European Journal of Cancer 124 (2020) 88–90

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Letter to the Editor

Challenging the believed proportion of ovarian cancer attributable to BRCA2 versus BRCA1 pathogenic variants

Nicola Flaum [a,b,*], Emma J. Crosbie [c,d], Emma R. Woodward [a,b], Fiona Lalloo [a,b], D. Gareth Evans [a,b,e,f,g]

[a] *Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, M13 9PL, UK*
[b] *Manchester Centre for Genomic Medicine and NW Laboratory Genetics Hub, Manchester University Hospitals NHS Foundation Trust, Manchester, M13 9WL, UK*
[c] *Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, M13 9PL, UK*
[d] *St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester, M13 9WL, UK*
[e] *Prevention Breast Cancer Centre and Nightingale Breast Screening Centre, University Hospital of South Manchester, Manchester, M23 9LT, UK*
[f] *The Christie NHS Foundation Trust, Manchester, M20 4BX, UK*
[g] *Manchester Breast Centre, Manchester Cancer Research Centre, University of Manchester, Manchester, M20 4BX, UK*

Received 19 July 2019; received in revised form 23 September 2019; accepted 6 October 2019
Available online 21 November 2019

Dear Editor,

High-grade serous ovarian cancer is known to be one of the most heritable cancers, with a three-fold increase in risk of developing the disease in women with a first-degree relative (FDR) with ovarian cancer [1]. Germline *BRCA1* or *BRCA2* pathogenic variants (PVs) have been reported in approximately 15% of patients with ovarian cancer, and 23% of women with high-grade serous ovarian cancer [2]. Women with *BRCA1* PVs have a 44%–61% cumulative lifetime risk of ovarian cancer and *BRCA2* a 17%–24% cumulative lifetime risk [3,4]. Most of these variants (approximately two-thirds) have been described in the *BRCA1* gene, at a frequency of 8–10% in the overall ovarian cancer population [2,5,6] compared with a frequency of 4.5–5.5% [2,5,6] for *BRCA2* in the overall ovarian cancer population.

On review of the 272 *BRCA1/2* mutations in patients with ovarian cancer identified by the Manchester Centre for Genomic Medicine from index patient full screens, a higher proportion of *BRCA2* to *BRCA1* PVs than generally described was noted with *BRCA2* PVs occurring in 39.0% of this cohort (106/272). In the group of women diagnosed with ovarian cancer who are older than 60 years, the frequency of *BRCA2* PVs rose to 69.6% (48/69), significantly greater than that of a *BRCA1* PV (chi-squared; $p = 3.88 \times 10^{-9}$, see Fig. 1). Age as a continuous variable against *BRCA1* and

* *Corresponding author*: Manchester Centre for Genomic Medicine, St. Mary's Hospital, Oxford Road Manchester M13 9WL, UK. Fax: +44 (0)161 276 6145.
E-mail addresses: Nicola.flaum@manchester.ac.uk (N. Flaum), Emma.crosbie@manchester.ac.uk (E.J. Crosbie), Emma.woodward@mft.nhs.uk (E.R. Woodward), Fiona.lalloo@mft.nhs.uk (F. Lalloo), Gareth.evans@mft.nhs.uk (D. Gareth Evans).

https://doi.org/10.1016/j.ejca.2019.10.018
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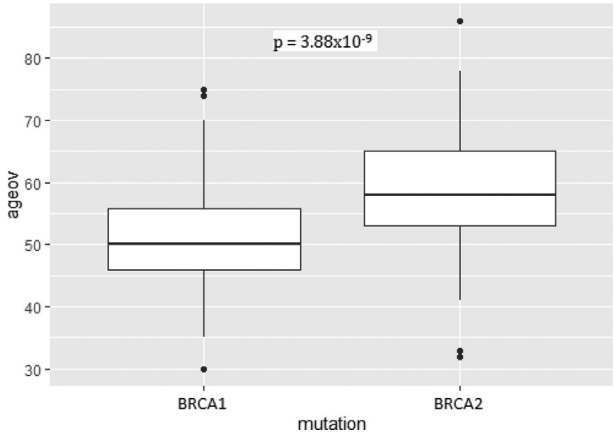

Fig. 1. Boxplot showing difference in age at diagnosis of ovarian cancer among women with pathogenic variants in BRCA1 versus BRCA2.

BRCA2 PVs was also significant (independent two-tailed t test; $p = 9.55x10^{-11}$). In the entire data set of 793 *BRCA1* and 780 *BRCA2* families containing 1,708 female *BRCA1* PV carriers and 1,647 *BRCA2* PV carriers, there were 672 confirmed ovarian cancers in *BRCA1* and *BRCA2* PV carriers, 425 (63.2%) in *BRCA1* and 247 in *BRCA2* (36.8%), similar to the frequencies found in index case screening. Again the majority of those aged ≥60 years with ovarian cancer were *BRCA2* carriers (97/161−60.2%), compared with 95/257 (37%) in those aged 50−59 years, 45/204 (22%) in 40−49 year olds and 10/50 (20%) aged <40 years.

Women were also more likely to carry a *BRCA2* PV compared with a *BRCA1* PV if they had fewer (minimum = 1, maximum = x) family members with ovarian cancer (Wilcoxon rank-sum test; p = 0.04). However, there was no significant difference between *BRCA1* and *BRCA2* frequency in sporadic cases without a family history (n = 48) compared with those with at least one affected family member (n = 224) (chi-squared; p = 0.12). Patients were also more likely to carry a *BRCA2* PV if they had a lower Manchester Score (a risk model incorporating details from a patient's personal and family medical history and pathology to give a score indicating likelihood of carrying a pathogenic *BRCA1* or *BRCA2* variant [7]) (Wilcoxon rank-sum test p = 0.00018). We also found in the Manchester cohort a higher proportion of *BRCA2* PVs than expected in index ovarian cancer cases compared with FDR (42.8% vs 28.8%, chi-squared; p = 0.00037) which likely reflects the younger age of most FDRs (median 48.4, interquartile range 39.52−59.99) and the substantial proportion of those testing positive undertaking risk-reduction salpingo-oophorectomies before age 45 years (415/717; 58% living more than 45 years).

The findings from this analysis are corroborated by some of those reported in the literature; Alsop *et al.* [2] in their 2012 study of 1,001 women with non-mucinous ovarian carcinoma demonstrated that of 109 women with either a *BRCA1* or *BRCA2* PV, 35.8% had variants in *BRCA2*; however in those diagnosed with ovarian cancer at 61 years or older this increased to 52.6%. Song *et al.* [3] in their 2014 study of 2,222 women with epithelial ovarian cancer also found increasing frequency of *BRCA2* variants at an older age (55.7% in those diagnosed at age >60 compared with 45.5% in those diagnosed at age<60 years, to 32.1% in those diagnosed <50 years, and 33.3% in those diagnosed <40 [3]). However, neither study highlighted the difference according to age or discussed their findings further. Our findings, backed up by our analysis of other studies [2,3] are at odds with the apparently higher risks for those aged >60 years with *BRCA1* for ovarian cancer of 55.9/1000 and 29.4/1000 per year compared with 15/1000 and 10.3/1000 in *BRCA2* in two other studies [4,8].

Our findings of a higher prevalence of *BRCA2* PVs in women who developed ovarian cancer at an older age, as well as those with fewer affected family members and a lower Manchester Score compared with women with *BRCA1* PVs, likely reflect the reduced penetrance of *BRCA2* particularly in relation to ovarian cancer compared with *BRCA1* [4,8,9]. The competing mortality from higher risk of early-onset breast cancer risk in *BRCA1* versus *BRCA2* may also contribute to this finding [4,10].

Our data, together with those previously reported [2,3], suggest that the proportion of *BRCA2*-affected patients with ovarian cancer, and in certain populations, the frequency of *BRCA2* PVs, may be higher than the previously thought. This is increasingly highlighted by population-based testing rather than risk-based testing. Future work could determine how cumulative risk of ovarian cancer is affected by incorporating this analysis and using patients aged 60 years as a threshold. We suggest that those women with ovarian cancer at an older age, with few or no affected family members, or with a lower Manchester Score are more likely to carry a *BRCA2* PV than a *BRCA1* PV, irrespective of the overall higher risk of ovarian cancer associated with *BRCA1* PVs. Physicians and genetic counsellors looking after these patients should consider this, given the differing risk profiles and risk management strategies, for individuals carrying PVs in *BRCA1* and *BRCA2* and their relatives.

Acknowledgements

N.F. is supported by a Cancer Research UK grant to Manchester Cancer Research Centre. E.J.C., E.R.W., and D.G.E. are supported by the National Institute for Health Research Manchester Biomedical Research Centre (IS-BRC-1215-20007).

Declaration of competing interest

None declared.

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