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Correspondence

Serous ovarian carcinoma in patients with Lynch syndrome: Caution is warranted

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In a recent issue of *Gynecologic Oncology,* Woolderink et al. reported on ovarian cancer characteristics among two cohorts of Dutch patients with Lynch syndrome (Woolderink et al., 2018). Detailed clinical and pathological descriptions based on large series of patients with genetic susceptibility to cancer are always welcome, and the authors should therefore be praised for their efforts. Such reports potentially help cancer geneticists determine which patients need germline genetic testing, and what genes should be analyzed. Furthermore, better knowledge of cancer risks among proven mutation carriers determines long-term management, i.e. surveillance and risk reduction. However, we would like to express some reservations regarding the findings by Woolderink et al., more specifically the reported number of high- and low-grade serous ovarian carcinomas among Lynch patients, an aspect that is not properly addressed in the discussion. The study included 878 women. Fifty-three had a history of ovarian cancer, nineteen of which (34%) were high or low-grade serous tumors. The high proportion of serous tumors is surprising, since recent literature strongly suggests that there is no association between serous ovarian carcinoma and Lynch syndrome. We have selected three high-impact papers to support our claims. Rambau et al. observed no protein expression loss for the four mismatch repair (MMR) genes, *MLH1, MSH2, MSH6, PMS2* in 175 serous ovarian carcinomas, while the proportion was 25/181 (13.8%) and 4/163 (2.4%) for endometrioid and clear cell tumors, respectively (Rambau et al., 2016). Expression loss as identified by immunohistochemistry (IHC) is suggestive of Lynch syndrome, as is microsatellite instability (MSI) within the tumor, and subsequent germline testing of MMR genes is required to confirm the diagnosis. In a series of 1893 women with epithelial ovarian cancer ascertained from three population-based studies, Pal et al. diagnosed Lynch syndrome in only 2/933 (0.2%) patients with serous carcinomas (Pal et al., 2012), a frequency that is inferior to estimations of Lynch syndrome frequency in the general population (Hampel and de la Chapelle, 2013; Haraldsdottir et al., 2017). Finally, Chui et al. performed central pathology review of tumor subtype on twenty mutation-confirmed Lynch syndrome ovarian carcinomas (Chui et al., 2014). Serous histology was not seen.

There are three possible explanations to account for these unexpected findings. First, the reported ovarian cancers might have been phenocopies, i.e. sporadic cancers not associated with the genetic susceptibility. The authors performed neither MMR IHC nor MSI testing to confirm that cancers were indeed due to Lynch syndrome. The vast majority, if not all Lynch syndrome-associated ovarian carcinomas, show MMR protein expression loss and/or microsatellite instability (Akbari et al., 2017; Libera et al., 2017). Furthermore germline mutations in the *BRCA1/2* and *RAD51C/D* ovarian cancer susceptibility genes were not formally excluded. The authors state that cases did have *BRCA1/2* germline testing, but analyses carried out fifteen or twenty years ago (the two reported cohorts began in 1987 and 1993, respectively) are unlikely to have been as sensitive as today, and to have included a search for large rearrangements. Second, pathology review was not performed, and some endometrioid or clear cell ovarian tumors may have been misclassified as serous. Up to 20% of serous carcinomas are reclassified after rigorous pathology review (Gilks et al., 2008; Köbel et al., 2013). Finally, some cases only had suspected Lynch syndrome, as the diagnosis was sometimes based on the clinical Amsterdam criteria while genetic testing was not performed.

Accurate data on histological types associated with cancer susceptibility syndromes remain paramount as they guide genetic counseling and gene testing. Despite the findings reported by Woolderink et al., it might not seem wise for cancer geneticists to emphasize the possibility of Lynch syndrome and systematically prescribe MMR germline analysis in patients with serous ovarian carcinoma. Admittedly, with the widespread use of susceptibility gene panels, one might argue that regardless of the clinical context all genes can easily be analyzed. Genetic counseling must nevertheless still be based on the history of the patient and her relatives. Furthermore, health systems funded by the state or by a national social security (e.g. United Kingdom, France) might not have the means to offer panel testing to all patients. Additionally, the information given to women with Lynch syndrome and their management will differ whether or not they have a risk of developing high-grade, often incurable serous carcinoma of the ovaries.

In conclusion, the number of serous ovarian carcinomas among Lynch patients in the Woolderink et al. study is intriguing, but in the

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absence of MMR immunohistochemistry, microsatellite analysis and pathology review, it is important to remain cautious. At this stage, we still consider the increased risk of ovarian carcinomas in Lynch syndrome to be limited to the endometrioid and clear cell types.

Conflicts of interest

The authors have no conflict of interest to declare.

Author contribution

Both authors reviewed the literature and wrote this Letter to the Editor.

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Patrick R. Benusiglio[a,*], Florence Coulet[b,c]

[a] *Consultation d'Oncogénétique, Unité fonctionnelle d'Oncogénétique, Département de Génétique, Groupe Hospitalier Pitié-Salpêtrière AP-HP, F-75013 Paris, France*

[b] *Laboratoire d'Oncogénétique, Unité fonctionnelle d'Oncogénétique, Département de Génétique, Groupe Hospitalier Pitié-Salpêtrière AP-HP, F-75013 Paris, France*

[c] *Sorbonne Université, Faculté de Médecine, F-75013 Paris, France*

E-mail addresses: patrick.benusiglio@aphp.fr, patrick.benusiglio@cantab.net (P.R. Benusiglio)

* Corresponding author.