Tumour lineage shapes BRCA-mediated phenotypes

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Background:
Mutations in BRCA1 and BRCA2 predispose individuals to certain cancers and disease-specific screening and preventative strategies have reduced cancer mortality in affected patients. These classical tumour-suppressor genes have tumorigenic effects associated with somatic biallelic inactivation, although haploinsufficiency may also promote the formation and progression of tumours. Moreover, BRCA1/2-mutant tumours are often deficient in the repair of double-stranded DNA breaks by homologous recombination, and consequently exhibit increased therapeutic sensitivity to platinum-containing therapy and inhibitors of poly-(ADP-ribose)-polymerase (PARP). However, the phenotypic and therapeutic relevance of mutations in BRCA1 or BRCA2 remains poorly defined in most cancer types.

Methods:
We analysed the germline blood and matched tumour tissue of 17,152 patients with cancer diagnosed with 1 of 55 cancer types in whom prospective clinical sequencing of up to 468 cancer-associated genes

was performed to guide treatment decisions for advanced and metastatic disease. We defined somatic loss-of-function (LoF) alterations in the BRCA1 and BRCA2 genes, and identified germline pathogenic and probable pathogenic variants using a clinically validated variant discovery pipeline and a custom pathogenicity classifier trained on expert curation by medical geneticists.

Results:
Here we show that in the 2.7% and 1.8% of patients with advanced-stage cancer and germline pathogenic or somatic loss-of-function alterations in BRCA1/2, respectively, selective pressure for biallelic inactivation, zygosity-dependent phenotype penetrance, and sensitivity to PARP inhibition were observed only in tumour types associated with increased heritable cancer risk in BRCA1/2 carriers (BRCA-associated cancer types). Conversely, among patients with non-BRCA-associated cancer types, most carriers of these BRCA1/2 mutation types had evidence for tumour pathogenesis that was independent of mutant BRCA1/2.

Conclusions:
Overall, mutant BRCA is an indispensable founding event for some tumours, but in a considerable proportion of other cancers, it appears to be biologically neutral—a difference predominantly conditioned by tumour lineage—with implications for disease pathogenesis, screening, design of clinical trials and therapeutic decision-making.

Conflict of Interest:
M.L.C. reports receiving travel/accommodation funding from Allergan, Sanofi-Aventis, and Daiichi Sankyo. W.A. reports receiving honoraria from Caret, advisory board activities for Clovis Oncology, Janssen, and MORE Health, travel/accommodation expenses from Clovis Oncology and GlaxoSmithKline, and research funding from AstraZeneca, Zenith Epigenetics, Clovis Oncology, and GlaxoSmithKline. L.Z. reports receiving honoraria from Future Technology Research LLC, Roche Diagnostics Asia Pacific, BGI, and Illumina. L.Z. has a family member with a leadership position and ownership interest in Shanghai Genome Center. J.B. is an employee of AstraZeneca, serves on the Board of Directors of Foghorn and is a past board member of Varian Medical Systems, Bristol-Myers Squibb, Grail, Aura Biosciences and Infinity Pharmaceuticals. He has performed consulting and/or advisory work for Grail, PMV Pharma, ApoGen, Juno, Lilly, Seragon, Novartis and Northern Biologics. He has stock or other ownership interests in Tango and Venthera, for which he is a co-founder. He has previously received honoraria or travel expenses from Roche, Novartis, and Lilly. E.M.O. reports receiving consulting fees from BioLineRx, Targovax, Halozyme, Celgene, Cytomx, and Bayer and research funding support from Genentech, Roche, BMS, Halozyme, Celgene, MabVax Therapeutics, and ActaBiologica. D.M.H. reports receiving research funding from AstraZeneca, Puma Biotechnology, and Loxo Oncology and personal fees from Atara Biotherapeutics, Chugai Pharma, Boehringer Ingelheim, AstraZeneca, Pfizer, Bayer, Debiophram Group, and Genetech. M.F.B. reports receiving research funding from Illumina and advisory board activities for Roche. D.B.S. reports advisory board activities for Loxo Oncology, Pfizer, Illumina, Lilly Oncology, Vivideon, and Intezyne.

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