pe>) through the Epidemiology Department of the institution. The institutional review board waived informed consent and approved this retrospective case series.

Routine pathological examination

TIL assessment on Hematoxylin and Eosin-stained slide was possible in 42 available samples. TIL and histological grade was prospectively evaluated by three experienced pathologists (JS, ET and HG), who were blinded to the clinical data, following international recommendations[7].

Immunohistochemistry staining

Tissue samples were fixed in 10% buffered formalin to obtain 4 µm paraffinized histological sections from 35 available tissue paraffin blocks. Sections were transferred onto adhesive slides and were dried at 60 °C for 30 min. After incubation with the primary antibodies, immunodetection was performed using biotinylated anti-mouse immunoglobulin, followed by peroxidase-labeled streptavidin. The labeled streptavidin biotin kit was used, and 3,3'-diaminobenzidine chromogen was used as a substrate. Immunohistochemical staining for androgen-receptor protein (AR antibody, Dako), estrogen-receptor protein (ER antibody, Zhongshan Bio), Mut L Protein Homolog protein (MLH1 antibody, Dako), DNA mismatch repair protein Msh2 (MSH2 antibody, Dako), MutS Protein Homolog 6 protein (MSH6, Dako) and Postmeiotic Segregation Increased 2 protein (PMS2 antibody, Dako) were carried out according to the manufacturer's instructions. Normal prostatic tissue was used as a positive control of AR. Phosphate-buffered saline was used to replace the primary antibody and served as the negative control.

Tumors that had more than 10% of cells exhibiting a moderate or strong intensity of AR expression were considered positive[7]. Additionally, slides of AR and ER staining were scanned in BX63 Olympus (Tokyo, Japan) and the analysis was performed through Visiopharm software in 34 male BC cases. Negative and positive cells were marked in blue and green by TissueMorph Software, (Visiopharm, Hoerlson, Denmark), and the proportion of cell count was obtained through the ratio of AR and ER on number of positive overall cells in 5 high power fields (Figure 1) under supervision of a pathologist as previously described (JS)[7]. Non-malignant stromal cells were used as internal positive controls for MLH1, MSH2, MSH6, and PMS2, while the loss of MMR was considered when lacking nuclear staining for at least one was found[13].

Determination of PIK3CA mutation

Tumor DNA from paraffin-embedded samples was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen; Hilden, Germany) in the available 14 tumor samples. TaqMan-based real-time PCR analysis was conducted using a LightCycler®96 Real-Time PCR System (Roche Applied Science, Mannheim, Germany) to detect the three "hot spot" PIK3CA mutations (H1047R, E545K and E542K). Custom TaqMan primers and probes were designed for the PIK3CA mutations (PI3KCA 760: c.1624 G (VIC) >A (FAM), PI3KCA 763: c.1633 G (VIC) >A (FAM), PI3KCA 775: c.3140 A (VIC) >G (FAM), ThermoFisher scientific). The thermal cycler protocol was as follows: 10 min at 96 °C, 39 cycles at 60 °C for 2 min, 98 °C for 30 s, and 60 °C for 1 min. All samples were analyzed in a single assay for each mutation. The mutational threshold was determined by measuring the WT HDx FFPE reference standards (Horizon Diagnostics, Cambridge, UK), and was 1%. In contrast, the threshold of reagents inducing false positives was assumed to be 0.5% of the mutation frequency.

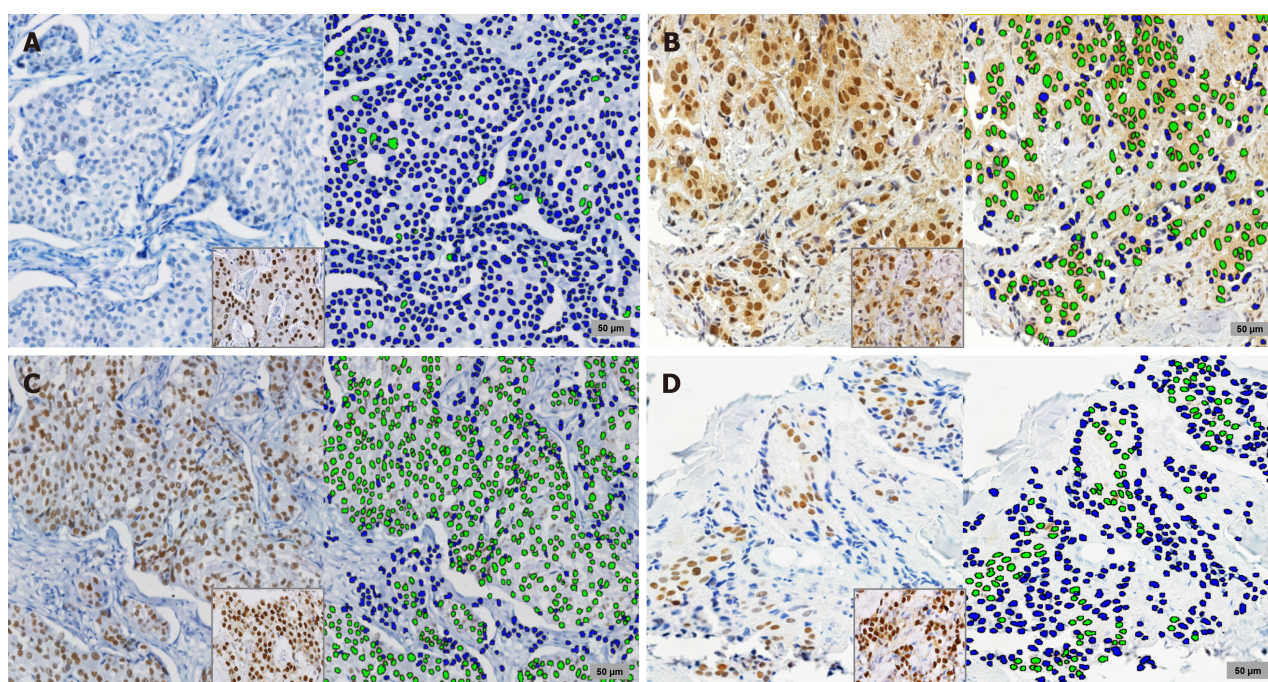


Figure 1 Immunohistochemical staining and automated scoring. Sections show positive staining for androgen receptor (A and B) and estrogen receptor (C and D) from the same tissue areas and the positive control. In the left, sections show images of the immunohistochemical studies ($\times 20$). In the right, the automated analysis is presented, where negative nuclei are highlighted in blue and positive nuclei in green.

Statistical analyses

Associations of clinical-pathological variables were performed by the Chi-square test or the Fisher's exact test. Associations of ordinary variables were performed by the Kruskal-Wallis test. Identification of co-expression of AR and ER was performed by the intraclass correlation test. Overall survival (OS) analysis was estimated using the Kaplan-Meier method. Log-rank or Breslow tests were used to find differences between categories, according to the case. A $P < 0.05$ was considered significant. Analyses were performed using the SPSS statistical package (version 26.0.0, IBM SPSS Statistical).

RESULTS

Patient's characteristics

There were included 54 male BC patients and their median age was 63 years. Twenty-eight (51.9%) tumors were located on the left side, concurrent in-situ component in 41.4% and the most frequent clinical stage was II (41.5%) (Table 1). A family cancer history was found in 12 (22.2%) cases. Regarding treatment, mastectomy, tumorectomy and no primary resection were performed in 72.2%, 7.4% and 20.4%, respectively. Axillary dissection, sentinel node biopsy and no study of nodes were performed in 59.3%, 5.5% and 35.2%, respectively. Neoadjuvant and adjuvant chemotherapy was administrated in 22.2 and 35.2% of the resected cases, while adjuvant radiation was used in 44.4%. Tamoxifen was used in ER-positive cases. Recurrence was found in 28.9% (11/38) of the cases who underwent a curative surgical treatment.

Biomarkers, clinical-pathological features, and the correlations

Most cases were ER-positive (85.7%), HER2-negative (87.2%) and belonged to Luminal-A phenotype (Table 1). ER status was not associated with MMR-loss ($P = 0.43$). No association between ER percentage and MMR-loss was found ($P = 0.22$).

Positive AR status was found in 85.3% of patients and the two TNBC cases were negative for AR. MMR-loss was associated with AR-negative (75% vs 10%, $P = 0.018$). A lower median percentage of AR-positive cells was found in cases with MMR-loss (5% vs 70%, $P = 0.02$).

Evaluation of similar areas for ER and AR found that a median of 3738 cells (52.9%) (range 0%-87%) from 7577 cells (range 2139-11883 cells) were positive for ER, and 3795

Table 1 Clinical-pathological features and overall survival impact in male breast cancer

Features	n	%	OS-5yr	P value
Age				
Median (yr)	63			0.105 ^a
< 63	25	53.7	56.0	
≥ 63	29	46.3	69.0	
Clinical stage (n = 53)				< 0.001 ^a
I	2	3.8	100.0	
II	22	41.5	86.4	
III	20	37.7	50.0	
IV	9	17.0	22.2	
Histological grade (n = 46)				0.006 ^a
1	7	15.2	85.7	
2	26	56.5	73.1	
3	13	28.3	30.8	
sTIL (n = 42)				0.397 ^b
< 10%	12	28.6	50.0	
≥ 10%	30	71.4	66.7	
ER status (n = 49)				0.567 ^a
Positive	42	85.7	66.7	
Negative	7	14.3	57.1	
PgR status (n = 49)				0.305 ^a
Positive	43	87.8	67.4	
Negative	6	12.2	50.0	
HER2 status (n = 47)				0.088 ^b
Positive	6	12.8	33.3	
Negative	41	87.2	70.7	
Ki67 (n = 40) (median 5%)				0.232 ^a
0%-5%	22	55.0	59.1	
> 5%	18	45.0	66.7	
Phenotype (n = 45)				0.356 ^a
Luminal A	27	60.0	63.0	
Luminal B	13	28.9	76.9	
TNBC	5	11.1	40.0	
AR (n = 35)				0.294 ^a
0%-9%	5	14.3	60.0	
≥ 10%	30	85.7	63.3	
Mismatch repair loss (n = 26)				0.501 ^a
No	20	76.9	65.00	
Yes	4	15.4	75.00	
Undetermined	2	7.7	100.00	
PIK3CA mutation H1047R (n = 14)				0.844 ^b
Positive	2	14.3	50.0	

Negative	12	85.7	75.0
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^aP: Breslow.

^bP: Log Rank. OS: Overall survival; TIL: Tumor infiltrating lymphocyte; TNBC: Triple negative breast cancer.

cells (55%) (range 0%-87.8%) from 7366 (range 2520-12135 cells) were positive for AR. Intraclass correlation coefficient of the means for AR and ER was 0.835 ($P < 0.001$) (Figure 2). A lower median of AR-positive tumor cell count proportion was also found in cases with MMR-loss (8% *vs* 65%, $P = 0.018$). No association between median of ER-positive tumor cell count proportion and MMR-loss was found ($P = 0.163$).

Median TIL was 10% and higher levels tended to be associated with Luminal-B ($P = 0.058$) (Figure 2). TIL $\geq 50\%$ was associated with higher grade ($P = 0.039$), but not to age ($P = 0.44$), clinical stage ($P = 0.59$), MMR-loss (20% *vs* 15%, $P = 0.72$) nor PIK3CA mutation status ($P = 0.53$).

Loss of MMR protein expression was found in 4 (15.4%) cases. It was not associated with age ($P = 0.69$), clinical-stage ($P = 0.68$), grade ($P = 0.53$), molecular subtypes ($P = 0.91$) or PIK3CA mutation status ($P = 0.41$).

PIK3CA mutations were found in 2 (14.3%) of the 14 evaluated cases and both were positive for H1047R (1321 copies/microL-15.07% and 1019 copies/microL-18.06%). Both cases belonged to the Luminal-A phenotype.

The association of prognostics and clinical-pathological features

Longer OS was associated with early stage ($P < 0.001$) and lower grade ($P = 0.006$). Survival was not associated with ER status ($P = 0.305$), phenotype ($P = 0.152$), AR status ($P = 0.613$), TIL level ($P = 0.397$), MMR protein loss ($P = 0.501$) nor PIK3CA mutation status ($P = 0.844$).

DISCUSSION

We found a high frequency of AR expression and low frequency of both MMR-loss and PIK3CA mutations in our BC series in male Peruvian population.

Expression of AR was found in 85% of our male BC cases which is in the previously described range (40%-90%)[1], however we didn't find its association with prognosis. Androgen-receptor is a key driver of proliferation and cell survival, and although some retrospective male BC series describe its association with better prognosis[3] others like ours not[4]. Additionally, recent basic research and clinical trials describe that AR can predict activity of targeting drugs[9].

Our findings of high rates of ER-positive status and Luminal phenotype have been extensively described in Caucasian series[2,5]. Large sample size studies describe that ER-positive status would have a favorable prognostic effect (similar to the female BC) and predicts response to endocrine modulation[5,14,15]. The fact that we did not find an association with OS could be because of the small size of our series.

There was absence of HER2 enriched phenotype in our series and HER2- positive status was very infrequent. This corroborates previously published information that HER2 overexpression is less frequent than in female series, but it is expected to behave as a predictive feature to anti-HER2 therapies[2,5].

Our findings of 15% of cases with MMR loss have not previously been described in male BC. The HNPCC syndrome is an autosomal dominant genetic disorder characterized by predisposition to extracolonic malignancies at various sites including BC, is detected by loss of MMR proteins and is associated with high response to anti-PDL1 therapy. Studies with small sample size in female BC describe the lack or reduced expression of hMSH2 and hMLH1 in less than 20%[11,16]. Boyd *et al*[17] described a case of male BC belonging to a large HNPCC kindred that harbors a germline mutation of the MLH1. And recently, Piscuoglio *et al*[2] developed a pathway and network analysis of 241 genes in a series of 59 male BC and described an enrichment of mutations affecting DNA repair-related genes. We found that MMR-loss was associated with the previously described marker of endocrine response[3,4], the lower AR expression. Furthermore, this association appears to be specific for this steroid marker and not for ER, despite AR and ER expression were co-related. Haricharan *et al* [18] suggest that alteration in DNA damage repair genes could produce endocrine resistance because of the finding that defects in MMR pathway genes doesn't allow an accurate CDK4 suppression by endocrine therapy.

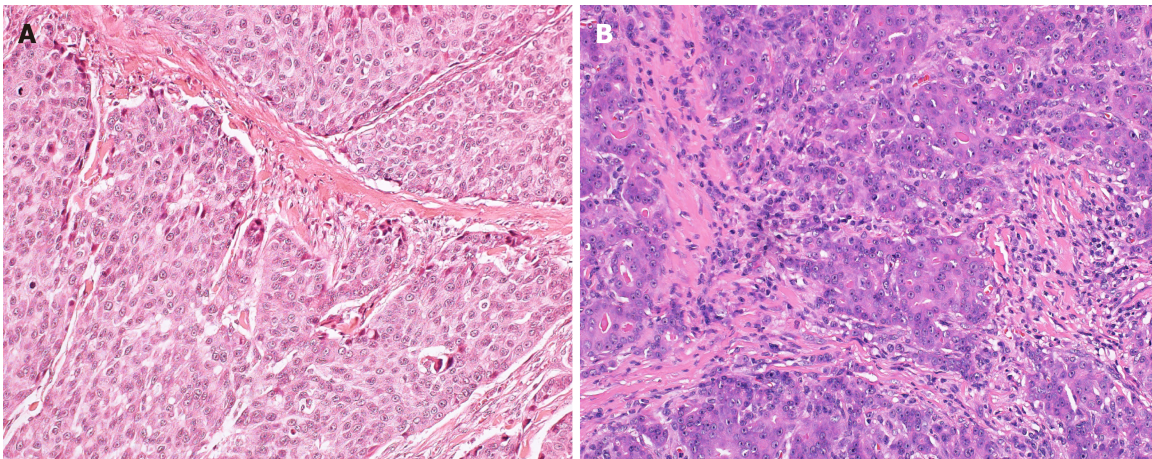


Figure 2 Evaluation of tumor infiltrating lymphocytes on hematoxylin-eosin staining (× 20). A: A Luminal-A breast cancer with low TIL level; B: A Luminal-B breast cancer with high TIL level.

PIK3CA mutations were found in only 2 of 14 evaluated male BC cases that is lower than previously reported by our group in women with BC[19,20]. Piscuoglio *et al*[2] sequenced 241 genes in 59 male BC and found that most recurrent mutations affected the PIK3CA gene (20%). However, these rates would be lower than their female counterparts that have been detected in approximately 30%-40% of female BC[21]. In vitro and translational research in tumor samples from clinical trials found that PIK3CA mutations reduce sensitivity to anti-HER2 drugs[22] and endocrine modulation[19,20]. Additionally, a recent study demonstrates that Alpelisib, a drug targeting the PIK3CA pathway, has activity in breast cancer cases with presence of the mutation [12].

TIL is a well-described prognostic and predictive biomarker for anti-PDL1-therapy in female BC[10]. Vermeulen *et al*[22] found that high TIL density evaluated by a method different than the currently recommended in international guidelines was associated with Luminal-B HER2-positive subtype and longer OS in a 1483 male BC series. We also found a trend of higher TILs in Luminal-B subtype but not a relationship with longer OS ($P = 0.378$). Contrary to the female counterpart or other malignancies, we did not find that higher TIL levels were associated with AR or ER percentage nor with MMR-loss.

Finally, our finding that early stage and lower grade features achieve significant association with better prognosis is consistent with previous reports, and supports the current management of this entity[2,5].

The weakness of our study was that several patients were lost of follow-up; however, obtaining information about their live status from the national registry allowed us to build OS curves. The number of included cases is also small because it is a very unusual entity, representing less than 0.5% of their female counterpart (18552 female new BC cases diagnosed in our center during the same period). Our strongness is the prospective evaluation of biomarkers by pathologists and biologist authors. Our results serve to complement male BC knowledge in the South American population, which has been under-studied.

CONCLUSION

We conclude that early-stage and low-grade features identify favorable prognoses in male BC. Most Peruvian BC cases are ER-positive, HER2-negative, AR-positive and Luminal-A tumors. MMR loss and PIK3CA mutations are infrequent, and MMR loss was associated with AR negative.

ARTICLE HIGHLIGHTS

Research background

Information about clinicopathological features associated with treatment response and

prognosis has been extensively described for female breast cancer, and differences regarding races has been described. Breast cancer in males is much less frequent, has important clinicopathological differences and is less studied than their female breast cancer counterpart.

Research motivation

Discussion and new information about features and biomarkers of Breast cancer (BC) in males have been included in recent cancer-related meetings, and more than 30000 articles have been published in the last two years. However, very few of them have evaluated a South American population.

Research objectives

To describe rates of currently accepted biomarkers for prognosis and for prediction of treatment response in Peruvian males with BC.

Research methods

Clinical files and tumor slides were reviewed. Tumor-infiltrating lymphocytes, mismatch repair proteins (MMR), PIK3CA gene mutations, estrogen (ER) and, androgen receptors (AR) were prospectively evaluated in available paraffin material.

Research results

In our series of 54 Peruvian males with invasive breast cancer, we found that most cases were Luminal-A phenotype (60%), ER-positive (85.7%), AR-positive (85.3%), and the median of tumor-infiltrating lymphocytes was 10%. MMR loss was found in 15.4% and PIK3CA mutation (H1047R) in 14.3% (all in the Luminal-A group). MMR loss was associated with AR-negative ($P = 0.018$). Longer overall survival was associated with early stages ($P < 0.001$) and lower grade ($P = 0.006$).

Research conclusions

Most breast cancer tumors in Peruvian males are ER and AR-positive, and MMR loss and PIK3CA mutations are infrequent. MMR loss was associated with hormone receptor-negative.

Research perspectives

Biomarkers identified for women with breast cancer need to be validated for the male counterpart. Research in race disparities needs to be extended also for males of non-Caucasian races. Association between MMR loss and activity of AR pathways requires further evaluation.

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