Mucinous carcinomas of the ovary and colorectum: different organs, same dilemma

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Mucinous carcinomas are uncommon histological types that affect several organ sites. Primary mucinous carcinomas of the ovary are distinct from other ovarian carcinoma types, but they can pose a particular challenge for correct diagnosis from metastases, which most usually originate from the colorectum. Correct diagnosis is the mainstay of treatment, because standard practice states that protocols are tailored to the primary organ site. Little is known of mutational alterations in primary and metastatic mucinous carcinomas of the ovary, and few markers exist that can discriminate between them. We reviewed commonalities between ovarian and colorectal mucinous carcinomas with respect to aetiology, molecular alterations, differential diagnosis, and implications for treatment. Although primary mucinous carcinomas of the ovary and colorectum share similar mutational patterns and unfavourable outcomes at advanced stage, compared with their non-mucinous counterparts, important differences exist with respect to mucin localisation and specific molecular alterations. Technologies—eg, next-generation sequencing—could aid identification of additional driver molecular changes that will help clarify the relationship between mucinous carcinomas from different organ sites. Perhaps, then, we can consider moving towards testing and adoption of therapeutic approaches tailored to molecular characteristics of mucinous carcinomas, irrespective of organ site, so patients’ survival can be optimised.

Introduction

Carcinomas classified as ovarian are the fourth most common malignant disease in women, accounting for 225 000 (4%) of all new cases and 140 000 (4%) of all deaths from cancer globally in 2008. Types of ovarian carcinoma—including high-grade serous, low-grade serous, clear cell, endometrioid, and mucinous—differ with respect to morphology, genetic alterations, biomarker expression, and clinical course, and these types are being recognised increasingly as separate entities.

Although differential diagnosis of other types of ovarian carcinoma is highly reproducible, differentiation of advanced primary ovarian mucinous carcinoma from metastases of other organ sites—most typically of the colorectum—can be difficult. Why should identification of the primary site matter? In standard practice, treatment protocols are tailored to organ site. Thus, a diagnosis of mucinous carcinoma as a primary of the ovary would initiate treatment with platinum-based taxane agents, whereas a metastatic carcinoma at the ovary originating from the colorectum would receive fluorouracil. This approach would be reasonable if commonalities between carcinomas of shared organ sites were greater (eg, predicted similar response to treatment) than those between carcinomas with shared molecular alterations, irrespective of organ site. However, oncologists have long noted that advanced ovarian mucinous carcinomas do not respond to treatment protocols as are tailored to organ site establishes the surgical approach, molecular and histological characteristics might be more useful to guide adjuvant treatment options.

Methods

Search strategy and selection criteria

Published data were identified from Medline with the search terms “mucinous adenocarcinoma” (with respect to the subheadings diagnosis, epidemiology, aetiology, genetics, immunology, pathology, pathophysiology, and therapy) and each of “colorectal neoplasms” or “ovarian neoplasms”. We also scanned the reference lists of relevant reports. Results were restricted to journal articles (excluding case reports) published in English between January, 1980, and October, 2010, in which adults (age ≥19 years) were studied. We placed primary emphasis on reports with at least 50 mucinous carcinomas and supplemented them with smaller studies when data were limited. Studies were included if criteria for definition of mucinous carcinomas were reported or if pathological re-review of tumour specimens was done. For ovarian mucinous carcinomas, 433 abstracts were identified and of these, 121 full-text articles were retrieved; 33 were included in this Review. For colorectal mucinous carcinomas, 429 abstracts were identified and of these, 130 full-text articles were retrieved; 22 were included in this Review. Targeted Medline searches for specific mutations were also undertaken. Data abstraction was done by both authors; studies were only included with both authors’ agreement.
Data synthesis
We did two types of meta-analysis based on a subset of information presented in this Review. For the first, we derived summary estimates and 95% CIs for studies reporting the frequency of molecular alterations in mucinous and non-mucinous carcinomas, using frequency of alteration and study sample size to calculate the SE for an individual study. 19 of 119 studies identified by our search strategy were eligible for inclusion. For the second meta-analysis, we derived summary estimates and 95% CIs for studies of survival outcomes, in which mucinous and non-mucinous carcinomas were compared, and we used the hazard ratio and 95% CI from every study’s multivariable-adjusted Cox’s proportional-hazards regression. Nine of 22 studies identified were eligible for inclusion. For both meta-analyses, we used Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ, USA), and a fixed-effects model, and we calculated statistical heterogeneity with Cochran’s Q χ² test (k–1 degrees of freedom). Statistical heterogeneity was present in the first meta-analysis so, for accuracy, we excluded studies that contributed to heterogeneity. No statistical heterogeneity was noted in survival studies.

Definition, prevalence, and epidemiology

Definition
The definition of mucinous carcinoma varies across organ sites. For this Review, we adhered to WHO classifications. Ovarian mucinous carcinomas form multicystic tumours and show conspicuous amounts of intracellular mucin (usually ≥50% of the cytoplasm) in more than 90% of tumour cells.¹¹ By contrast, an adenocarcinoma of the colorectum is classified as mucinous if at least 50% of the tumour’s volume is composed of extracellular mucin, for which the historical term colloid or gelatinous carcinoma has been used.¹² These carcinomas are distinct from those with signet-ring cells, which have specific molecular alterations and clinical behaviour and are not discussed here.

Prevalence
Mucinous carcinomas are uncommon types of ovarian and colorectal cancer. Historically, ovarian mucinous carcinomas made up about 12% of all ovarian neoplasms; however, recent estimates place prevalence at roughly 3% in North American populations.¹¹ This diminished proportion is due to: refinement of criteria that distinguish metastatic mucinous carcinomas—including pseudomyxoma peritonei of gastrointestinal (appendiceal) origin—from primary ovarian mucinous carcinomas; refinement of criteria that distinguish mucinous borderline tumours from mucinous carcinomas; and review of additional cases from series that are population-based rather than from tertiary referral centres, which could see complex cases for a second opinion and which might have overestimated prevalence.¹³ For this reason, past reports of prevalence of ovarian mucinous carcinomas are probably unreliable. Likewise, colorectal mucinous carcinomas are uncommon. National cancer registries provide the most representative estimates, ranging from about 4% in Asian countries¹⁴ to roughly 11% in North American women.¹⁵ Typically, prevalence of colorectal mucinous carcinomas does not differ by much between women and men. Chart reviews from individual institutions are probably biased upwards and cite generally higher prevalence, especially in western Europe.³,⁶,⁷

Common features associated with both ovarian and colorectal mucinous carcinomas, compared with their non-mucinous counterparts, include higher prevalence in patients younger than 40 years¹⁴,¹⁵ and larger tumour size at diagnosis.³,⁵ Some differences are also noted. Whereas a higher proportion of ovarian mucinous compared with non-mucinous carcinomas are diagnosed at a low stage (54% vs 10% at stage I/II, respectively),¹⁶ colorectal mucinous carcinomas seem equally as likely as non-mucinous carcinomas to present at a low stage in population-based series (47% vs 51% at stage I/II, respectively).¹⁶,²⁰ Reports of high-stage diagnosis of colorectal mucinous carcinomas could be from non-representative cases that are included in the consultation files of hospital series. National registry data also support a higher proportion of mucinous carcinomas in the right colon compared with the left colon.¹⁵

Epidemiological risk factors
Risk factors for ovarian mucinous carcinomas differ from those for other histological types. Perhaps the most consistent and strongest risk is cigarette smoking. Current or recent smoking, and a higher number of pack-years, was associated with about a two-fold increase in risk of ovarian mucinous carcinoma compared with non-mucinous carcinomas, which had no or weak associations.²¹,²² Risks were similar or stronger for mucinous tumours of borderline malignancy or adenomas.²¹,²²

By contrast, few epidemiological studies have been done of colorectal mucinous carcinomas. In a population-based series, an increase in risk with body-mass index was reported.²¹ Factors associated with colorectal non-mucinous carcinomas are more widely reported. A decline in risk is linked to raised physical activity, aspirin or non-steroidal anti-inflammatory drug use, augmented daily vegetable intake, and positive oestrogen status in women, whereas factors associated with an increase in risk are cigarette smoking and high body-mass index.²³

Aetiology and molecular alterations

Aetiology
Normal mucinous epithelium consists of three types of mucus-secreting cells, which line the stomach (gastric), endocervix (endocervical), and intestine (intestinal).
Normal intestinal epithelium is lined with absorptive non-mucinous enterocytes, which are interspersed with mucin-secreting goblet cells that increase in number progressively towards the distal rectum. Mucus gel provides protection to epithelial cells that line the intestinal tract. The precise cell of origin for colorectal mucinous carcinomas is unknown, but they show a strong association with premalignant serrated neoplasms, which are proposed to be a distinct entity among colonic adenomas.25

The aetiology of ovarian mucinous carcinoma remains puzzling. None of the above-mentioned normal mucinous cell types exists within the ovary. Mucinous metaplasia might be seen occasionally in ovarian endometriosis, which is associated with ovarian mucinous borderline tumour of the endocervical type. This tumour type is not discussed here because almost all ovarian mucinous carcinomas show features of intestinal type. Although the cell of origin remains enigmatic, progression of ovarian mucinous carcinomas can be recorded as a morphological continuum from benign mucinous cystadenoma areas, via atypical proliferating (borderline) mucinous tumours with or without intraepithelial carcinoma, to mucinous carcinomas. This progression model is not unlike that proposed for colorectal carcinomas in general.26 For clinical management reasons, definition of a precursor lesion that implies a specific risk of progression is desirable; however, the threshold at which increased risk for ovarian mucinous tumours should be considered is highly controversial.27

Findings of small array-based studies of between three and nine ovarian mucinous carcinomas suggest that these cancers have a distinct mRNA expression profile compared with other types of ovarian carcinomas. These data relate ovarian mucinous carcinomas more closely to colonic epithelium or colorectal neoplasms.7,28 Melis and colleagues29 undertook mRNA expression profiling of 20 colorectal mucinous and 151 colorectal non-mucinous carcinomas. Genes encoding the intestinal (MUC2) and gastric (MUC5AC) mucin proteins were among the highest overexpressed genes in mucinous versus non-mucinous carcinomas. Comparison of these three studies, however, did not indicate any overlap of highly expressed genes between ovarian and colorectal mucinous carcinomas.

Molecular pathways
Frequencies of commonly altered molecular pathways are summarised in table 1. High microsatellite instability (MSI-H)—usually defined as instability or loss of at least 30% of a set of microsatellite markers—was reported in 22% of ovarian mucinous carcinomas,30 31% of colorectal mucinous carcinomas,34–37 30%40 of colorectal non-mucinous carcinomas,41 and 88%42 of colorectal non-mucinous carcinomas. Frequency of KRAS mutations in ovarian mucinous carcinomas was somewhat higher than that reported in colorectal mucinous and non-mucinous carcinomas.38 About 20% of colorectal mucinous carcinomas had BRAF mutations28,39,40 and 39% had mutations in either KRAS or BRAF.39 Amplification of HER2 (also known as ERBB2) was noted in 18% of ovarian mucinous carcinomas43 but was rare in colorectal mucinous and non-mucinous carcinomas.44,45 Assuming average alterations in KRAS, BRAF, or HER2 are mutually exclusive, then alterations in the mitogen-activated protein kinase (MAPK) pathway could arise in roughly 61% of ovarian mucinous carcinomas, 40% of colorectal mucinous carcinomas, and 38% of colorectal non-mucinous carcinomas. Nuclear expression of β-catenin—a result of mutations in either CTNNB1 or APC genes and indicative of aberrant signalling in the wingless (WNT) pathway—was seen in 9% of ovarian mucinous carcinomas,46 24% of colorectal mucinous carcinomas,42 and 88% of colorectal non-mucinous carcinomas.42 TP53 mutations were also recorded.28,41,42,43,46 By comparison of these frequencies, ovarian and colorectal mucinous carcinomas seem to be distinct from colorectal non-mucinous carcinomas and have in common a higher prevalence of MSI-H and lower frequency of alterations in the WNT signalling pathway and TP53. Changes in MAPK signalling seem to be highest in ovarian mucinous carcinomas.

In studies of colorectal mucinous carcinomas, results for molecular alterations by sex were not presented, and in many reports, sex of patients was not disclosed. Since prevalence of colorectal mucinous carcinomas does not differ much by sex, we could speculate that prevalence of molecular alterations also does not differ by sex; however, this idea needs confirmation.

The molecular landscape of mucinous carcinomas is poorly understood, owing in part to insufficient sample sizes, because mucinous carcinomas are rare, and to the scarcity of comprehensive mutation and expression analyses. We still know very little about mutations that arise alone or with another change, or those that are mutually exclusive. At least three scenarios are plausible. First, most mucinous carcinomas could develop along a low-grade pathway by acquisition of alterations in the MAPK cascade (eg, in KRAS)42,43 without other changes...
(eg, in TP53). In support of this idea, findings of a small study without clearly defined mucinous tumour content showed that none of eight borderline ovarian mucinous tumours had a TP53 mutation whereas two had a change in KRAS. Second, a subset of tumours with a MAPK pathway alteration could eventually progress to a high-grade mucinous carcinoma by further change-of-function mutation at TP53. We postulate that a third subset of mucinous carcinomas could develop as high grade from the outset, similar to serous ovarian carcinogenesis, with a mutation in TP53 but not within the MAPK pathway. For example, Pieretti reported that KRAS mutations were prevalent in 33%—and TP53 alterations in 26%—of ovarian mucinous carcinomas, but we are unclear if mutations were mutually exclusive. Large and comprehensive studies are needed to confirm these hypotheses.

Pathology
Diagnostic reproducibility

Morphologically, mucinous carcinomas can be separated into two subtypes—cystic and colloid—on the basis of intracellular or extracellular mucin localisation (figure 1). By definition, cystic mucinous carcinomas of the ovary or pancreas (eg, invasive pancreatic mucinous cystic neoplasms) contain little extracellular mucin but conspicuous amounts of intracellular mucin (usually ≥50%) in at least 90% of tumour cells. These tumours typically grow as cystic gland-forming neoplasms. By contrast, colloid (also known as gelatinous) mucinous carcinomas originating from the gastrointestinal tract, lung, breast, or skin are characterised by abundant extracellular mucin in 50% or greater tumour volume, by definition.

Refined use of morphological criteria has greatly increased interobserver reproducibility for diagnosis of primary ovarian mucinous carcinomas from other primary ovarian carcinoma types, which poses little difficulty in practice. More tricky is to consistently diagnose primary colorectal mucinous carcinomas from colorectal non-mucinous carcinomas. Diagnosis of colorectal mucinous carcinomas depends on extracellular mucin content, and the threshold of 50% or greater to classify mucinous carcinomas is arbitrary and controversial. In some studies of colorectal mucinous carcinomas, key molecular alterations were examined across different proportions of mucin content. Colorectal carcinomas with mucin components of 0%, 1–49%, and 50% or more showed MSI-H prevalence of 9%, 18%, and 37%, respectively; KRAS mutations were seen in 27%, 47%, and 31%, respectively; BRAF alterations were noted in 9%, 19%, and 27%, respectively; and P53 immunohistochemical overexpression was present in 55–56%, 24–41%, and 27–31%, respectively. Since no clear morphological differences exist between various proportions of mucin in colorectal mucinous carcinomas, this phenotype is still controversial. Hence, what is the relevance of a minor (<30%) mucinous component in colorectal carcinomas that do not meet the definition of mucinous?
Prevalence of ovarian mucinous carcinoma has declined strikingly within the past decade as a result of a diagnostic shift in two directions. First, in 2003, consensus was reached on criteria that separate benign mucinous tumours from invasive mucinous carcinomas. The lower limit of ovarian mucinous carcinoma was defined either as presence of stromal invasion exceeding microinvasion (>5 mm)—in the form of a destructive growth pattern characterised by irregular nests or groups of tumour cells scattered haphazardly in the stroma—or as an expansile growth pattern characterised by invasion as large sheets of neoplastic glands with no intervening stroma. Second, in a series of studies, morphological features were described that distinguish primary ovarian mucinous carcinomas from metastatic carcinomas of the ovary. These features include mucin localisation, tumour distribution (laterality), tumour size, surface involvement, lymphovascular invasion, destructive invasion, small invasive glands, desmoplastic response, and presence of signet-ring cells. Using these criteria, in a large Gynecological Oncology Group clinical trial, three pathologists judged a series of 44 ovarian mucinous carcinomas and agreed in 63% of cases to reclassify primary ovarian mucinous carcinomas as metastatic to the ovary.

Why is the distinction between primary ovarian and metastatic mucinous carcinomas so difficult to make? Subjective assessment based on many criteria with potentially contradicting information can be tricky, particularly in a time-constrained intraoperative setting. In practice, pathologists use a decision tree with mucin localisation, disease distribution, and growth pattern as the most pertinent information (figure 2). These criteria can differentiate mucinous carcinoma types in most patients. For example, if mucin is extracellular and tumour is encountered within the peritoneum, the clinical term pseudomyxoma peritonei can be applied. Pseudomyxoma peritonei is almost always appendiceal in origin and associated with low-grade appendiceal mucinous neoplasms or appendiceal colloid mucinous carcinomas. Colloid mucinous carcinomas from other sites, including the colorectum, can rarely cause pseudomyxoma peritonei. If mucin is extracellular and tumour is confined to the ovary, the clinical term pseudomyxoma ovarii can be applied. This diagnosis should initiate a search for an ovarian mature teratoma, which can give rise to a mucinous tumour producing large amounts of extracellular mucin.

More difficult scenarios arise within the group of advanced cystic mucinous carcinomas that show intracellular mucin. These, in fact, comprise only 1-2% of advanced-stage ovarian carcinomas. For any cystic mucinous carcinomas associated with extraovarian disease, a high level of suspicion should alert to the possibility of spread to the ovary from other...
gastrointestinal organs. Extravarian disease is usually associated with bilateral ovarian involvement. A phenotype very similar to ovarian mucinous carcinoma can be mimicked by low-grade non-mucinous carcinomas from the colon, pancreas, biliary system, stomach, and endocervix. The converse is also true: ovarian mucinous carcinomas with high nuclear atypia (grade 3) are often mucin-depleted, and morphological features resemble other higher grade non-mucinous carcinomas that are typically absent of conspicuous intracellular mucin. Because features favouring both primary and metastatic tumour can be present in the same patient, pathologists must use personal judgment when applying criteria from the decision tree.

Unfortunately, only a few immunohistochemical markers are useful for distinction of primary site. The cytokeratin CK7 and the transcription factor CDX2 showed opposing patterns of expression in ovarian and colorectal mucinous carcinomas that metastasise to the ovary (table 2). Some researchers suggest that the pattern of expression (strong or focal diffuse vs patchy diffuse staining) is useful to assign origin of mucinous carcinomas. CK7 could offer the best discriminatory value among markers assessed to date, yet it is limited by its ability to distinguish between ovarian mucinous carcinomas and colorectal mucinous carcinomas that metastasise to the ovary. Most studies in table 2 were restricted to women, in whom primary ovarian mucinous carcinomas and ovarian mucinous carcinoma metastases from the colorectum were evaluated concurrently.

Other groups propose that expression of mucin core protein can be used as a marker of cell lineage, to distinguish ovarian and colorectal mucinous carcinomas, particularly mucinous carcinomas that metastasise to the ovary. However, considerable overlap exists in immunohistochemical expression of MUC2 (intestinal origin) and MUC5AC (gastric origin) between ovarian and colorectal mucinous carcinomas (table 2), with no apparent translation into practical use. Expression of mucin proteins in metastatic colorectal mucinous carcinomas is lower than in primary colorectal mucinous carcinomas, suggesting either that mucinous carcinomas undergo further loss of differentiation as they metastasise or that metastatic colorectal carcinomas were, in fact, non-mucinous. Although a molecular marker for ovarian versus colorectal mucinous carcinomas would be ideal, mucin proteins could indicate mucinous cell lineage rather than site of origin.

### Table 2: Frequency of expression of selected markers used for differential diagnosis of metastatic colorectal and primary ovarian mucinous carcinomas

<table>
<thead>
<tr>
<th>Marker</th>
<th>Primary ovarian mucinous carcinomas</th>
<th>Primary colorectal mucinous carcinomas</th>
<th>Colorectal mucinous carcinomas metastatic to the ovary</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>90% (79–96)</td>
<td>10%</td>
<td>18% (11–29)</td>
</tr>
<tr>
<td>CDX2</td>
<td>28% (18–42)</td>
<td>59%</td>
<td>78% (66–86)</td>
</tr>
<tr>
<td>MUC2</td>
<td>100%</td>
<td>52% (44–59)</td>
<td>51%</td>
</tr>
<tr>
<td>MUC5AC</td>
<td>50% to 100%</td>
<td>52%</td>
<td>2% to 33%</td>
</tr>
</tbody>
</table>

Data in parentheses are 95% CIs. Summary estimate could not be calculated because of statistically heterogeneous individual frequencies. 86% frequency reported by Ishizu.

### Treatment

**Surgery, chemotherapy, and stage-dependent outcome**

The current standard treatment for mucinous carcinomas is surgery followed by adjuvant chemotherapy. For ovarian mucinous carcinomas, the standard chemotherapy regimen combines platinum-based therapy with a taxane; for colorectal mucinous carcinomas, standard agents are fluoropyrimidines such as fluorouracil. When stage at diagnosis is not considered, overall survival rates are better for ovarian mucinous carcinomas than for non-mucinous ovarian carcinomas, probably because more than 80% of ovarian mucinous carcinomas are diagnosed and treated at low stage. By contrast, findings of many studies show that colorectal mucinous and non-mucinous carcinomas have similar survival rates. Despite diagnostic uncertainty with respect to primary site of many metastatic mucinous carcinomas, the outcomes of women reclassified as having metastatic mucinous carcinomas compared with advanced primary ovarian mucinous carcinomas did not differ by much.

When survival rates are stratified by stage, however, a different picture emerges. Mucinous carcinomas diagnosed at a high stage generally have an unfavourable outcome compared with non-mucinous types, irrespective of organ site (figures 3 and 4). At stage I/II, patients with ovarian mucinous carcinomas have a lower risk of death than those with non-mucinous carcinomas (figure 3A), which is attributable to confinement of slow-growing mucinous carcinomas to the ovary. For patients at stage IA/IB, 10-year survival was greater than 95% irrespective of whether chemotherapy was administered, suggesting that these patients might not need adjuvant treatment after surgery. In view of the good outcome and no comprehensive staging, an indirect conclusion is that lymph-node metastases are uncommon in individuals at stage IA/IB. At high stages, however, risk is more than two-fold greater for both death and tumour progression (figure 3B). The poorer outcome at high stages has been attributed to a reduced response to standard chemotherapy, with rates as low as 26% versus 65% for ovarian non-mucinous carcinomas.

Compared with non-mucinous types and irrespective of stage at diagnosis, patients with colorectal mucinous carcinoma are at increased risk of tumour progression (figure 4A), higher risk of death (figure 4B), and have a poorer response to treatment (figure 4C). In other words, individuals with non-mucinous carcinomas are at least three times more likely than those with colorectal mucinous carcinomas to respond to standard treatment of fluorouracil after surgical resection. Similarities...
between ovarian mucinous and colorectal carcinomas suggests that standard treatment for colorectal carcinomas, including fluorouracil, could play a part in treatment of ovarian mucinous carcinomas. Since colorectal mucinous carcinomas do not respond to fluorouracil, ovarian mucinous carcinomas are unlikely to also. Therefore, better treatment is needed for mucinous carcinomas irrespective of organ site.

These data also highlight the importance of surgery for patients with locally advanced or metastatic mucinous carcinomas. Focus should be on optimum peritoneal debulking with no presence of residual macroscopic disease. Perioperative hyperthermic intraperitoneal chemotherapy (eg, mitomycin at 42°C) has been studied in the setting of minimum disease, but efficacy is unproven to date and is currently the basis of a US National Cancer Institute phase 3 randomised pilot study of survival outcome in patients with colon adenocarcinoma.

New treatments

Without evidence-based justification for adherence to standard chemotherapy regimens (other than subscribing to current practice), the patient with mucinous carcinoma loses; alternative therapeutic options are needed. Several trials are in progress, in which new agents are being tested that target mutations similar to those identified in mucinous carcinomas of either ovarian or colorectal origin, with potential for cross-organ application. These include MGAH22 (targets HER2 amplification; NCT01148849), general MAPK inhibitors such as AZD6244 (formerly called ARRY-142886; AstraZeneca, Wilmington, DE, USA; NCT00888134), and we speculate that platinum-based taxanes could be considered for mucinous carcinomas positive for TP53 mutations. These agents are targeted to specific molecular profiles of mucinous carcinomas and might have greater benefit in patients than the current one-fits-all standard regimens. In view of challenges associated with accrual of patients in clinical trials, particularly individuals with high-stage disease, novel approaches to trial design will be of importance, and intergroup collaboration will be needed to obtain adequate sample sizes. This approach can only improve on the current situation, whereby few trials focus individually on ovarian or colorectal mucinous carcinomas.

Conclusions

Here, we report that both ovarian and colorectal mucinous carcinomas do not respond to standard chemotherapy regimens. Furthermore, primary mucinous carcinomas of the ovary and colorectum share similar mutational patterns compared with non-mucinous colorectal carcinomas. These similarities include higher prevalence of MSI-H and lower frequency of alterations to the WNT signalling pathway and TP53, with changes to MAPK signalling seemingly higher in ovarian mucinous carcinomas. A limitation of our Review is that we restricted ourselves to commonly reported molecular alterations and that, despite our comprehensive literature search,
prevalence of some mutations was reported in only one study, which could also have had a small sample size.

New treatment strategies are needed for both ovarian and colorectal mucinous carcinomas, and we propose that the search for these might be more successful if cross-organ comparisons are made. However, an approach of similar treatments for mucinous carcinomas must be substantiated with proof of a close ontological relation. We are unclear whether ovarian and colorectal mucinous carcinomas originate from the same cell type. They are both classified as mucinous carcinomas but they show important differences in mucin localisation. Similar mutational patterns but different specific alterations (eg, increased frequency of MAPK alterations in ovarian mucinous carcinomas) are also seen. Comparable gene-expression profiles have been noted.48 but to date, no common highly expressed genes have been reported.

Can we prove a common origin for mucinous carcinomas of the ovary and colorectum? New-generation sequencing could identify additional driver alterations that will help clarify the relation between mucinous carcinomas from different organ sites.76 Perhaps then we can categorise mucinous carcinomas according to a specific set of molecular alterations (eg, in the MAPK pathway), irrespective of organ site, and include mutation as a criterion in clinical trials to assess survival benefit of treatments that target the same molecular signature. We foresee a disease-based classification system consisting of modalities such as site, histological type, and molecular alteration that can be used to prioritise patients to specific adjuvant treatment. This work can only be achieved through continued collaboration with pathologists, oncologists, and cancer researchers alike.

Contributors
LEK did the literature search, data extraction, and data synthesis, provided statistical expertise, and wrote and revised the report. MK did the literature search, data extraction, and data synthesis, and wrote and revised the report.

Conflicts of interest
LEK declares that she has no conflicts of interest. MK received fellowship support from El Lilly Canada in 2007–08.

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