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Comment

Emerging cancer risks in *BRCA2* pathogenic germline variant carriers

Patrick R Benusiglio ^{1,2*}, Antoine Dardenne ³, Vincent Fallet ⁴, Jacques Cadranel ⁴

1. Sorbonne Université, UF d'Oncogénétique Clinique, Département de Génétique Médicale, Hôpital Pitié-Salpêtrière, AP-HP, 47-83 Boulevard de l'Hôpital, F-75013 Paris, France.

2. Sorbonne Université, INSERM, Unité Mixte de Recherche Scientifique 938 et SIRIC CURAMUS, Centre de Recherche Saint-Antoine (CRSA), Equipe Instabilité des Microsatellites et Cancer, F-75012 Paris, France.

3. Sorbonne Université, Service de Chirurgie Digestive, Hôpital Saint-Antoine, APHP, F-75012 Paris, France.

4. Sorbonne Université, GRC-04 Theranoscan et Service de Pneumologie et Oncologie Thoracique, Hôpital Tenon, APHP, F-75020 Paris, France.

*Corresponding author patrick.benusiglio@aphp.fr

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Carriers of pathogenic germline variants (PGV) in *BRCA2* could soon be offered gastric cancer screening using gastroscopy. In the longer term, some might even take part in lung cancer screening programs. Indeed, while the risks of breast, ovarian, pancreatic and prostate cancer have been documented for years, recent data show an increased risk of gastric cancer, and suggest an association with lung cancer. This article focuses specifically on *BRCA2*, while sidelining its sister gene *BRCA1*, as evidence for a broad cancer spectrum is much stronger for the former.

Li *et al.* studied 2,157 *BRCA2* families via the international Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) (1). Relative risks (RR) for gastric cancer were 3.69 (95%CI 2.40-5.67), which translated into an absolute risk of 3.5% by age 80 years. RR were actually higher in females compared to males, but due to a lower baseline incidence in females, absolute risks ended up being equal.

A completely different approach led to similar results. In a multi-institutional Japanese study, the authors compared the prevalence of *BRCA2* PGV between 10,705 gastric cancer cases and 38,153 controls (2). Gastric cancer odds ratio associated with *BRCA2* were 4.7 (95%CI 3.1-7.1). Absolute risks of gastric cancer were much higher than in the CIMBA study at 19.3% by age 85 years, something that was expected given the higher incidence rate in East-Asian populations. Importantly, there was no indication of an excess of canonical *BRCA2*-associated cancers among relatives of cases, which would have led to ascertainment bias. The same authors performed a complementary study that included 1,433 cases and 5,997 controls with documented *Helicobacter Pylori* (HP) status (3). There was an additive interaction between HP and *BRCA2*. Individuals with both a PGV and HP infection had an excess disease risk as compared to those with either risk factor alone. Relative excess risk was estimated at 16.01 (95%CI 2.22-29.81) for homologous recombination genes overall.

There is now convincing evidence that loss of *BRCA2* function drives gastric cancer development. High homologous recombination deficiency (HRD) scores were for example detected in 100% of gastric cancers (4 out of 4) in *BRCA2* PGV carriers, in an in depth somatic study of non-canonical cancers associated with the gene (4).

Let us move on to lung cancer. Not all readers might be aware that lung cancer is sometimes a hereditary disease, and that most hereditary lung cancers are of the adenocarcinoma type (5). Indeed, there are now well established susceptibility genes, the main ones being *TP53*, *EGFR*,

and *ATM*. Up to 1% of lung cancers could be directly attributable to a PGV (6,7). As for *BRCA2*, while the evidence is weaker than for gastric cancer, recent and well conducted studies do hint at an association.

Diossy *et al.* explored mutational signatures in lung adenocarcinomas from the Cancer Genome Atlas (8). Out of two cancers occurring in *BRCA2* PGV carriers, one had both a HRD signature and loss of the wild-type allele.

In a whole exome sequencing (WES) study of UK Biobank lung cancer cases (n=1,868, all types) and controls (n=182,206), *BRCA2* was one of only three genes for which there was evidence of an association, alongside *ATM* and *TP53* (9). *BRCA2* PGV carriers had an increased risk of lung cancer with an OR of 1.95 (95%CI 1.12-3.38).

The European Society for Medical Oncology precision medicine working group recently analysed 6145 paired tumour-normal samples of non-small cell lung cancers (10). A *BRCA2* PGV was found in 1% of cases (n=61), compared to a prevalence of 0.35% in the general population (11).

As for the previously-cited CIMBA study of 2,157 *BRCA2* families, there was no increased risk of lung cancer overall. However, RR in females PGV carriers was 2.84 (95%CI 1.23-6.60) (1). Admittedly, subgroup analyses must be treated with caution, and there are reasons to believe this apparent association could be explained by methodological considerations (12). Still, the simple suggestion of an increased risk is intriguing in the context of positive case-control and paired tumour-normal studies.

Going back to the surveillance of carriers, it would be premature to recommend lung cancer screening to all *BRCA2* PGV carriers. However, one might one day incorporate *BRCA2* status into multivariable models to determine eligibility for low-dose computed tomography, in association with other factors such as smoking history, ethnicity, and environmental exposure (pollution, radon, asbestos) (13). Regarding gastric cancer, prospective studies are warranted to assess the benefit of systematic, regular screening gastroscopies. In the meantime, we would suggest offering *HP* screening using a urea breath test to all carriers, with gastroscopy and eradication if present, and starting whenever possible before the age of 30 years (14).

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Conflicts of interest

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Author contributions

PB reviewed the literature and wrote the first draft. PB, AD, VF and JC discussed the evidence, made carrier management proposals, revised the manuscript and approved the final version.