1906P Lung cancer predisposition in women with previous breast cancer identified by whole exome sequencing

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Background: Women treated for breast cancer (BC) are at risk to develop a subsequent lung cancer (LC; relative risk ranging from 1.38 to 5.05), especially in case of smoking history and if adjuvant radiation (aRT) was administered for BC. We hypothesized that genetic variants might predispose patients (Pts) to develop LC after BC. Our aim was to perform whole exome sequencing (WES) to identify genes associated with such predisposition.

Methods: 28 women with diagnosis of LC after BC (Study Population, SP) were enrolled, as well as 32 women treated for BC and with no secondary cancer after a follow-up $\geq$10 years (control population; CP). DNA was extracted from tumors and normal tissue samples from both SP and CP. Libraries were prepared with Agilent SureSelect All Exon kit and sequenced on Illumina HiSeq2500. Variant calling was performed with FreeBayes software.

Results: The median age of SP at BC diagnosis was 63.5 years (range: 47-76); the median interval between diagnosis of BC and occurrence of LC was 4.5 years (range: 0-11). 13 Pts (46%) were never-smokers and, among the 21 Pts who had received aRT, 13 (62%) developed ipsilateral LC. At somatic analysis, no common mutation among known driver genes was shared between each BC and LC pair in SP Pts. WES performed on BC and LC samples identified two mutational signatures (S1 and S2). S1 (C>T substitutions) was observed in all BC samples and 16/28 (57%) LC samples and was more frequent in never-smokers (11 vs. 5 Pts) and among Pts who developed ipsilateral LC after aRT (10 vs. 6 Pts). S2 (C>A transversions) was observed in 12/28 LC samples (43%) and was strongly associated with smoking habit (10 vs. 2 Pts). When compared with COSMIC libraries, S2 results were similar to COSMIC 4, common in LC samples collected from smokers. Since S1 was largely shared between paired BC and LC samples, we explored the eventuality of a genetic predisposition to S1-related malignancies with a gene-based burden test over rare germline variants in normal tissue of S1-LC Pts compared with CP Pts; 249 candidate genes were identified (FDR<0.05).

Conclusions: Our data identified two mutational signatures underlying the LC development. Germline analysis suggests that genetic variants may contribute to increase the risk of LC after BC.

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