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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	CytoExpert was used to collect flow data. ImageStudioLite was used to image western blots. Cellometer Auto was used to count cells.
Data analysis	The ImageJ measure tool was used to quantify yeast-three-hybrid growth. The ImageJ colony area plug-in was used to measure clonogenic survival colony area. Fiber lengths were then measured using DNA Stranding software.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

All data is included in the figures and supplementary files of this manuscript.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	As our study revolves around ovarian cancer, all patients reported on were of the female sex.
Reporting on race, ethnicity, or other socially relevant groupings	All collected patient information is reported in the study.
Population characteristics	All collected patient information is reported in the study.
Recruitment	Patient information was collected by our collaborators through their participation in other studies (PMID: 29361470,). Patients were selected based on their RAD51C variant status. As these variants are rare, we included all available patients.
Ethics oversight	Patient harboring RAD51C-L238R provided written informed consent before enrollment. The trial was approved by the Institutional Review Board of the Center for Cancer Research, National Cancer Institute, USA. This study was approved by Basser Center for BRCA and the National Cancer Institute.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size calculations were not performed as our experiments show an average of yeast, mammalian cell culture and biochemistry experiments.
Data exclusions	For SCR assays outliers were removed using ROUT test with Q=10%. For clonogenic survival assays, whole replicates were removed when controls plates did not work (growth lower than expected in comparison with drug treated plates). Values were removed if the three technical replicates were not reproducible in a given clonogenic survival experiment.
Replication	Experiments were performed three to five times with the exception of the clonogenic survival assay for RAD51C-V166G exposure to 0.5 micromolar Olaparib which was performed with two biological replicates and three technical replicates. Experiments were found to be reproducible.
Randomization	Randomization is not relevant to our study as we performed a screen and had no expectations for outcomes.
Blinding	Blinding is not relevant to our study as we performed a screen and had no expectations for outcomes.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	RAD51C antibody (1:500; Abcam Cat# ab55728, RRID:AB_945135), Kar2 antibody (1:2,000; Santa Cruz, sc-33630), Tubulin Antibody (1:1,000; Cell Signaling Antibody#2144S), vinculin antibody (1:500; Santa Cruz SC73614) secondary antibodies (1:5,000; Licor IRDye 680RD goat anti-rabbit 926-68071 and Licor IRDye 800CW goat anti-rabbit 926-32211)
Validation	RAD51C Antibody: https://www.abcam.com/products/primary-antibodies/rad51c-antibody-ab55728.html Kar2 Antibody: https://datasheets.scbt.com/sc-33630.pdf Tubulin Antibody: https://www.cellsignal.com/products/primary-antibodies/a-tubulin-antibody/2144?_requestid=519011 Secondary Licor IRDye 680RD: https://www.licor.com/bio/reagents/irdye-680rd-goat-anti-rabbit-igg-secondary-antibody Secondary Licor IRDye 800CW: https://www.licor.com/bio/reagents/irdye-800cw-goat-anti-rabbit-igg-secondary-antibody

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	PJ64a yeast cells were sourced from Rodney Rothstein and used in several publications by our group (PMID: 23460207,PMID: 26936927). U2OS RAD51C knockout cells were sourced from and fully characterized by Mauro Modesti (PMID: 31584931). Wild-type complemented cell line was created in a previous publication by our lab (PMID: 36099300). RAD51C variant stable cell lines were created for this study.
Authentication	RAD51C knockout cell line or variant expressing stable cell lines were authenticated through regular gDNA RAD51C sequencing. These cell lines were also authenticated through western blot analysis. Yeast cells were not authenticated.
Mycoplasma contamination	Cells were regularly tested for mycoplasma and cells were grown in mycoplasma prophylactic to prevent contamination. If contamination was identified, cells were tossed and replaced with freshly thawed mycoplasma free cells.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were utilized in this study.

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	U2OS cells were trypsinized, washed and resuspended in PBS. Cells were either immediately analyzed or fixed in PFA for later analysis.
Instrument	CytoFlex 6L
Software	CytoExpert was used to analyze flow data.
Cell population abundance	In SCR assays, 20,000 events are measured. Of these events, around 30% are considered viable cells based on SSC and FSC. Of the viable cell population, between 0% and 20% are GFP positive based on FITC and PE-A.
Gating strategy	RAD51C knockout uncomplemented, wild-type complemented or variant complemented cells were analyzed through flow. Gating was based off of size (FSC/SSC) and GFP positive expression (FITC/PE).

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.