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Risk of breast cancer in patients with lymphangioleiomyomatosis

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare metastasizing pulmonary disease that shares some clinical, cellular, and molecular similarities with metastatic breast cancer to lung. LAM cells have been identified circulating in various body fluids of patients and, intriguingly, diverse evidence indicates that these cells may originate from a different organ to the lung. Following on from these observations, we hypothesized the existence of a common risk basis between LAM and breast cancer, and suggested increased risk of breast cancer among LAM patients. Here, by studying two additional LAM cohorts with more detailed epidemiological, life-style, and disease-related data, we show consistent results; a potential excess of estrogen-receptor-positive young breast cancer cases in LAM. This observation further suggests the need of prospective studies to precisely assess the association between both diseases.

Rare neoplasms pose specific challenges including relatively frequent misdiagnosis, lack of comprehensive information, and incomplete knowledge on their causes [1]. LAM is a rare metastasizing neoplasm that appears predominantly in women of childbearing age and is characterized by cystic lung destruction [2]. LAM lung lesions are heterogeneous at the cellular phenotypic level, but are typically characterized by the proliferation of smooth muscle-like cells that are frequently positive for the estrogen receptor (ER), progesterone receptor, and stem cell-like markers, among other described molecules [3]. In sporadic LAM patients, disease cells generally carry loss-of-function mutations in the tumor-suppressor tuberous sclerosis complex 2 (*TSC2*) gene [4], which results in abnormal activation of the mechanistic target of rapamycin (mTOR); allosteric inhibitors of this kinase show substantial clinical benefit [5]. Germline mutations in this gene or in *TSC1* cause the multisystem disease TSC, and women with this condition may also develop LAM [2]. Intriguingly, LAM cells have been identified circulating in various body fluids of patients [6] and, thus, are assumed to be metastatic with lung tropism; however, their tissue of origin remains a subject of debate. Based on cell morphology and biomarkers, the origin of LAM cells has been postulated to be in the neural crest lineage, lymphatic system, and/or the uterus [7–9]. In parallel, our group has postulated an alternative origin in a specific mammary progenitor cell subpopulation [10]. In fact, breast tumors with metastatic lung tropism show abnormally enhanced mTOR activity [11,12]. These observations prompted us to assess the association between LAM and subsequent breast cancer; our results combining epidemiological data from three cohorts indicated a higher incidence of breast cancer among LAM patients than in the general population [10].

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Table 1
Epidemiological and clinical features of the studied LAM cohorts.

Country (LAM patients, *n*)	Average age (95% CI) of LAM diagnoses	Age at invasive breast cancer diagnoses	TSC* diagnoses *n* (%)	AML† diagnoses *n* (%)	Uterine leiomyoma diagnoses *n* (%)	Perivascular epithelioid tumor and/or retroperitoneal lymphangioma
Brazil (*n* = 102)	36.2 (33.7–38.7)	38, 53	30 (29%)	60 (59%)	25 (25%)	20 (20%)
Poland (*n* = 76)	38.4 (35.9–40.9)	49, 50	21 (28%)	33 (43%)	16 (21%)	30 (39%)

* Tuberous sclerosis complex.
† Angiomyolipoma, renal.

Since our earlier observations could have important implications for the clinical management and study of LAM and cancer, we sought to analyze additional cohorts from different countries. The data collected included personal, epidemiological and life-style information (including parity, birth control measures, smoking, and age at menarche and menopause), LAM disease-related data (including diagnoses of angiomyolipoma, uterine leiomyomas, endometriosis, and tumors in the retroperitoneal space), and cancer diagnoses (including breast cancer features and diagnosis of any cancer type). The largest patient cohorts with complete data collection were from Brazil (n = 102) and Poland (n = 76) (Table 1). Four Caucasian invasive breast cancer cases were recorded (two in each cohort), with ages at diagnosis from 38 to 53 years. The average age at diagnosis of breast cancer in these populations was 55–60 years [13,14]. Despite being relatively young, all four patients developed ER-positive tumors, which is an equivalent observation to those reported in our earlier study [10]. Only one case developed breast cancer metastasis and, on this occurrence, lung was the target tissue. The same patient presented a relatively high level of circulating estradiol (2073 pmol/L) in ovulation phase two years prior to breast cancer diagnosis. While tumor and hormone marker levels were not particularly remarkable in the other cases, one patient underwent hysterectomy and oophorectomy due to hemorrhagic ovarian cysts four years before breast cancer diagnosis.

The age of LAM diagnosis of the four breast cancer cases was not particularly young, ranging from 39 to 49 years. Two also had renal angiomyolipomas and none received hormonal therapy for LAM, although two received *in vitro* fertilization procedures before their breast cancer diagnosis. However, there is no evidence that these procedures increase the risk of this neoplasia [15]. In addition, none of the four cases was diabetic and only one had been a smoker for a number of years.

Next, we compared the number of incident breast cancer cases observed in the two cohorts with the number of expected cases, based on country-specific incidence rates for the period 2000–2016 [13,14]. The standardized incidence ratios (SIRs) were greater than 1 in both cohorts; 3.01 and 4.21 in those from Brazil and Poland, respectively (Table 2). The 95% confidence intervals (CIs) were 0.53–10.97 and 0.75–15.34, which correspond to values of p = 0.14 and 0.08, respectively. The combined analysis of both cohorts yielded an SIR of 3.51 (95% CI 1.20–9.04, p = 0.03). A few other clinical centers from other countries compiled information, but the numbers of patients with complete data were relatively low for analysis: Italy (n = 24, one breast case recorded), New Zealand (n = 6, no cases), and The Netherlands (n = 4, no cases).

The results of this study of two large cohorts of LAM with detailed clinical and epidemiological data are consistent with previous findings from three other countries [10] and suggest an association between LAM and ER-positive breast cancer in young women. Meanwhile, two additional breast cancer cases diagnosed at 49 and 53 years of age have arisen in the Spanish LAM cohort, which already showed a SIR > 2 [10]. Of note, none of the Spanish breast cancer cases developed lung metastasis. Collectively, these observations might indicate the need for prospective studies to accurately determine the association between this rare metastasizing lung neoplasm and breast cancer.

Declaration of Competing Interest

Dr. Torre reports grants from Boehringer Ingelheim outside the submitted work; Dr. Harari reports personal fees from Roche, grants from Actelion, grants and personal fees from Boehringer Ingelheim, outside the submitted work; and Dr. Pujana reports grants from Roche Pharma, grants from Astellas Pharma outside the submitted work.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and the international epidemiological study was approved by the Ethics Committee of the Hospital de Henares (PI-753). The data from the cohorts (irreversibly encoded) were provided for combined analysis at the Spanish study center.

Transparency document

The Transparency document associated with this article can be found in the online version.

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Table 2
Observed and expected breast cancer cases in Brazilian and Polish LAM cohorts.

Country	Person-years	Observed cases (*n*)	Expected cases (*n*)	SIR	95% CI	P value
Brazil	598.43	2	0.66	3.01	0.53-10.97	0.14
Poland	373.73	2	0.48	4.21	0.75-15.34	0.08
Global	972.16	4	1.14	3.51	1.20-9.04	0.03

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