Retrospective evaluation of pathogenic genetic findings with potential association to late treatment toxicities from a large observational study on long-term breast cancer survivors. Illarramendi J, Asín G, Manterola A, Ernaga A, Pasalodos S, Salgado JE, De La Cruz S, Ramos MA , Alonso A, Morales L, Artigas M, Martínez JP, Arraras JI, Illarramendi JJ. Services of Hematology, Medical Oncology, Radiation Oncology and Genetics. University Hospital of Navarra. Pamplona. Spain.

Introduction: Breast cancer (BC) patients comprise the main group of cancer survivors. Late treatment effects are of special concern in this population. Although genome variants may predispose to some late effects we are unaware of large studies reflecting common practices of overall genetic testing for concurrent diseases in long-term survivors. We aim to collect evidence on pathogenic genetic findings related to monogenic diseases in a large group with long follow-up.

Methods: Observational study (ILL-CAR 2018-01). Approved by the Regional Ethics Board. All patients signed the informed consent for the study. Entry criteria included BC patients with a follow-up of at least 10 years from the time of their first therapy. Detailed clinical data were retrieved from a comprehensive electronic medical record, comprising all the information on hospital and primary care in our regional health system. Information on genetic findings predisposing to late toxicities was collected. Genetic variants predisposing to cancer were not included, with the exceptions of new cancers considered related to the previous BC treatment. Studies on thrombophilia and pharmacogenomics were not considered.

Results: 2,847 patients (p.) were included and are available for full analysis. Median follow-up from first therapy of BC: 18.7 years (10-55.3). Pathogenic variants considered to predispose to late toxicities were found in the following genes: HFE (homozygotes and compound heterozygotes, 7), LDLR (4), APOB (1), MYPBC3 (1), PRKAR1 (1), DMPK (1), PKD1 (1), SMN1 (1), PTEN (1), ATP7B (1). Potential late toxicities linked to this genes included cardiovascular, osteoarticular, endocrine, hepatic, neurologic and gynecologic (uterine cancer after tamoxifen). 17 further p. took part in populational studies with whole genome sequencing, with no findings that were considered as potentially related to late toxicities. A progressively larger number of p. with late toxicities, mainly cardiovascular, were evaluated for monogenic disorders, without further results at this moment.

Conclusions: The current impact of pathogenic genetic variants predisposing to disorders of monogenic transmission as a potential cause of late toxicities in BC survivors was low in this study. This group of patients remains as a major target for further genetic studies on this subject.

Keywords: breast cancer, survivors, genetic diseases.