Alleotyping of Endometriosis with Adjacent Ovarian Carcinoma Reveals Evidence of a Common Lineage

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ABSTRACT

Endometriosis is a common gynecological disease in which tissue similar to the endometrium proliferates at sites outside the uterine cavity. Malignant transformation of endometriosis to endometrioid and clear cell ovarian carcinomas has been documented in histological studies, but no molecular genetic evidence exists to support that endometriosis is the clonal precursor of such malignancies. We examined 14 cases of endometriosis synchronous with ovarian cancer for loss of heterozygosity on 12 chromosome arms, X chromosome inactivation, and TP53 mutation to determine whether they shared genetic alterations. In all four of the cases where the carcinoma had arisen within endometriosis and in five of the seven cases where the carcinoma was adjacent to the endometriosis, common genetic lesions were detected, consistent with a common lineage. A TP53 mutation was also detected in one case of endometriosis adjacent to carcinoma. These findings support the numerous histological observations that endometrioid and clear cell ovarian carcinomas may arise through malignant transformation of endometriotic lesions.

INTRODUCTION

Endometriosis is a common gynecological disease in which endometrial-like glandular epithelium and stroma is found at locations outside the uterine cavity, most commonly the ovary. The most likely origin of the disease is implantation of viable endometrium refluxed into the peritoneal cavity during menstruation (1). Although endometriosis generally follows a benign course, it does exhibit some characteristics reminiscent of malignancy, including local invasion and metastases. A relationship between endometriosis and endometrioid and clear cell cancers of the ovary have been long suspected based on their frequent co-occurrence in surgical specimens (2–5). Based on histological observations and clinically documented cases, the frequency of malignant transformation of ovarian endometriosis is about 1%, but the actual frequency is probably significantly higher. In a long-term follow-up of over 20,000 Swedish women hospitalized for endometriosis, Brinton et al. (6) observed a 1.9 relative risk of ovarian cancer. The risk increased dramatically to 4.2 (95% confidence interval, 2.0–7.7) among subjects with a long-standing history of ovarian endometriosis.

Many of the risk factors associated with both endometriosis and ovarian cancer are the same and include earlier menarche, more regular periods, shorter cycle lengths, and lower parity. For endometriosis, the increased risk is consistent with an increased opportunity for menstrual contamination of the peritoneal cavity, whereas for ovarian cancer, these factors are thought to increase the number of ovolutions and therefore the potential for malignant transformation of damaged epithelium. However, it is possible that part of the increased ovarian cancer risk is due to an increased risk of endometriosis-associated endometrioid and clear cell subtypes. This idea is supported by Rosenblatt and Thomas (7), who found that tubal ligation, which prevents menstrual reflux and is protective for endometriosis, was also protective for clear cell and endometrioid ovarian cancers (relative risks of 0.2 and 0.32) but not serous and mucinous cancers. Although much of the data are circumstantial, there does appear to be a strong case for suggesting that endometriosis has malignant potential and is the precursor of some, and possibly all, endometrioid and clear cell ovarian cancers.

The first molecular genetic evidence that at least a subset of endometriotic lesions may be premalignant came from our analysis for LOH4 at candidate ovarian TSG loci in a series of 40 cases of endometriosis (8). We detected LOH on chromosome arms 9p, 11q, and 22q in 28% of cases, suggesting that the development of endometriosis might require the inactivation of the same set of TSGs involved in ovarian tumorigenesis. In this study, we have extended these findings by analyzing for genetic alterations present in endometriosis synchronous with ovarian carcinoma to determine whether the carcinoma had arisen de novo or by clonal expansion from the endometriosis.

MATERIALS AND METHODS

Source of Specimens. Fourteen archival paraffin-embedded specimens of ovarian endometriosis synchronous with ovarian carcinoma were accessed through the Department of Pathology, Southampton General Hospital. Histological diagnosis was confirmed by a specialist gynecological pathologist (A. H.) and are summarized in Table 1. Additionally, 17 endometrioid ovarian carcinomas without evidence of synchronous endometriosis were accessed either as fresh tumor biopsies or as archival paraffin-embedded specimens.

Microdissection and DNA Extraction. DNA was extracted from selected regions by microdissection as described previously (8). Briefly, serial 10-μm-thick sections were dehydrated in xylene and hydrated in 95% ethanol. One section was stained with H&E and mounted with a coverslip and used as a template. The remaining sections were mounted onto slides but left unstained for tissue removal. The areas of interest were scraped off using a 21-gauge needle under a dissecting microscope. For each case, cells were dissected from at least four consecutive sections.

Clonality Analysis. Clonality analysis was performed by examining the X chromosome inactivation pattern of the human androgen receptor (AR) gene as described previously (8).

LOH Analysis. The following markers were used to assess for LOH on the following chromosome regions: 2q (D2S95), 4q (D4S395), 4q (D4S175), 5p (D5S406), 5q13.1–14 (D5S424), 5q (D5S346), 5q22.3–3.13 (D5S399), 6q14–15 (D6S284), 7p13 (D7S691), 7p15-pter (D7S481), 9p21 (D9S171, D9S161), 11q23-ter (D11S1336 and D11S1328), 17p13.1 (TP53CA), 17q21 (D17S855), 17q21 (D17S806), 22q13 (D22S304, PDGFB, D22S284, D22S302, CYP2D6, and D22S274) and Xq11.2–12 (AR). The sequences of the primers were obtained from various databases accessed through the National Center for Human Genome Research (http://www.nih.gov). Details of the PCR conditions and analysis of PCR products have been described previously (8).

SSCP and Sequencing Analysis of TP53. PCR amplification of exons 5–8 of TP53 were performed in the carcinoma and endometriosis components of all 14 cases using the primers and conditions described previously (9–11).

Statistical Calculations. The probability of common LOH events occurring as independent events were calculated according to Jacobs et al. (12) with

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3 The abbreviations used are: LOH, loss of heterozygosity; TSG, tumor suppressor gene.
the vast majority of women, endometriotic implants become atrophic endometriosis noted in the pathological report. Cases (cases 30, 36, 136, 202, 287, and PE6) were identified after review of tissue slides from 19 ovarian endometrioid carcinomas were arising within the endometriotic cyst. DNA was extracted from three of these endometriotic cysts (E1, E2, and E3). E1 was analyzed for clonality, LOH, and TP53 mutation, whereas E2 and E3 were analyzed for TP53 mutation only.

### RESULTS

**Histological Features of Cases with Synchronous Endometriosis and Ovarian Cancer.**

Fourteen cases of ovarian endometriosis synchronous with ovarian carcinoma (Table 1), presenting between 1991 and 1995, were analyzed. In each case, histological diagnosis was confirmed by a specialist gynecological pathologist (A. H.). Eight cases (cases 38, 70, 90, 108, 267, 8, and 9) were identified after reviewing 220 endometriosis pathology reports. The remaining six cases (cases 30, 36, 136, 202, 287, and PE6) were identified after reexamination of tissue slides from 19 ovarian endometrioid carcinomas cases. In none of these six cases was the presence of synchronous endometriosis noted in the pathological report.

An interesting feature of these patients was that the majority (9 of 13, 70%) were >50 years of age and likely to be postmenopausal. However, 6 of our 14 cases showed clear histological features of active endometriosis (endometriarial glands and stroma), including an 80-year-old patient.

In four cases (cases 38, 78, 108, and 267), the carcinoma was present within the endometriotic cyst and was of endometrioid or mixed endometrioid and mucinous subtypes. Three of these cases also contained areas of endometriosis with cytological atypia (cases 78, 108, and 267). In seven cases, the carcinoma was located adjacent to the endometriosis (cases 8, 30, 36, 136, 202, 287, and PE6) and were of the endometrioid or mixed endometrioid and clear cell subtypes. In the remaining three cases, the carcinoma and endometriosis were present in contralateral ovaries and were of endometrioid, mucinous, or mixed endometrioid and clear cell subtypes.

### Microdissection and DNA Extraction

Areas of carcinoma, endometriosis, and in three cases (cases 78, 108, and 267) atypical endometriosis were carefully microdissected from surrounding normal areas as illustrated for case 38 in Fig. 1. In cases of mixed ovarian cancer subtypes, only areas of endometrioid carcinoma were microdissected. Cells were microdissected from at least four consecutive sections for each case. In case PE6, there were several endometriotic cysts adjacent to the carcinoma (Fig. 2). DNA was extracted from these three endometriotic cysts (E1, E2, and E3). E1 was analyzed for clonality, LOH, and TP53 mutation, whereas E2 and E3 were analyzed for TP53 mutation only.

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**Table 1 Clinical and pathological features of endometriosis synchronous with ovarian carcinoma**

<table>
<thead>
<tr>
<th>Case</th>
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<th>Histology</th>
<th>Location</th>
<th>Stage</th>
<th>Grade</th>
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<td>1a</td>
<td>I</td>
<td>P</td>
</tr>
<tr>
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<td>76</td>
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<td>1a</td>
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<tr>
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<td>68</td>
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<td>Within</td>
<td>1a</td>
<td>II</td>
<td>P</td>
</tr>
<tr>
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<td>34</td>
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<td>1a</td>
<td>II</td>
<td>P</td>
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<tr>
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<td>I</td>
<td>P</td>
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<tr>
<td>30</td>
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<td>NA</td>
<td>P</td>
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<tr>
<td>36</td>
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<td>III</td>
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<td>P</td>
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<tr>
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<td>P</td>
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<td>Left ovary</td>
<td>P</td>
<td></td>
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<tr>
<td>90</td>
<td>60</td>
<td>E, no atypia</td>
<td>Left ovary</td>
<td>1a</td>
<td>I</td>
<td>P</td>
</tr>
</tbody>
</table>

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DNA derived from paraffin-embedded tissue is commonly damaged and/or present in minute amounts and can cause PCR artifacts (such as random preferential allele amplification), which can confuse the interpretation of LOH and clonality assays. A critical factor in eliminating such artifacts is to extract DNA from as many cells as possible to maximize the DNA yield. The smallest number of cells we used was on the order of 400 cells (for example, cyst 3 in Fig. 2 has ~100 cells, and four sections were extracted). Because the DNA was extracted into a final volume of 30 μl, each 1 μl used per PCR reaction contained ~12 genomes. This represents the smallest number, and in most cases, DNA was extracted from at least 2000–5000 cells. To distinguish preferential allele amplification from true LOH, all experiments were repeated at least three times, and a locus was only scored as showing LOH when it was observed on every occasion. As a further control, the normal DNA controls included not only purified high molecular weight blood DNA but also normal archival endometrium or normal areas from the same slide as the endometriosis. Only when LOH was observed consistently in independent experiments and no loss was observed in the normal archival DNA was a locus scored as showing LOH.

**Clonality Analysis.** Assessment of clonality was only possible for cases 9, 108, and PE6; the endometriosis and carcinoma areas were monoclonal (Table 2). In cases 106 and PE6, the same X chromosome inactivation pattern was observed in the endometriosis and adjacent carcinoma, whereas in case 9, where the carcinoma and endometriosis components were present on contralateral ovaries, the X-inactivation involved the opposite alleles.

**LOH Analysis.** LOH analysis was performed on all components of the 14 cases of endometriosis synchronous with ovarian carcinoma and the 17 solitary ovarian endometrioid ovarian carcinomas using 25 microsatellite markers on the following chromosome regions: 2q, 4q, 5q, 6q, 7p, 9p, 11q, 17p, 17q, 22q, and Xq. These regions were selected for the study either because they are thought to harbor TSGs involved in the development of ovarian and other epithelial cancers (14–15) or have been reported to be specifically involved in endometrioid ovarian cancer (16).

The LOH results for the 14 cases of endometriosis synchronous...
with ovarian carcinoma are summarized in Table 2. Among the carcinoma components, a total of 65 LOH events were detected, with all showing LOH with at least one marker. Seventeen of these LOH events, occurring in nine cases (case 30, 36, 38, 78, 108, 136, 202, 267, and PE6), were also detected in the associated endometriosis, examples of which are shown in Fig. 3. In all 17 instances, the LOH involved the same allele as the associated carcinoma, consistent with a common lineage. There was only one LOH event detected in endometriosis that was not also present in the carcinoma (Fig. 3), but this occurred in case 90, where the endometriosis and carcinoma were from contralateral ovaries. None of the three cases where the endometriosis and carcinoma were from contralateral ovaries displayed any common LOH. Five of the seven cases with carcinoma adjacent to the endometriosis displayed common LOH events. All four cases with the carcinoma arising within the endometriotic cysts (cases 38, 78, 108, and 267) displayed at least two common LOH events. In particular, case 38 harbored three common LOH events on 9p, 11q, and 22q. The LOH on 9p and 22q appeared to encompass an identical region in the endometriosis and carcinoma because adjacent microsatellite markers were heterozygous.

In some cases, the LOH detected in the endometriosis components involved smaller regions than observed in the associated carcinoma. In particular, LOH on chromosome 5q in cases 36 and PE6 was observed only with marker D5S346 and D5S424, respectively, whereas the carcinoma had LOH with all of the 5q markers.

The probability that these common LOH occurred as independent events were calculated according to Jabobs et al. (12) with the modification of Abeln et al. (13), which takes into account the probability of LOH occurring at a specific locus. The locus-specific probabilities were derived from the observed LOH frequencies observed in our 31 cases of endometrioid ovarian cancer and were estimated to be 0.29 on 4q, 0.46 on 5q, 0.29 on 6q, 0.54 on 9p, 0.37 on 11q, and 0.47 on 22q. The probability of independent origin among the nine cases with common LOH ranged from \( P = 0.23 \) for case 202, where only one common LOH event was observed, to \( P = 0.01 \) for case 38 in which three common LOH events were observed. In six of the nine cases, the probabilities were \( P < 0.05 \) or less, indicating that it is very unlikely that these occurred by chance. Additionally, these probability estimates do not take into account the fact that the regions of LOH in some cases appeared to be identical in each component.

**TP53 Mutation Analysis.** TP53 mutations were detected in the carcinoma components of cases 30 (CGT>TGT, codon 273) and 267 (1-bp deletion in codon 152), but these were not detected in the adjacent endometriosis components. However, in case PE6 where the carcinoma was surrounded by three apparently independent endometriotic cysts (Fig. 2), a Tyr-to-Cys mutation in codon 220 was detected in endometriosis cyst E3 but surprisingly not in the adjacent carcinoma. Only one TP53 mutation (GTC>GAC codon 157) was detected among the 17 cases of solitary endometrioid ovarian cancers.

**LOH in Endometrioid Ovarian Carcinoma.** A total of 31 endometrioid ovarian carcinomas were analyzed and comprised the 14 cases synchronous with endometriosis and 17 without evidence of synchronous endometriosis. Comparison of the grade and stage (Table 3) demonstrated that the cases with synchronous endometriosis were more frequently early stage and low grade than those without associated endometriosis, although only the association with grade was statistically significant (\( \chi^2 \) test, \( P = 0.005 \)).

The locus-specific LOH frequencies did not differ significantly between the groups with and without endometriosis so the LOH frequencies were combined (Table 4). LOH among the carcinomas was common with 29 of 31 (94%) showing LOH with at least one marker. LOH was detected on all chromosome arms with frequencies between 14% for chromosome 5p and 54% for chromosome 9p. The frequency of LOH with respect to tumor grade and stage for both groups were assessed, but because the numbers in each group were small, no statistically significant correlations were evident. However, LOH on chromosome arms 5q, 9p, 11q, 17p, 22q, and Xq were relatively common in grade 1 (40%–80%) and/or stage I (33%–57%) tumors, suggesting these are early events in endometrioid tumorigenesis.

LOH in Endometriosis. We have reported previously LOH analysis of 40 cases of solitary endometriosis using a limited number of chromosome arms. We extended the LOH analysis to include all of the markers used for the synchronous cases, and the results are summarized in Table 4. To calculate the overall frequency of LOH in endometriosis, the results for the 14 endometriosis cases synchronous with ovarian carcinoma have been included in the calculations.

Twenty-three of the 54 (43%) endometriosis cases demonstrated LOH with one or more markers on chromosome arms 4q (2%), 5q (10%), 6q (7%), 9p (21%), 11q (19%), and 22q (19%). Nine cases (17%) showed LOH on two chromosome arms and two (4%) showed LOH on three chromosome arms.

Comparison of LOH in Endometriosis and Endometrioid Carcinoma. A comparison of the LOH frequencies detected in solitary endometriosis, endometrioid synchronous with carcinoma and solitary endometrioid ovarian carcinoma is shown in Table 4. The overall LOH frequency among all of the endometriosis cases was lower and

### Table 3 Stage and grade of endometrioid ovarian carcinoma with and without synchronous endometriosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</tr>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*EC, endometrioid carcinoma; E, endometriosis. Only 16 cases were available for stage and 15 for grade.

** Only 11 cases were available for stage and grade.
involved fewer loci than the solitary carcinomas. Among the solitary endometriosis cases, LOH was only detected on chromosome arms 5q, 9p, 11q, and 22q. LOH was also detected at these loci in the endometriosis cases with associated carcinoma, but the frequencies were consistently higher than in the solitary cases. LOH was also detected on chromosome arms 4q and 6q in the endometriosis cases with carcinoma. Interestingly, the chromosome arms showing the highest LOH frequencies among the endometriosis cases (5q, 9p, 11q, and 22q) were also among those showing frequent LOH in low grade and early stage endometrioid ovarian cancers.

**DISCUSSION**

Histological and epidemiological observations have consistently demonstrated an association between endometriosis and ovarian cancer (2–5, 17–20), and although much of the data are circumstantial, there is a strong case for suggesting that endometriosis has malignant potential and may be the precursor of some, and possibly all, endometrioid and clear cell ovarian cancers. Our goal has been to test this hypothesis by analyzing for genetic alterations in endometriosis contiguous with, or adjacent to, ovarian carcinoma.

The finding of common LOH events in 9 of 11 (82%) cases of endometriosis with adjacent or contiguous carcinoma supports the view that they have a common genetic lineage. These common genetic alterations are very unlikely to have occurred as independent events based on statistical analysis and because in some cases they encompassed the same small chromosomal segment. The possibility that the areas of endometriosis in these cases represented differentiated components of the carcinomas is not supported by the fact that in all cases, the endometriosis harbored fewer genetic alterations than the carcinoma, as would be expected if it were the precursor of the tumor. The only cases where a common lineage could not be established were those cases in which the endometriosis and carcinoma were obtained from contralateral ovaries.

We detected only three TP53 mutations among the total of 56 (5%) endometrioid ovarian carcinomas, which indicates that the TP53 mutation is of less relevance in the development of this histological subtype. The low frequency of mutation in the carcinomas was reflected in the absence of TP53 mutations in any of the 40 solitary endometriotic cysts we examined in a previous study (8) and in only 1 of 14 of the cases reported here. This mutation was detected in cyst E3 from case PE6 and was particularly intriguing because it was not detected in the adjacent carcinoma or endometriotic cysts. This was unexpected because an endometriotic cyst harboring a TP53 mutation seemed the most likely precursor of an adjacent carcinoma. LOH analysis has not been performed on this cyst; therefore, it is not possible to determine whether it shares some other common genetic alterations that could establish a relationship between the adjacent carcinoma.

Our previous LOH analysis of 40 solitary endometriotic cysts demonstrated that about one-third of these harbored deletions on chromosomes 9p, 11q, or 22q (8). In this study, we examined additional chromosomes and confirmed that LOH is relatively common on chromosomes 9p (10 of 48, 21%), 11q (8 of 43, 22%), and 22q (10 of 53, 15%), and we also detected LOH on chromosome arms 5q (5 of 47, 12%) and 6q (3 of 45, 8%). If endometriosis is the precursor of endometrioid and clear cell ovarian cancers, then LOH on these chromosomes should also be common in the cancers. Comparison of the LOH frequencies (Table 4) revealed a striking trend of increasing LOH on chromosome 5q, 6q, 9p, 11q, and 22q in solitary endometriosis, endometriosis with associated carcinoma, and endometrioid ovarian carcinoma.

As a result of these studies, we are in a position to propose a preliminary model for the development and malignant transformation of endometriosis. The first step is the implantation and proliferation of ectopic endometrium. It is not clear whether this is dependent on the acquisition of genetic alterations, but by the time these implants have developed into small endometriotic cysts, over one-third will harbor LOH, predominantly on chromosomes 9p, 11q, or 22q. Because the majority of endometriotic cysts remain benign, these genetic alterations may only be involved in the maintenance of the endometriotic cysts, with other mutations in other genes being required for the promotion to a premalignant state. The detection of LOH on chromosome 5q in 6% of solitary cysts and 25% of cysts with synchronous carcinoma suggests that one of these genes may reside on chromosome 5q. LOH on chromosome 6q first appears in endometriosis with adjacent carcinoma (27% of these cases), and this might be associated with malignant transformation. It is interesting to note that Tibiletti et al. (21) has shown that deletions involving chromosome 6q are very common in early ovarian cancers of all histological types and has suggested that this may be one of the earliest lesions in the pathogenesis of ovarian cancer. LOH on chromosomes 5q, 9p, 11q, and 22q are also common in early-stage and/or low-grade endometrioid ovarian cancers, consistent with the LOH pattern observed in endometriosis.
The data presented here support the view that endometriosis can undergo malignant transformation and raise the questions of how frequently transformation occurs and what proportion of endometriotic and clear cell ovarian carcinomas arise via this route. The frequency with which endometriosis undergoes transformation is difficult to determine, but based on histological observations, it has been estimated to occur in about 1% of all cases. Epidemiological studies of women with endometriosis have generally involved few patients and have been of insufficient duration to assess the magnitude of risk of developing a carcinoma. In the largest study, 62 women were followed for a mean of 8.1 years (22), one of whom (1.6%) developed an ovarian carcinoma within an endometriotic cyst, which is broadly in line with the risk estimated from histological observations.

The proportion of endometrioid and clear cell ovarian carcinoma arising via endometriosis is also difficult to assess. Numerous studies have established that between 30 and 40% of endometrioid and clear cell ovarian cancers contain histologically identifiable areas of endometriosis (Table 5), with about one-third showing a direct transition to malignancy. Even this remarkably high figure is likely to be an underestimate, because in many instances, evidence of the precursor endometriotic lesion would be destroyed by outgrowth of the carcinoma. Interestingly, when we reexamined 19 cases of endometrioid ovarian cancer, in which only 2 cases were reported as carcinoma with endometriosis, an additional 6 cases with endometriosis in the same ovary were found. This suggests that the presence of endometriosis may be routinely omitted in pathological reports, thereby underestimating its biological significance.

It is possible to estimate the proportion of ovarian cancer that may arise via an endometriotic precursor, assuming that endometriosis affects about 10% of women (23), and 1% of these cases will undergo malignant transformation. Based on these estimates, about 1 in a 1000 women would be expected to develop an endometrioid or clear cell ovarian cancer from endometriosis. This estimate is remarkably similar to the incidence observed in clinical practice, where about 1% of women develop ovarian cancer, of which ~10–15% are of endometrioid or clear cell type (i.e., 1 of 1000 to 1 of 1500 women). Although these calculations are based on best estimates, it is consistent with the hypothesis that endometriosis is the precursor of the majority, if not all, endometrioid and clear cell ovarian cancers.

In summary, we have shown that genetic alterations are relatively common in endometriosis, implying that TSG alterations are likely to be involved in the proliferation and maintenance of endometriotic implants. The finding of common genetic abnormalities in endometriosis synchronous with ovarian carcinoma reinforces the histological and epidemiological data, suggesting that endometriosis is the precursor of all endometrioid and clear cell ovarian cancers. However, the absolute risk of malignant transformation is small, and the vast majority of endometriotic lesions follow a benign course. The challenge now is to identify the small subset of endometriosis cases with the greatest risk of malignant transformation.

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REFERENCES

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