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Beating the odds: molecular characteristics of long-term survivors of ovarian cancer

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Beating the odds: molecular characteristics of long-term survivors of ovarian cancer

High-grade serous ovarian cancer, the most common form of the disease, is often fatal. This study investigated the genomic and immune characteristics of tumors from women who survived more than 10 years after their initial diagnosis, and compared them with short-term and moderate-term survivors.

This is a summary of:
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The problem

Little is known of the determinants of survival in women with high-grade serous ovarian cancer beyond the extent of surgery and mutations in DNA repair genes (such as *BRCA1* or *BRCA2*), which are associated with better survival — at least in the short term[1,2]. Fewer than 15% of women with this disease survive more than 10 years after their diagnosis[3]. Exceptional survivors may provide insights that can be applied to the treatment of women likely to experience a more typical disease trajectory.

The discovery

As part of a US Department of Defense (DOD) Ovarian Cancer Research Program (OCRP) initiative[4] and with collaborators in the US, UK, Canada and Australia, we analyzed 60 patients with advanced-stage, high-grade serous ovarian cancer who survived more than 10 years after their initial diagnosis. We examined their clinical histories and used whole-genome sequencing, transcriptome and methylome profiling of their primary tumor samples, and compared these with data from 66 short-term (<2 years) or moderate-term (2–10 years) survivors.

Tumors from long-term survivors were more likely than those from short-term and moderate-term survivors to have several alterations in genes associated with DNA repair, probably rendering them highly sensitive to chemotherapy or reducing their ability to acquire drug resistance. Long-term survivors also had more frequent somatic variants than short-term or moderate-term survivors, resulting in an increased predicted neoantigen load and enhanced immune responses. Patients clustered into survival groups based on genomic and immune cell signatures. Women with *BRCA1*-altered tumors (a feature normally associated with favorable responses to chemotherapy) fell into three groups based on their molecular signatures, including an unusually poor survival group who had molecular evidence of carcinogen exposure consistent with a history of tobacco consumption. A subset of long-term survivors whose tumors had *CCNE1* amplification (usually associated with chemo-resistance) had evidence of enhanced immune activity.

Collectively, our work indicates that combinations of germline and somatic gene alterations, tumor cell phenotypes and differential immune responses can contribute to long-term survival in ovarian cancer (Fig. 1).

Future directions

Our findings indicate that multiple alterations in DNA repair, including evidence of both *BRCA1*-type and *BRCA2*-type homologous recombination deficiency[5] within a tumor, might result in particularly profound survival outcomes. The long-term survival of patients whose tumors had *CCNE1* amplification is intriguing, and suggests that an engaged tumor-immune microenvironment can overcome the poor primary treatment response typically associated with this biomarker. An unanticipated finding was the importance of tobacco exposure, a modifiable lifestyle factor, in influencing the survival outcomes in patients with *BRCA1* alterations, and serves as a warning to currently healthy mutation carriers.

Patients with exceptional survival are rare and the availability of fit-for-purpose biospecimens with associated in-depth, longitudinal clinical follow-up data limited the total number available for molecular analysis in this study. However, the work provided specific observations that are now being tested in a much larger patient series involving hundreds of long-term survivors and matched comparison groups, using archival diagnostic pathology samples retained from initial surgery.

The treatment of our cohort of long-term survivors mostly predated the introduction of inhibitors of poly(ADP-ribose) polymerase 1 (PARP). As the features associated with response to platinum chemotherapy have previously been shown to predict responses to PARP inhibitors, subsequent genomic and immunological studies should include patients who have had an exceptional response to these drugs.

Dale W. Garsed and David D. L. Bowtell
Peter MacCallum Cancer Centre, Melbourne, Australia.

EXPERT OPINION

"This study describes whole-genome sequencing, RNA sequencing and methylome array profiling of bulk tumor tissues from 60 long-term and 66 short- and/or medium-term survivors. Given the relatively rare type of cancer investigated, the size of the study is commendable. The team find associations for molecular features enriched or depleted in short-, medium- or long-term survivors. Perhaps the most clinically relevant insight comes from the stratification of *BRCA1*-tumors into three groups with different outcomes." **Kate Lawrenson, Cedars-Sinai Medical Center, Los Angeles, CA, USA.**

FIGURE

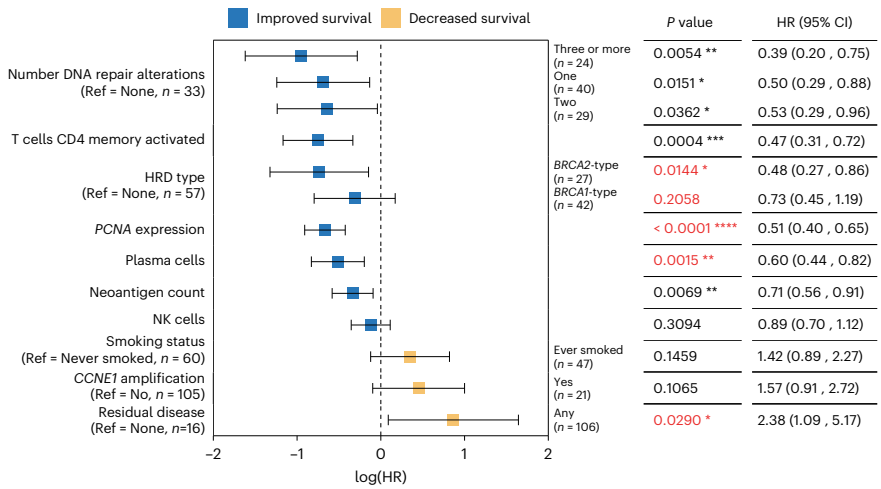


Fig. 1 | Key features associated with exceptional survival in high-grade serous ovarian cancer. Hazard ratio (HR, squares) and 95% confidence interval (CI; whiskers) for overall survival using a univariate Cox proportional hazard regression model for features identified in the study. Features are ordered from smallest to largest hazard ratio, and *P* values < 0.05 in a multivariable model are colored red. **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001. HRD, homologous recombination deficiency; NK, natural killer; Ref, reference.
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BEHIND THE PAPER

Ask most oncologists and they will recount one or more patients whose exceptional survival surprised them, given the bleak nature of their initial diagnosis. How such patients beat the odds is intriguing and important, as they have achieved an outcome — long-term survival — that researchers and clinicians worldwide are striving to attain.

When we began this work almost a decade ago, we were often told that such patients with ovarian cancer must have either been cured surgically or carry *BRCA1* or *BRCA2* mutations, but we have found that these are not necessary or, in the case of *BRCA1/2* mutations, sufficient for long-term survival. The extraordinary willingness of patients with ovarian cancer, clinicians, and researchers allowed the formation of this international consortium to identify and characterize a very rare cohort of patients, propelled by funding and guidance provided by the leadership of the US DOD OCRP. **D.D.L.B.**

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This review article outlines current studies into exceptional treatment responses and survival in patients with cancer, and considers approaches to identify and analyze these patients.
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This paper presents a pan-cancer whole-genome sequence analysis tool to classify homologous recombination deficiency and discriminate *BRCA1*- and *BRCA2*-type loss.

FROM THE EDITOR

"Ovarian cancer comes with a dismal prognosis for patients. This dataset is truly impressive, affording a rare glimpse into the molecular make-up of tumors from long-term survivors. The study confirms that ovarian cancer is complex and heterogeneous, and that there are no universal hallmarks of these rare tumors. Nevertheless, the insights gleaned from this work offer a new perspective of the disease, with many opportunities for downstream analyses." **Safia Danovi, Senior Editor, *Nature Genetics*.**