A retrospective study of the epidemiology and histological subtypes of ovarian epithelial neoplasms at Charlotte Maxeke Johannesburg Academic Hospital

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Background: Epithelial ovarian neoplasms constitute the majority of ovarian tumours and are the most common malignant ovarian neoplasm. They are the eighth leading cause of cancer deaths worldwide. This study evaluated the epidemiology and histological subtypes of epithelial ovarian neoplasms at a single institution.

Methods: This retrospective, quantitative analysis evaluated 123 epithelial ovarian neoplasms between 2013 and 2017 and classified them according to age, biological behaviour and histological subtype.

Results: Of 123 cases, 64 (52.0%) tumours were benign, 30 (24.4%) were borderline and 29 (23.6%) tumours were malignant. Serous cystadenoma was the most common benign tumour (42.2%). Mucinous borderline tumours were the most common borderline neoplasm (50.0%). High-grade serous carcinoma was the most common carcinoma (58.6%). Patients presented at an older age with borderline tumours and malignant tumours, compared with patients with benign tumours.

Conclusion: The current study demonstrated that serous tumours were the most common type of benign and malignant tumours whilst mucinous neoplasms were the commonest subtype of borderline tumours. These findings are congruent with multiple similar studies. A higher number of borderline tumours were seen in this cohort in comparison with previous studies. This suggests a need for additional sampling of borderline tumours, over and above the international standard, in our population, to definitely exclude invasive malignancy. This study also demonstrated the histological progression of benign serous and mucinous tumours to borderline tumours and low-grade serous carcinoma and mucinous carcinoma, respectively, which supports the stepwise tumour progression model of these tumours.

Keywords: benign, borderline, epithelial ovarian neoplasm, malignant, ovarian carcinoma, ovarian tumour

Introduction

Primary ovarian neoplasms originate from one of three cell lines: epithelial, stromal and germ cell, with most being of epithelial origin.1 Epithelial ovarian neoplasms are classified as benign, borderline and malignant neoplasms based on how closely the tumour cells resemble resident cells of the female genital tract.1-3 Malignant epithelial ovarian neoplasms are the eighth leading cause of cancer deaths worldwide with estimated five-year survival rates below 45%.4 The latest available South African data documented 590 new ovarian cancers, accounting for 1.42% of all new cancers in females, in 2017.5 Coburn et al. showed that serous carcinoma (SC) (including low-grade SC and high-grade SC) consistently had the highest incidence rates in 30 countries assessed.6 Notably, data for the African continent are missing from that study.

Risk factors for ovarian cancer include a family history, especially mutations in breast cancer genes 1 and 2 (BRCA1 and BRCA2), early menarche, increased lifelong number of menstrual cycles, late menopause, nulliparity/low parity, high body mass index and cigarette smoking.7-9 Protective factors include sterilisation, previous hysterectomy and the combined oral contraceptive pill.10

Benign epithelial neoplasms comprise a simple layer of epithelium lacking cytological atypia, whereas borderline neoplasms are architecturally complex, demonstrating cytological atypia but lacking destructive stromal invasion.11-13

Due to their tumour heterogeneity, malignant neoplasms have been further classified into two broad groups.14 Type I tumours account for approximately 10% of ovarian cancer-related deaths and comprise low-grade serous carcinoma (LGSC), clear cell carcinoma (CCC), endometrioid carcinoma (EC), Brenner tumour, seromucinous carcinoma and mucinous carcinoma (MC).14 With the exception of CCC, these tumours are considered morphologically and behaviourally low-grade.14 When disease is confined to the ovary, patient prognosis is favourable, but this worsens in advanced stages.14 Type I tumours are genetically more stable than type II tumours and have activating mutations of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit a (PIK3CA), catenin β1, Kirsten rat sarcoma viral oncogene homolog (KRAS)/B-Raf proto-oncogene, serine/threonine kinase (BRAF)/mitogen-activated protein (MAP) extracellular signal-related kinase (ERK), and inactivating mutations in phosphatase and tensin homolog (PTEN), AT-rich interaction domain 1A (ARID1A), chromatin remodelling pathways and mismatch repair mechanisms.14,15 Tumours that have BRAF mutations, which are associated with cellular senescence, have a favourable prognosis when compared with tumours with KRAS mutations or KRAS/BRAF wild-type tumours.1,3,4,16

LGSC develops in a series of stepwise processes from surface epithelium, to ovarian epithelial inclusions, cystadenoma, borderline serous tumours and finally, invasive LGSC.9,17-19 There is no progression from LGSC to HGSC.20

EC and CCC comprise approximately 15% of epithelial ovarian carcinomas and arise from endometriotic cysts/endometriomas...
based on morphological and molecular assessments. MC and malignant Brenner tumours are the least common epithelial neoplasms. Some authors postulate that both mucinous and Brenner tumours arise from transitional cell epithelium located at the tubal-peritoneal junction, whilst others suggest metaplastic change of surface ovarian epithelium as the precursor lesion. Type II carcinomas include high-grade serous carcinoma (HGSC), carcinosarcoma and undifferentiated carcinomas (UC). HGSCs comprise the majority of SC and exhibit extensive chromosomal instability, inactivating TP53 and retinoblastoma (RB) protein mutations and activating mutations in cyclin E1, forkhead box M1 (FOXM1), and Notch3 pathways.

The pathogenesis of HGSC is less clear than that of LGSC. Theories suggest that HGSC develops from surface epithelial metaplastic transformation to tubal-type epithelium that undergoes malignant change or from serous tubal intraepithelial carcinoma (STIC) where exfoliation of the transformed epithelial cells from the fallopian tube results in transport to, and deposition on, the ovary.

In cases showing morphological overlap between the subtypes of ovarian carcinoma, immunohistochemistry is an useful adjunct. The diagnostic algorithm of Köbel et al. for the subclassification of histological types of ovarian carcinoma showed that Napsin-A is highly sensitive for CCC, positive WT-1 staining and mutant-type staining of PS3 (diffuse homogeneous staining or diffuse loss) correlated strongly with HGSC, negative WT-1 was found consistently in CCC and MC, while progesterone receptor (PR), oestrogen receptor (ER) and trefoil factor 3 (TFF3) positivity favoured EC.

Our study aimed to quantify the total number of epithelial ovarian neoplasms seen at a single referral institution over a four-year period and to further classify them into their histological subtypes, biological potential (benign, borderline or malignant), and age distribution. This would allow for the identification of prevalent biological subtypes of these tumours and possible identification of at-risk age groups for borderline or malignant tumours with specific histological subtypes in our patient population.

Materials and methods

Ethical clearance was granted by the University of the Witwatersrand Human Research Ethics Committee (Medical), prior to the commencement of data collection (certificate number M180499).

This was a retrospective, quantitative analysis of 123 epithelial ovarian neoplasms histologically diagnosed at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over a four-year period.

Cases included in the study were from female patients over 18 years of age, who had a histological diagnosis of an epithelial ovarian neoplasm. Cases were excluded if slides could not be retrieved, the patient’s age was unknown or patients were under the age of 18 years.

Haematoxylin and eosin (H&E) stained slides were reviewed independently, and in the absence of knowledge of the histological diagnoses, by both authors. The diagnoses were then compared with the final histopathology reports. There was 100% concordance between our diagnosis and the diagnosis of the original cases, which were reported by several different histopathologists. In cases with immunohistochemistry, there was no discrepancy with the final diagnosis. Histological distinction was not made between Müllerian/endocervical type and intestinal-type mucinous tumours.

Limitations in this study include a small sample size, which cannot be extrapolated to the entire population. Exclusion of paediatric cases may have also resulted in a skewed age range.

Results

This study showed variable age distribution and biological potential of each epithelial ovarian tumour subtype (Table 1; Figure 1). The age range was between 19 and 83 years (Table 1).

The mean age of patients presenting with benign epithelial lesions was 45 years, whereas the mean age of patients with borderline lesions was 56 years and the mean age of patients with malignant tumours was 49 years. The average age differed significantly across the biological types of tumours ($p = 0.003$). The average age of those with a borderline tumour was significantly higher than for those with a benign tumour (Figure 1). There was no statistically significant correlation between histological subtype and the average age of patients ($p = 0.071$).

Of 123 cases, 64 (52.03%) were classified as benign, 30 (24.39%) as borderline tumours and 29 (23.58%) as malignant tumours (Table 1).

Table 1 shows that a statistically significant number ($p = 0.000$) of tumours were benign (52.03%). There was a statistically significant relationship between certain histological subtypes and biological potential ($p = 0.000$) as tumours with endometrioid morphology were more frequently benign than borderline or malignant, whilst tumours with mucinous morphology were more often borderline neoplasms than benign or malignant neoplasms. Tumours with serous or clear cell morphology were more frequently malignant in contrast to their benign or borderline counterparts (Table 1; Figure 2).

The most common benign histological tumour was serous cystadenoma, followed by mucinous cystadenoma. The remainder of the histological diagnoses in descending order of frequency were: endometriomas/endometrioid neoplasms, Brenner tumours, mixed histological types, and seromucinous cystadenomas (Figures 2 and 3).

Borderline mucinous neoplasms were the most common of the borderline tumours in this study, followed closely by borderline serous neoplasms (Figures 2 and 4). The remainder of the borderline tumours all showed the same frequency (Figure 2). Borderline endometrioid and clear cell tumours were not identified in this study.

HGSC was the most common of the carcinomas, followed by LGSC (Figures 2 and 5). MC, CCC and EC comprised the remainder of malignant neoplasms in descending order of frequency (Figures 2 and 5).

Benign and borderline tumours presented more commonly as a unilateral mass, whereas malignant tumours frequently showed bilateral ovarian involvement (62%) (Figure 6). All cases of LGSC presented as bilateral masses and ranged in size from 5 to 16 cm. Eleven cases of HGSC presented as bilateral masses...
ranging from 2 to 24 cm. The six cases of unilateral HGSC ranged from 4 to 14 cm. All four cases of MC presented as unilateral masses and ranged in size from 25 to 42 cm. The single case of EC in this cohort was unilateral and measured 12 cm. The unilateral case of CCC measured 30 cm and the bilateral case of CCC ranged from 20 to 30 cm. None of the reported cases had a concurrent appendectomy.

Immunohistochemistry was performed on seven cases of HGSC and both cases of CCC. Five cases of HGSC showed strong diffuse staining for P53, indicating TP53 mutation, and four cases showed strong nuclear positivity for WT-1. A single case of HGSC showed absence of P53 staining, indicating TP53 mutation. P53 in the cases of CCC showed heterogenous wild-type staining. Napsin-A was not performed on these cases. Immunohistochemical stains such as CK7, CK20, CDX2 and SATB2 for MCs were not undertaken. In addition, immunohistochemistry was not performed on LGSCs, or on the single case of EC.

**Discussion**

**Distribution of biological potential and laterality**

This study shows that most epithelial ovarian neoplasms were benign, with an almost equal distribution between borderline and malignant neoplasms. Studies have shown benign tumours to be the most frequent neoplasm but showed that malignant tumours were more common than borderline tumours. Distribution of biological potential and laterality

**Age distribution**

There was wide age variation between benign, borderline and malignant neoplasms, which is consistent with previous studies.26,29

**Table 1: Distribution of biological potential, age and histological subtypes of epithelial ovarian neoplasms**

| Number | Benign | Borderline | Malignant |
|--------|--------|------------|-----------|
| A: Total number of cases (absolute/percentage) of benign, borderline and malignant neoplasms | 123 | 64 (52.03) | 30 (24.39) | 29 (23.58) [p-value = 0.000] |
| B: Age distribution (absolute/percentage) of benign, borderline and malignant neoplasms | | | | |
| Age (years) | n (%) | n (%) | n (%) |
| 18–30 | 14 (21.9) | 3 (10.1) | 1 (3.4) |
| 31–40 | 11 (17.2) | 2 (6.7) | 6 (20.7) |
| 41–50 | 14 (21.9) | 6 (20.0) | 9 (31.0) |
| 51–60 | 17 (26.6) | 7 (23.3) | 9 (31.0) |
| 61–70 | 7 (10.9) | 6 (20.0) | 3 (10.3) |
| 71–80 | 1 (1.6) | 3 (10.0) | 0 (0) |
| >80 | 0 (0) | 3 (10.0) | 1 (3.4) |
| C: Distribution (absolute/percentage) of histological subtypes of benign, borderline and malignant neoplasms | | | |
| Serous | 27 (42.2) | 12 (40.0) | Low-grade: 5 (17.2) |
| Mucinous | 23 (35.9) | 15 (50.0) | High-grade: 17 (58.6) |
| Seromucinous | 1 (1.6) | 1 (3.3) | 0 (0) |
| Endometrioid | 8 (12.5) | 0 (0) | 1 (3.5) |
| Clear cell | 0 (0) | 0 (0) | 2 (6.9) |
| Brenner | 3 (4.7) | 1 (3.3) | 0 (0) |
| Mixed histology | 2 (3.1) | 1 (3.3) | 0 (0) |

ANOVA, Pearson’s chi-square test and Fisher’s exact statistical tests used to analyse data.
Benign epithelial ovarian neoplasms
Serous and mucinous cystadenomas were the most common tumours in our study, which is congruent with other studies. These two histological subtypes show an increased risk for progression to their malignant counterparts, suggesting that the patient population in our study is at higher risk for malignancy. Guleria et al. have suggested that older patients presenting with benign cystadenomas are at higher risk of developing malignancy. Most benign tumours in our study showed unilateral involvement. This suggests that older patients who underwent unilateral cystectomy should be monitored closely for the possibility of malignancy in the other ovary.

Figure 2: Histological distribution per category of benign, borderline and malignant tumours.

Figure 3: H&E photomicrographs of benign epithelial ovarian neoplasms; original magnification 400x. A and B are from a mucinous cystadenoma. A shows a single layer of epithelium with goblet cells (arrow) whilst B shows a gastric epithelial lining. C and D demonstrate a benign Brenner tumour. Bland transitional-type epithelium (yellow star) is set in a prominent fibrous stroma (red star). E shows an endometriotic cyst/endometrioma lined by columnar epithelium with underlying endometrial stroma (black arrow), haemorrhage (green arrow) and haemosiderin (yellow arrow). F demonstrates a serous cystadenoma lined by ciliated tubal-type epithelium (arrow).
Five cases of LGSC were identified with an age range of 25–53 years. In two cases occurring in patients in their thirties, background borderline serous tumours were identified. In addition, a 25-year-old patient was diagnosed with bilateral LGSC with incidental STIC in the fallopian tube. This very young age of presentation is not congruent with the current epidemiology. However, it is possible that the patient may harbour a BRCA familial mutation. STIC is associated with HGSC and is not routinely identified with LGSC. It is thus postulated that this patient may harbour multiple genetic aberrations.

Two LGSCs arose in the background of a borderline serous neoplasm and four borderline serous neoplasms arose from benign serous cystadenomas. These findings are consistent with the progression of serous cystadenoma to borderline tumours and finally to LGSC. One borderline tumour demonstrated foci of micro-invasion and this heterogeneous composition is well described. These findings reiterate the importance of thorough macroscopic tumour sampling to exclude malignancy.

Three cases of MC arose in the background of a borderline mucinous tumour and benign mucinous cystadenoma. Four cases of borderline mucinous tumours showed foci of intraepithelial carcinoma. These findings support the molecular pathogenesis and stepwise progression from benign mucinous cystadenoma to borderline mucinous tumour, and finally to invasive MC.

All four MCs were bilateral and greater than 13 cm. According to a diagnostic algorithm by Yemelyanova et al., for differentiating primary mucinous ovarian tumours from metastatic tumours, a unilateral mucinous tumour greater than 13 cm in size greatly...
favours a tumour of primary ovarian origin. This algorithm should be supplemented with immunohistochemical stains if uncertainty exists. The cases in our study did not undergo ancillary investigations and were considered to be primary mucinous carcinomas of the ovary by the reporting pathologists in each instance.

Borderline mucinous and serous neoplasms constituted most atypical tumours in our study, which is consistent with previous findings. Two borderline tumours (one serous and one mucinous) demonstrated microinvasion, in which isolated single cells or small clusters of epithelial cells resembling surface epithelium, < 5 mm in diameter, were seen. Microinvasion in serous borderline tumours has not been demonstrated to have an adverse effect on prognosis as suggested by a lack

Figure 5: Photomicrographs of malignant ovarian neoplasms. A shows gland formation (arrows) in an ovarian EC. B shows nuclear atypia and clear to lightly eosinophilic cytoplasm in an ovarian CCC. C shows atypical mucinous glands in an ovarian MC. D shows LGSC with moderate cytological atypia and an induced stromal response. Foci of psammomatous calcification are shown (arrows). E shows multineucleation (black arrow) and prominent nucleoli (green arrow) indicating high-grade, bizarre cytomorphology in ovarian HGSC. F shows a solid growth pattern of ovarian HGSC, in comparison with the micropapillary architecture of HGSC shown in E. Numerous mitotic figures are seen in one field (arrows). G shows diffuse, homogenous nuclear staining for P53, indicating TP53 mutation. H shows strong nuclear positivity for WT-1 (original magnification: A, B, C, D, E, F and H: x400, G x200).

Figure 6: Number of unilateral or bilateral tumours per category of benign, borderline and malignant neoplasms.
The peak incidence of malignant tumours in our study occurred between 41 and 60 years of age, which is similar to findings by Mondal et al. The majority of malignant tumours in the current study demonstrated serous morphology (specifically HGSC), followed by MC, CCC and EC respectively. Transitional cell carcinoma was not identified in this cohort. A meta-analysis of the global literature between 2003 and 2012 showed that South Africa had the third highest median value of relative frequencies out of 17 countries, for both LGSC and HGSC combined. This mirrors findings in the present study in which SC, particularly HGSC, was the most frequent malignant neoplasm followed closely by LGSC. Piszczan et al., however, showed that adenocarcinoma not otherwise specified was the most common histological subtype.

From our study, the histological distribution of epithelial ovarian carcinomas at our institution follows the trend of ovarian carcinomas in Western countries (Table 2). This is specifically true with regard to both LGSC and HGSC.

Our study showed a wide age distribution (40–83 years of age) in patients with HGSC and in patients with LGSC (25–53 years of age), which is similar to previous studies. Patients with LGSC present at a younger age than patients with HGSC, which may indicate that other factors, such as hormonal exposure or environmental factors, play a role in the development of HGSC. However, further research in this field is suggested.

In our study, a single HGSC showed an associated STIC in the ipsilateral fallopian tube. HGSC requires extensive examination of the fimbriated end of the fallopian tube (SEE-FIM protocol) for STICs. Five cases of HGSC showed strong diffuse staining for P53, indicating TP53 mutation, and four cases showed strong nuclear positivity for WT-1. A single case of HGSC showed diffuse loss of P53, which also indicates strong nuclear positivity for WT-1. This immunohistochemical profile is supportive of a diagnosis of HGSC.

CCC is described in patients > 50 years of age and in a single ovary, which contrasts with the two documented cases in our study that occurred in patients under the age of 50, with both unilateral and bilateral involvement. PS3 staining in the cases of CCC showed wild-type staining and Napsin-A was not performed. A single case of EC (which is reported to have a wide age range), was diagnosed in a 46-year-old patient in the present study. EC is frequently associated with endometriosis, which was not identified in the present study but may be attributed to insufficient tumour sampling or extensive tumour involvement obscuring any underlying endometriosis.

Mixed tumours
Three cases from the present study showed mixed histological findings: one case demonstrated a mucinous cystadenoma with a Brenner tumour in one ovary and a serous cystadenoma in the contralateral ovary, whilst two cases of borderline mucinous neoplasms had concomitant Brenner tumours. The association of mucinous ovarian neoplasms and Brenner tumours is well documented. Wang et al. have shown a monoclonal origin of mucinous and Brenner tumours, suggesting that transitional epithelium of the Brenner tumour undergoes metastatic reprogramming to mucinous epithelium, which proliferates to a mucinous tumour. This suggests that patients with benign Brenner tumours are at risk of developing MC and should be followed up.

Treatment, staging and prognostic factors
The most crucial factor in determining treatment modalities for epithelial ovarian carcinoma is staging at the time of presentation. Staging is performed according to the Union for International Cancer Control (UICC) Tumour/Nodes/Metastases (TNM) Classification of Malignant Tumours and the Fédération Internationale de Gynécologie et d’Obstétrique (FIGO) system. The recently published UICC TNM classification has created a separate staging category for lymph node only, positive disease without peritoneal deposits, thereby conferring a better prognosis and lower staging in patients without peritoneal dissemination. STIC has been recognised as a precursor lesion to HGSC and further highlights the importance of proper examination of the fallopian tube epithelium.

For patients in child-bearing years presenting with stage I or II disease and a low risk of recurrence, fertility-sparing surgery is a viable treatment option. Approximately 25% of ovarian carcinomas are diagnosed at early stages and an estimated 14% of those cases involve women under the age of 40 who are concerned with preserving fertility. Fertility-sparing surgery involves unilateral (salpingo-)oophorectomy and complete surgical staging. Factors considered for possible fertility-sparing treatment include tumour grade (and the risk of recurrence associated with that grade), treatment outcomes in stage IC disease and the presence of ‘high-risk’ histologic subtypes, particularly CCC. If these factors are favourable, patients can be considered for fertility-sparing treatment.

Patients presenting with advanced stage disease are treated with primary radical surgery, involving removal of the ovaries, uterus and cervix with possible removal of the pelvic peritoneum, followed by chemotherapy. This first-line chemotherapy regime includes intravenous platinum-based therapy every 21 days for six cycles. Adjuvant therapies include all—or a combination—of radiotherapy, hormone therapy and targeted therapy, which may be included based on chemotherapeutic response. In some cases of advanced stage disease, complete surgical debulking may not be possible due to extensive tumour adhesions. In such cases patients may be treated with primary chemotherapy and then reassessed for surgical resection. In patients with stage I and grade 1 or 2 tumours, chemotherapy and adjuvant therapies may be omitted.

Following surgery and chemotherapy, patient response to treatment is assessed using imaging studies and according to Response Evaluation Criteria In Solid Tumours (RECIST). Under RECIST, tumour size and/or suspected involved lymph nodes are measured radiographically, on computed tomography (CT) scan or magnetic resonance imaging (MRI), and compared with original tumour size to determine if there has been complete or partial response, progressive or stable disease compared with pre-treatment measurements. Despite a good response to primary treatment, a large proportion of patients develop recurrent disease. Platinum-based chemotherapy remains the mainstay for treatment.
However, in cases showing a poor response, targeted therapy has demonstrated improved outcomes.\textsuperscript{51,52}

Targeted therapies include poly (ADP-ribose) polymerase (PARP) inhibitors and anti-angiogenic modalities.\textsuperscript{52} PARP inhibitors target DNA repair mechanisms in order to induce cell death by increasing the number of double-stranded DNA breaks.\textsuperscript{52} These have been successfully used in the treatment of \textit{BRCA}-mutated HGSC.\textsuperscript{52} Oral PARP inhibitors are used as maintenance therapy following response to platinum-based chemotherapy, to create a time interval between chemotherapy cycles.\textsuperscript{52}

Anti-angiogenic targeted therapy, such as bevacizumab, a vascular endothelial growth factor-A inhibitor, in conjunction with chemotherapy has shown great efficacy in the management of advanced stage ovarian carcinoma.\textsuperscript{52} Important prognostic factors include the age at initial diagnosis, tumour stage, extent of success of surgical debulking, histological subtype, tumour grade, and response to chemotherapy following surgical intervention.\textsuperscript{53}

### Conclusion

This study provides data on surface epithelial tumours in our local population and has demonstrated many findings that

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**Table 2: Summary of histological distribution of epithelial ovarian carcinomas from previous studies.**

| Name of study                                                                 | Authors            | Year   | Country                        | Serous | Mucinous | Endometrioid | Clear cell | Other epithelial |
|-------------------------------------------------------------------------------|--------------------|--------|--------------------------------|--------|----------|-------------|------------|-----------------|
| International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. | Coburn et al.      | 2003–2007 | Denmark                        | 1 260  | 213      | 250         | 106        | 340             |
|                                                                                              | Norway             | 883    | 117                            | 175    | 82       | 346         |
|                                                                                              | Finland            | 985    | 245                            | 333    | 114      | 144         |
|                                                                                              | Iceland            | 39     | <11                            | <11    | <11      | <11         |
|                                                                                              | Austria            | 175    | 33                             | 35     | <11      | 72          |
|                                                                                              | Switzerland        | 388    | 48                             | 83     | 30       | 185         |
|                                                                                              | France             | 964    | 156                            | 199    | 60       | 412         |
|                                                                                              | Germany            | 191    | 41                             | 43     | <11      | 133         |
|                                                                                              | UK                 | 5 980  | 2 895                         | 1 499  | 924      | 5 155       |
|                                                                                              | Netherlands        | 2 138  | 486                            | 520    | 282      | 1 061       |
|                                                                                              | Spain              | 506    | 140                            | 162    | 84       | 271         |
|                                                                                              | Estonia            | 344    | 72                             | 30     | 21       | 102         |
|                                                                                              | Slovenia           | 420    | 63                             | 123    | 40       | 112         |
|                                                                                              | Czech Republic     | 1 797  | 425                            | 519    | 90       | 1 391       |
|                                                                                              | Slovakia           | 822    | 245                            | 229    | 70       | 437         |
|                                                                                              | Italy              | 881    | 184                            | 251    | 78       | 582         |
|                                                                                              | Malta              | 49     | 17                             | 29     | <11      | 41          |
|                                                                                              | United States of America | 3 379  | 390                            | 776    | 381      | 1 606       |
|                                                                                              | Canada             | 360    | 70                             | 94     | 61       | 209         |
|                                                                                              | Quito, Ecuador     | 78     | 23                             | 14     | <11      | 73          |
|                                                                                              | Goania, Brazil     | 54     | 34                             | 11     | <11      | 107         |
|                                                                                              | Israel             | 767    | 44                             | 105    | 26       | 280         |
|                                                                                              | New Zealand        | 482    | 78                             | 94     | 70       | 196         |
|                                                                                              | Australia          | 2 371  | 354                            | 445    | 294      | 810         |
|                                                                                              | Singapore          | 279    | 105                            | 150    | 171      | 108         |
|                                                                                              | Japan              | 728    | 385                            | 296    | 469      | 612         |
|                                                                                              | Thailand           | 131    | 90                             | 80     | 83       | 67          |
| Histologic pattern, bilaterality and clinical evaluation of 957 ovarian neoplasms: a 10-year study in a tertiary hospital of eastern India | Mondal et al.      | 2011   | India                          | 109    | 32       | 12          | 15         | 5               |
| A pathological and clinical study of 706 primary tumours of the ovary in the largest tertiary hospital in Ghana | Akakpo et al.      | 2017   | Ghana                          | 71     | 9        | 9           | 1          | 10              |
| Clinical characteristics and survival of patients with malignant ovarian tumours in Addis Ababa, Ethiopia | Piszczan et al.    | 2019   | Ethiopia                       | 121    | 41       | 4           | 2          | 187             |

*Adapted from Coburn et al.,\textsuperscript{6} Mondal et al.,\textsuperscript{26} Akakpo et al.,\textsuperscript{27} and Piszczan et al.\textsuperscript{38}
are congruent with findings in some African countries and international studies. The high incidence of HGSC, followed closely by LGSC, demonstrated in our cohort is consistent with international trends. Furthermore, several cases in the present study demonstrate the stepwise progression of cancer development described in LGSC and MC. The higher incidence of borderline tumours in the current study compared with many other studies indicates a need for additional sampling once a histological diagnosis of a borderline neoplasm has been made to definitively exclude microinvasion and/or frank invasion.

Our study may provide a stepping stone for larger South African studies, which may facilitate comparison of South African data with international findings. Furthermore, this may lead to collaborative studies with other African nations, which may contribute to data on ovarian epithelial tumours for the continent.

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