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Correspondence

Ovarian carcinoma histotype in Lynch syndrome

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To the Editor,

We read with great interest the recent paper by Ryan et al., published in *Gynecologic Oncology* (Ryan et al., 2017). The highlights of this study on ovarian cancer (OC) in patients with Lynch syndrome, according to the authors, include the observation that in terms of OC subtype frequency, "Endometrioid OC was most common, followed by high-grade serous, clear cell and mixed histology". We note, however, that slides from these cases were not reviewed as part of this study, and therefore their study design does not allow them to accurately determine the histotype of the ovarian carcinomas in their series. The evolution in histotype diagnosis is well documented in the literature, such that when current (WHO, 2014) criteria are applied, the diagnosis of ovarian carcinoma histotype correlates with genetic abnormalities in the tumors, and importantly, risk of one of the two common autosomal hereditary cancer syndromes, i.e. Lynch syndrome, caused by mutations in the mismatch repair genes or Hereditary Breast and Ovarian Cancer Syndrome (HBOCS), caused by BRCA1 and BRCA2 mutations (Kommoss et al., 2016; Chui et al., 2014; Chui et al., 2013; Lu et al., 2012; Mills and Longacre, 2016). There is considerable literature, uncited by the authors, indicating that patients with Lynch syndrome are at increased risk of the endometriosis-related histotypes (e.g. endometrioid and clear cell) but not high-grade serous carcinoma, while patients with HBOCS are at increased risk for developing high-grade serous carcinoma. This has important implications for screening patients presenting with ovarian cancer for hereditary cancer syndromes. Patients with high-grade serous carcinoma are at sufficiently low risk of Lynch syndrome that there is no evidence to support screening with MMR immunostaining, in contrast to patients with endometrioid or clear cell carcinomas, where the risk is comparable to that of patients presenting with colorectal or endometrial carcinoma.

Ryan et al. report six cases of high-grade serous carcinoma in their series, diagnosed between 1973 and 2006. Given that this diagnostic entity was only formally accepted in the 2014 update of the WHO classification of ovarian carcinoma, and therefore this diagnostic terminology was not widely used during the era when these cases where diagnosed, there is no way to verify these diagnoses in the absence of slide review. It is our opinion that the literature would be better served if the authors had simply recorded the diagnoses as they were written in the original pathology report rather than attempting to fit these tumors into modern diagnostic categories, which may or may not be accurate. For example, 5 of 6 "high-grade serous carcinomas" in their study were stage I or II, while 5 of 6 high-grade serous carcinomas (on average) in unselected case series would be expected to be Stage III or IV. Why this difference? Do high-grade serous carcinomas in Lynch syndrome have an unexpectedly indolent behavior? It is much more likely, in our opinion, that they are not high-grade serous carcinomas but it is more correct to state that we simply do not know.

The difference between historic and current histotype diagnoses is significant (for example, 46% of histotype diagnoses from a 2003 clinical trial were changed on review, using modern diagnostic criteria, and the review diagnoses proved to be highly reproducible (98% agreement between two observers) (Kommoss et al., 2016)) and has clinical impact; when reviewing cases where only a pathology report is available, with no slides for review, and the report is more than 5 years old, it is best to view the histotype designation with skepticism. Reflex testing of current cases, with accurate histotype diagnosis, is a different matter entirely.

We worry that this paper will be read and cited as evidence supporting the screening of patients with high-grade serous carcinoma for Lynch syndrome, or as evidence that high-grade serous carcinoma in Lynch syndrome has a different natural history from that of sporadic high-grade serous carcinoma. To have gathered the "largest reported series of OC from proven Lynch syndrome carriers" undoubtedly creates a significant resource, but until pathology, genomics and clinical history are given equal importance, a study such as this cannot resolve any lingering debate regarding the relationship between germline mutations and ovarian carcinoma subtype.

The authors declare that they have no conflicts of interest.

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C. Blake Gilks
Dept of Pathology, Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada
Corresponding author at: Rm 1253, 1st floor JPPN, Dept of Pathology, Vancouver General Hospital, 910 West 10th Ave, Vancouver, BC V5Z 4E3, Canada.
E-mail address: Blake.Gilks@vch.ca.

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Blaise A. Clarke
Dept of Pathology and Pathobiology, Toronto General Hospital, University of Toronto, Toronto, ON, Canada

William D. Foulkes
Dept of Human Genetics, McGill University, Montreal, QC, Canada

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