Exploring the Histogenesis of Ovarian Mucinous and Transitional Cell (Brenner) Neoplasms and Their Relationship With Walthard Cell Nests

A Study of 120 Tumors

Jeffrey D. Seidman, MD; Fatemeh Khedmati, MD

Context.—The origin of and relationship between ovarian mucinous and transitional cell (Brenner) neoplasms are enigmatic. The reported association ranges from 1% to 16%, and whether there is an association with Walthard cell nests is unknown.

Objective.—To clarify the histologic relationship between mucinous and Brenner tumors.

Design.—A total of 40 mucinous cystadenomas, 67 Brenner tumors, and 13 combined tumors were studied. Peritoneal surfaces were examined for Walthard nests in 83 patients compared with 272 controls.

Results.—A total of 25% of tumors with a mucinous component contained a Brenner component, and 16% of tumors with a Brenner component contained a mucinous component. Most calcifications were spiculated (non-psammomatous). In 6 combined tumors, the relative volume of the 2 components was less than 1:3000 (transitional-mucinous). Walthard nests were found in 50% of patients with Brenner tumors and 59% of patients with mucinous tumors. This was significantly higher than the 28% found in controls (P = .002 and P < .001, respectively). The number of fallopian tube blocks examined was correlated with the likelihood of finding Walthard nests, and accordingly, sampling accounted for 39% of the increase with Brenner tumors but strengthened the association with mucinous tumors.

Conclusions.—The strong association of mucinous and transitional cell components, similar type of calcification, complementary size distributions, and frequent identification of a transitional component in the face of an exceedingly small estimated proportion of that component suggest that this association has been underestimated. The association of Brenner tumors with Walthard nests, although significant, appears weak and not strongly supportive of a histogenetic relationship. The stronger association of Walthard nests with mucinous tumors remains unexplained.

The relationship between ovarian mucinous and transitional cell neoplasms is enigmatic. Occasional mucinous cystadenomas contain a relatively small nodule of Brenner (transitional cell) tumor, with a reported incidence of about 1.3% of ovarian mucinous neoplasms ranging up to 4% in 1 series.1–12 Also, Brenner tumors often have mucinous epithelial cells lining the center of transitional cell nests, and they occasionally develop a discrete mucinous component identical in other respects to mucinous cystadenoma. Estimates of Brenner tumor associated with mucinous neoplasm range up to approximately 16%, with a mean of about 9%.13–21 We believe that there may be an important relationship between mucinous and transitional cell neoplasms that can provide clues to the pathogenesis and progression of ovarian mucinous epithelial tumors. We reviewed an unselected series of tumors to further examine this relationship.

The histogenetic origin of ovarian Brenner tumors is unclear, and historically proposed origins have included the ovarian surface epithelium, mesonephric remnants, rete ovarii, mucinous tumors, teratomas, and Walthard cell nests. Although the ovarian surface epithelium is generally regarded as the most likely origin of Brenner tumor, the evidence for this is not compelling. More compelling, although circumstantial, is the evidence for Walthard nests (WNs), largely because the transitional-like epithelium of these nests is morphologically identical to the epithelial nests in Brenner tumors. We evaluated whether there is an association of Brenner tumor or mucinous cystadenoma with WN.

MATERIALS AND METHODS

This study was approved by the institutional review board of the Washington Hospital Center, Washington, DC. A consecutive series of benign ovarian epithelial tumors containing a mucinous component and/or a transitional cell component accessioned to the surgical pathology service from 2000 to 2006 was evaluated. Consultation cases were excluded. Tumors also containing serous, endometrioid, and/or clear cell components were excluded. Tumors that contained a pure mucinous epithelial proliferation...
of at least 1 cm in diameter were classified as mucinous cystadenoma (Figure 1). Transitional cell nests of any quantity within the ovarian stroma were classified as Brenner tumor (Figure 2). Tumors containing both components (combined tumors; Figure 3) were required to have transitional cell nests of any quantity clearly within the tumor, including the outer fibrous wall, and either: (1) at least a 1-cm diameter area of pure mucinous epithelial proliferation or (2) at least 10% of the tumor was composed of pure mucinous glands. The 1-cm criterion for mucinous tumors, although arbitrary, is in widespread use. Neither a minimum quantity of transitional cell nests nor a fibromatous stromal component has been required for diagnosing Brenner tumors in virtually all previously published reports. Mucinous tumors associated with a mature cystic teratoma were excluded because these are considered of germ cell origin and pose no histogenetic problem. In contrast, Brenner tumors associated with teratomas were retained because this association is not completely understood. The uncommon seromucinous (müllerian mucinous or endocervical-like-type mucinous) tumors were excluded because they have distinctly different clinical and pathologic features from the more common intestinal-type mucinous cystadenoma, comprise fewer than 10% of ovarian mucinous tumors, and have no association with Brenner tumors.22,23

In the mucinous component, the following features were evaluated: goblet cells (Figures 1 and 3, C), luteinized stromal cells, pseudoxanthoma cells, muciphages, and stromal changes, including pseudomyxoma ovarii, foreign body–type giant cell reaction, mural nodules, and nodular stromal fibrosis. Evidence of atypia or proliferation similar to that seen in atypical proliferative mucinous tumors was evaluated as defined by the Borderline Ovarian Tumor Conference.24 Accordingly, if the mucinous epithelium contained atypia and/or proliferation resembling that seen in atypical proliferative (borderline) mucinous tumor but was found in less than 10% of the tumor, it was classified as a mucinous cystadenoma with focal atypia. Calcification was characterized as spiculated or nonspiculated (Figure 4). As mucinous cystadenoma typically has a thick fibrous outer wall, nodular stromal fibrosis was noted only when there was clear-cut nodularity that was separate or significantly beyond the expected thickness (2–3 mm) of a typical fibrous wall. When both mucinous and transitional components were present, the size (maximum diameter) of each component was estimated by evaluating the topography of the 2 elements on the histologic slides in conjunction with the gross description, unless the 2 components were intimately admixed. This assessment was usually possible because in these tumors, the Brenner component is almost always solid and firm, whereas the mucinous component is soft, gelatinous, and cystic, with grossly visible mucus.

For pure Brenner tumors, tumor size and the presence and type of calcification were assessed. In addition, the presence or absence of mucinous epithelial cells confined within transitional cell nests was noted. For this latter assessment, unequivocal cytologic features of mucinous differentiation were required; intracellular or extracellular mucin alone, a frequent finding in Brenner tumors, was considered insufficient. Tumors in which the only evidence of a mucinous component was mucinous epithelium within transitional cell nests were retained in the pure Brenner category in accordance with the criteria described above. For Brenner tumors smaller than 1 cm, the location with respect to the hilus and the ovarian surface epithelium were recorded when possible.

Walshard nest was defined as a transitional epithelium-lined nest or cyst on the serosa of the pelvic peritoneum (Figure 5). Nonneoplastic controls included ovaries that were either normal or had adhesions and/or functional cysts. Controls were derived from consecutive current (2006) cases. After the accumulation of about 200 nonneoplastic controls, accrual of neoplasms was continued due to smaller numbers. The presence or absence of WNs was recorded. All pelvic peritoneal surfaces were examined for these, but the fallopian tube serosa and fimbrial region contained the vast majority of WNs. The number of blocks containing fallopian tube tissue was recorded.

Tumor volumes were estimated based on the volume of a sphere: \( V = \frac{4}{3} \pi r^3 \). Block volumes were estimated assuming a 2.5 × 2.0 × 0.2-cm block of tumor that is 50% solid and 50% cystic.

**RESULTS**

There were 120 tumors in 105 patients after 2 mucinous neoplasms associated with mature cystic teratomas and 1 seromucinous (müllerian mucinous) tumor were excluded. There were 40 mucinous cystadenomas, 67 Brenner tumors, and 13 tumors showing both lines of differentiation. Thus, 25% of tumors with a mucinous component contained a Brenner component, and 16% of tumors with a Brenner component contained a mucinous component.

**Mucinous Cystadenoma**

The mean age of the 39 patients was 48.7 years, and the median was 49 years (range, 21–83 years). One patient was pregnant. Indications for surgery included uterine leiomyomas or pelvic or adnexal mass in the majority, and dysmenorrhea or pelvic pain in most others. A total of 40 mucinous tumors were sampled with a mean of 8.7 blocks (median, 5 blocks; range, 2–55 blocks). A total of 21 tumors were in the left ovary, 17 were in the right ovary, and 1 patient had bilateral tumors. The mean tumor diameter was 10.2 cm, and the median was 9.0 cm (range, 1–30 cm). Tumors were usually multicystic with mucus-containing cysts, often with a few scattered intervening solid areas. All tumors were of intestinal type, as evidenced by the presence of goblet cells (Figure 1). Fifteen cases (most cases [62.5%] with calcification) contained spiculated calcifications (Figure 4, B). Among the 6 with nodular stromal fibrosis, 5 contained spiculated calcification. The frequencies of other histologic features were as follows: calcification, 24 cases (60%); pseudoxanthoma cells, 19 cases (47.5%); muciphages, 17 cases (42.5%); luteinized stromal cells, 16 cases (40%); nodular stromal fibrosis, 6 cases (15%); necrosis, 5 cases (12.5%); pseudomyxoma ovarii (Figure 1), 4 cases (10%); giant cell reaction, 4 cases (10%); and mural nodules, 1 case (2.5%). Five cases (12.5%) were classified as mucinous cystadenoma with focal atypia.

Endometriosis was present in the ipsilateral ovary in 2 cases. The contralateral ovary had serous cystadenoma in 3 patients, endometriosis in 2, stromal hyperplasia in 3, and stromal hyperthecosis in 1.

**Brenner Tumor**

The mean age of the 53 patients was 56.3 years, and the median was 54 years (range, 22–89). Indications for surgery included uterine leiomyomas, pelvic or adnexal mass, and pelvic pain. Nearly all tumors were incidental findings, with the exception of the few largest ones. A total of 67 Brenner tumors were sampled, with a mean of 2.5 blocks (median, 1 block; range, 1–20 blocks). In 44 patients, the tumor was solitary and unilateral (15 left, 25 right, 4 unknown). A total of 9 patients had multiple tumors, which were unilateral in 7 (3 left, 3 right, 1 unknown) and bilateral in 3. The mean diameter was 1.73 cm, and the median was 0.50 cm (range, 0.02–20 cm). The majority of tumors smaller than 1 cm were not identified grossly, and nearly all larger tumors were solid with yellowish-white firm cut surfaces. Twenty tumors (30%) contained mucinous epithelium. Forty-four tumors (66%) were less than 1.0 cm. Calcification was present in 29 tumors (43%), which
Figure 1. Mucinous cystadenoma: Mucinous gland with epithelium containing goblet cells (hematoxylin-eosin, original magnification ×400).

Figure 2. A, Brenner tumor. Transitional cell nests embedded in a dense fibrous stroma (hematoxylin-eosin, original magnification ×200). B, Microscopic (3-mm) Brenner tumor in ovarian hilus (hematoxylin-eosin, original magnification ×40).

Figure 3. Combined tumors (3 different cases). A, Combined tumor displaying a single layer of mucinous epithelium with cystically dilated transitional cell nest in the stroma below (hematoxylin-eosin, original magnification ×200). B, Combined tumor displaying a single layer of mucinous epithelium on the left and transitional cell nests within the stroma on the right (hematoxylin-eosin, original magnification ×100). C, Combined tumor displaying separate layers of mucinous epithelium with goblet cells, with transitional cell nests in the stroma in between (hematoxylin-eosin, original magnification ×100).
was spiculated in 26 cases (90% of cases with calcification; Figure 4, A). Calcification was present in 9 (20%) of the 44 tumors less than 1 cm compared with 19 (83%) of the 23 tumors greater than or equal to 1 cm ($P < .001$; 2-tailed $\chi^2; 1 df$). The majority (58%) of the small tumors (<1 cm) in which the exact location could be evaluated were in or close to the hilum, and 50% of all small tumors were within 2 mm of the ovarian surface. In 5 cases, the tumor was both close to the hilum and within 2 mm of the surface.

The ipsilateral ovary had serous cystadenoma in 6 patients, endometriosis in 2, tubo-ovarian abscess in 1, and mature cystic teratoma in 2. The contralateral ovary had serous cystadenofibroma in 5 patients, fibroma in 3, fibrothecoma in 2, mature cystic teratoma in 2, endometriosis in 1, stromal hyperthecosis in 1, stromal hyperplasia in 2, stromal Leydig cell hyperplasia in 1, tubo-ovarian abscess in 2, and an atypical proliferative seromucinous (müllerian mucinous) tumor in 1. One patient had FIGO (International Federation of Gynecology and Obstetrics) stage III peritoneal serous carcinoma involving the surfaces of both ovaries. One patient had a tubal pregnancy. Two patients had tubal serous adenofibroma involving the fimbriae.

### Combined Tumors (Containing Both Mucinous and Brenner Components)

The mean age of the 13 patients was 68 years, and the median was 71 years (range, 41–83 years). Most patients presented with a pelvic or adnexal mass. Combined tumors were sampled with a mean of 9 blocks (median, 10 blocks; range, 2–18 blocks). All were unilateral; 7 tumors in the left ovary and 6 in the right. A total of 9 tumors contained discrete components, and in 4, the mucinous and Brenner components were intimately admixed (Figure 3). Among the latter 4 cases, 3 had approximately equal quantities of the 2 components, and 1 had a Brenner component occupying approximately 5% of the tumor. If the total tumor diameter is used for the size of each component in the intimately admixed tumors, the mean diameter of the mucinous component was 12.2 cm (median, 10 cm; range, 1–27 cm), and the mean diameter of the Brenner component was 6.3 cm (median, 1.9 cm; range, 0.1–25 cm). Among 9 tumors with discrete components, the Brenner component was smaller than the mucinous component in 6 (Table 1). In these 9 cases, the mean size of the Brenner component was 1.7 cm (median, 0.8; range, 0.1–5 cm), and the mean size of the mucinous component was 10.1 cm (median, 9.5 cm; range, 1–27 cm).

A total of 10 tumors contained calcification (77%), 8 had pseudoxanthoma cells (62%), 8 had muciphages (62%), 7 had pseudomyxoma ovarii (54%), 4 had giant cells (31%), 4 had necrosis (31%), 2 had luteinized stromal cells (15%),

| Table 1. Proportional Volume Relationships in 6 Mucinous Tumors With a Small Brenner Component* |
|------------------|------------------|------------------|----------|----------|
| Mucinous Size     | Volume           | Brenner Size     | Volume   | Ratio    |
| 1                 | 6                | 56.5             | 0.1      | 0.00074  | 45.935  |
| 2                 | 8                | 134              | 0.15     | 0.00176  | 76.136  |
| 3                 | 10.5             | 303              | 0.2      | 0.00418  | 72.488  |
| 4                 | 14.5             | 798              | 0.45     | 0.04770  | 16.279  |
| 5                 | 15               | 881              | 0.8      | 0.26800  | 3287    |
| 6                 | 27               | 5152             | 1.4      | 1.436    | 3587    |

* Sizes are in centimeters, and volumes are in cubic centimeters. B indicates Brenner tumor; M, mucinous cystadenoma.
Figure 6. Size distribution of Brenner tumors (A) and mucinous cystadenomas (B).


did and 1 had a mural nodule (8%). In 1 case, a few fragments of hair with foreign body giant cell reaction were found in the wall of a cyst within the tumor, indicating an associated benign cystic teratoma. The contralateral ovary had serous cystadenoma in 1 patient and stromal hyperplasia in 3. A total of 2 patients had pelvic peritoneal endometriosis, and 1 had endometriosis of the rectovaginal septum.

Comparison of Groups

The mean age of patients with Brenner tumors and mucinous tumors was each significantly different from that of patients with combined tumors ($P = .002$, $P < .001$, respectively; 2-tailed Student’s $t$ test). The distribution of tumor size for Brenner and mucinous tumors is shown in Figure 6. The estimated relative volumes of the 2 components are shown in Table 1.

Walthard Nests

A total of 50% of Brenner tumors and 59% of mucinous cystadenomas were associated with WNs, compared with 28% of controls ($P = .002$ and $P < .001$, respectively; 2-tailed $t$ test; Table 2). Among controls, the identification of WNs was strongly associated with the number of blocks of tube examined, with near-perfect correlation (correlation coefficient = 0.99). As shown in Table 3, when 4 or more blocks were examined, WNs were found in more than half. The regression line of the number of blocks (x-axis) versus proportion having WNs (y-axis) had a slope of 14.96, an $y$-intercept of $-5.35$, and a correlation coefficient of 0.99 ($P = .006$).

The mean number of blocks of tube examined in patients with Brenner tumor was 2.8, compared with 2.3 in controls. In view of the strong correlation and based on the calculated regression line, a mean number of blocks of tube of 2.8 should be associated with a WN frequency of 36.5%. Therefore, 39% of the increased frequency with Brenner tumors (from 28% to 50%) can be attributed to sampling. In contrast, 2.0 tube blocks were examined for mucinous cystadenomas, yielding an expected frequency of WN of 25%, 11% lower than controls, indicating a stronger relationship that is not weakened by sampling issues.

COMMENT

The putative morphologic precursors of the majority of ovarian epithelial tumors are well described; however, the origin of mucinous and transitional cell neoplasms is unknown. It is generally agreed that serous ovarian neoplasms arise from the ovarian surface epithelium and its derivatives. Evidence indicates that the majority and perhaps nearly all endometrioid and clear cell neoplasms of the ovary arise in endometriosis. Although mucinous neoplasms can arise in endometriosis, this appears to be relatively uncommon. Other postulated origins of mucinous tumors include Brenner tumors and mucinous metaplasia of surface epithelial inclusions. The occasional teratomatous origin of mucinous tumors is well known, and these tumors are regarded as a distinct entity of germ cell origin. Postulated origins of Brenner tumors also include the ovarian surface epithelium, teratomas (which are associated with Brenner tumors in 3% of cases), WNs, mesonephric remnants, and rete ovarii.

The current data show the intimate relationship between mucinous and transitional cell differentiation in benign ovarian neoplasms and document that 11% of all tumors, in 12% of all patients in this group, contain both...
components. Furthermore, if Brenner ‘‘tumors’’ smaller than 1 cm and unassociated with mucinous neoplasms are considered transitional cell inclusions rather than tumors, 17% of tumors in the entire group (and in 19% of patients) would contain both components. Because of sampling issues discussed below, this is likely to be an underestimate. Another finding suggesting a close relationship is the type of calcification found in mucinous tumors. Spiculated calcification (Figure 4), which we found in the majority (62.5%) of mucinous tumors containing calcification, has a distinctly different appearance from the psammomatous calcification often found in serous tumors and sometimes in endometrioid and clear cell tumors (an observation also made by Russell10) but is essentially identical to the calcification found in a typical Brenner tumor. These findings support our working hypothesis that mucinous and Brenner tumors have a common origin, and that the majority of apparently pure intestinal-type mucinous ovarian tumors currently classified as being of surface epithelial origin in fact arise from transitional cell/Brenner tumors or nests.

The frequent presence of mucinous epithelium associated with Brenner tumors has been recognized since the 1920s.25 The term metaplastic Brenner tumor was introduced in 1985 by Roth et al26,27 and was defined as a Brenner tumor with an unusual degree of cyst formation and prominent mucinous metaplasia. At that time, the authors felt that metaplastic Brenner tumor was a different entity from a Brenner tumor with an associated mucinous cystadenoma, the latter situation characterized by the presence of a distinct separate mucinous neoplasm.28 With this definition, 4 of our 13 combined tumors can be considered metaplastic Brenner tumors and a few additional tumors that we classified as pure Brenner tumors would probably also qualify for this designation.

Typical Brenner tumor consists of epithelial nests with transitional (urothelial) features occurring in the ovary, usually within a circumscribed nodule of fibrotic stroma; however, there are no widely used criteria for distinguishing small numbers of transitional cell nests within the ovarian cortex from a bona fide Brenner tumor. A size of 1.0 cm is generally used for the other ovarian epithelial cell types for distinction of a simple cyst from a ‘‘neoplasm’’ or cystadenoma, but this criterion has not been applied to Brenner tumors. Historically, essentially all studies of Brenner tumors have included tumors measuring less than 1 cm, and many studies contain tumors as small as 1 mm in diameter. The presence of transitional cell nests within the ovarian stroma appears to be relatively uncommon and is not even mentioned in recent authoritative chapters on the pathology of normal and non-neoplastic ovaries, probably because virtually any quantity of such nests is classified as a Brenner tumor.30 Evidence suggests that such nests occur in about 1% of ovaries.31 The 1-cm criterion is arbitrary and is based not on data, but rather on old, erroneous concepts.32 If 1 cm were used to define Brenner tumors, about half of the reported cases would be eliminated; in the current study, two thirds of cases would be too small to qualify for a neoplasm. Regardless of their name, microscopic transitional cell nests or microscopic Brenner tumors are the immediate precursors of larger Brenner tumors, and it is not necessary to conduct an investigatory search for transitional cell nests analogous to surface epithelial inclusions in the ovarian stroma, because this Brenner tumor ‘‘precursor’’ can be found by simply altering the arbitrary definition of a Brenner tumor to conform to that of the other surface epithelial tumor types. Thus, if all transitional cell proliferations smaller than 1 cm were considered transitional cell inclusions, this would define most Brenner tumors out of existence. The origin of these inclusions, however, remains unknown. Although some investigators are convinced by Arey’s demonstration using 3-dimensional reconstruction of the origin of Brenner tumors from WNs continuous with the ovarian surface epithelium,33 in our opinion, these data are less than convincing; as this report is based on 2 cases, more data are needed.

Mucinous ovarian neoplasms represent the largest ovarian tumors on record. When atypical features are found, extensive sampling of such large tumors has been recommended to completely evaluate for the presence of atypical proliferative (borderline) areas and for localized areas of invasion34; however, it has been shown that extensive sampling does not increase the identification of such features to a degree sufficient to alter the diagnosis in the vast majority of cases.34

During the past few decades, it has become clear that neoplasms of virtually all sites are heterogeneous. General principles of tissue sampling aim to accurately represent the range of histologic appearances of a tumor in a reasonable number of slides. Small tumors measuring no more than a few centimeters in diameter are rarely a problem. As the volume of a tumor increases with the cube of the radius, however, the proportion of tumor volume that is represented on the slides drops rapidly, and thus the slides become less likely to accurately reflect the full range of appearances. If, for example, a guideline of 1 section per centimeter of maximum tumor diameter is used, and assuming a spherical tumor in which 50% of the volume is solid and 50% is occupied by cyst lumens, a tumor 10 cm in diameter would be sampled with 10 sections, a proportion that accords each section to be representative, on average, of 26.2 cm³ of tumor. But for a tumor 15 cm in diameter, this level of sampling would require 34 sections, and for a 20-cm tumor, 80 sections. If a 5-cm tumor were considered properly sampled with 5 sections, then a 20-cm tumor would require 319 sections to achieve the same level of sampling per unit volume. The exponential increase in tumor volume as the diameter increases linearly makes reasonable or adequate sampling of large tumors a goal that for practical purposes is rarely, if ever, attained. Thus, the range of histologic appearances of large tumors is much more difficult to capture on the number of sections generally obtained in practice. With routine sampling techniques, sufficiently small foci having an appearance distinct from the remainder of the tumor will not be sampled and will therefore be undetected in a substantially, perhaps overwhelmingly, large proportion of cases.

If the combined mucinous/transitional cell tumors with discrete components are considered mucinous cystadenomas with foci of associated Brenner tumor, which is a typical and reasonable interpretation of this morphology, then of 49 mucinous cystadenomas in the current study, 9 (18%) had foci of Brenner tumor. This proportion is much higher than that reported by others (mean, 1.3%; P < .001), and may in part reflect our extensive sampling of these tumors. Among these 9 cases, 6 had Brenner components that were smaller than the mucinous component. If the Brenner foci are assumed to be solid and representative of their extent, and the mucinous components are
and our opinion it is nothing short of astonishing that these foci of Brenner tumor were found. In the tumor with the smallest proportional Brenner component, this component occupied 1:76:136 of the tumor volume and was found in 1 of a total of 4 sections examined of this 6-cm tumor. The largest proportional Brenner component among the 6 cases was 1:3287 in a 27-cm tumor that was sampled with 9 sections. In the former case, 4 sections of tumor would sample approximately 1.5% of the tumor volume, and in the latter case, 9 sections would represent 0.09% of the tumor volume.

In our opinion, these observations suggest that our finding that 18% of mucinous cystadenomas contain a Brenner component may be a considerable underestimate. The relatively small number of blocks needed to find such foci must indicate either that those tumors have many such foci and/or that a much larger proportion of apparently pure mucinous tumors contain such foci. Otherwise, we are faced with the proverbial needle in the haystack in which, based on the proportions calculated above, the likelihood of finding the Brenner component (the needle) is so remote that its relatively easy identification indicates that one of the underlying assumptions must be wrong.

Our data and those of others indicate that very large Brenner tumors and very small mucinous cystadenomas are uncommon. Examination of the size distribution of our cases (Figure 6) indicates that Brenner tumors are skewed to the left (even if tumors smaller than 1 cm are excluded), and that of mucinous tumors to the right. Such a skewed size distribution is not observed in the other cell types of surface epithelial tumors.21 If the mucinous and Brenner groups are combined, the size distribution flattens, and although it does not appear to approximate a typical normal distribution, the skews are much less apparent, and the range of sizes approaches that seen with the other types of surface epithelial tumors.

Despite general agreement that most mucinous neoplasms arise from the ovarian surface epithelium, it is uncommon to find a mucinous epithelial inclusion or mucinous metaplasia in an inclusion in an otherwise normal ovary,26,35 and only a handful of documented cases have been reported.5,36–38 As early as 1943, Barzilai27 recognized that mucinous (“pseudomucinous”) epithelium was never found in the normal ovary. Only 1 of our 40 mucinous cystadenomas (2.5%) was smaller than 3 cm. Thus, mucinous neoplasms are rarely diagnosed when small. This could be because they grow rapidly or, alternatively, when small, are for some reason not recognized as mucinous.

The high proportion of combined tumors, the similar types of calcification, and the complementary size distributions together suggest to us that these tumors have a common origin. We propose that intestinal-type mucinous tumors and Brenner tumors have the same histogenesis and arise from microscopic transitional cell nests. As these tumors grow, they become more likely to harbor a neoplastic mucinous component. Once the mucinous component is established, it overtakes the tumors mass, leading to marginalization of the transitional component, so that the latter component frequently becomes occult. This hypothesis is consistent with the size distribution of the tumors and their gross and microscopic pathology, explains the inability to identify the Brenner component in most large mucinous tumors, even when exhaustively sampled, and proposes a more conceivable origin of the vast majority of mucinous neoplasms. Accordingly, small mucinous neoplasms are rarely diagnosed because when small, they are Brenner tumors with foci of mucinous differentiation that fall within the accepted spectrum for typical Brenner tumor.

Our finding that WNs are 79% more common in women with Brenner tumors compared with controls (50% and 28%, respectively) is of some interest; however, this association is mitigated by sampling issues. The strong correlation of the likelihood of finding WNs with increased sampling of the fallopian tube in controls yields an expected frequency of 36.5%. This indicates that the increased frequency of WNs with Brenner tumors is equivalent to only 30% rather than 79%, and therefore 39% of the increase found with Brenner tumors can be attributed to sampling.

Of more interest is the association of WNs with mucinous neoplasms, as this is not at all mitigated by sampling in this study. In fact, the 28% versus 59% frequency in controls compared with mucinous tumors, respectively, is more than a 100% increase. Furthermore, when corrected for sampling of the tube, 25% of mucinous tumors would be expected to be associated with WNs. Thus, the increase is equivalent to 136%.

Walther nests are quite common and were found in most cases in which 4 or more blocks of fallopian tube were examined. This suggests that when the tubes are extensively sampled, WNs can be found in most women. Since there do appear to be significant differences between controls and both mucinous and Brenner tumors, it would appear more likely that the quantity of WNs is more important than their presence. However, our study was not designed to test this hypothesis.

Our findings suggest that the mucinous-transitional cell relationship is stronger than previously acknowledged. The presence of WNs appears more closely associated with mucinous tumors compared with Brenner tumors. Quantification of WNs may be valuable to clarify this relationship in future studies. A recent study found amplification of 12q14-21 in both a mucinous carcinoma and an associated Brenner tumor, suggesting a clonal relationship.39 Further comparisons of molecular features associated with transitional and mucinous cell types of ovarian tumors may be of value in elucidating their histogenetic relationship.

The authors thank Thomas Godwin, MD, Anna Yemelyanova, MD, and Robert Kurman, MD, for helpful comments.

References


