

Gain of OGP, an Estrogen-Regulated Oviduct-Specific Glycoprotein, Is Associated with the Development of Endometrial Hyperplasia and Endometrial Cancer

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ABSTRACT

Purpose: Lesions in the endometrium are difficult to differentially diagnose. The present study examined whether oviduct-specific glycoprotein is differentially expressed in normal, hyperplastic, and malignant endometrium.

Experimental Design: The expression of oviduct-specific glycoprotein was characterized by immunohistochemical methods with whole sections of endometrium from 90 women. An endometrial cancer tissue microarray with 200 cases of endometrial cancer was also assessed for oviduct-specific glycoprotein, estrogen receptor, and PTEN expression.

Results: In normal endometrium, there was focal oviduct-specific glycoprotein expression in the basalis layer, where the stem cells reside, in 10 of 15 cases. On average, atypical hyperplastic endometria stained more intensely than hyperplastic endometria ($P = 0.017$), whereas the percentage of positively stained cells was not significantly different. The mean staining indices (intensity \times percentage of positive cells score) for hyperplasia and atypical hyperplastic were 4.7 and 5.5 and were significantly higher than

staining indices seen in normal cycling endometria or well-differentiated endometrioid endometrial carcinomas ($P < 0.0001$ and $P < 0.001$, respectively). The endometrial cancer tissue microarray showed that of 139 endometrioid endometrial carcinomas, 11 cases were strongly oviduct-specific glycoprotein positive, whereas the other 128 cases were negative or weakly positive. Analysis of Kaplan-Meier curves with log-rank statistics showed a trend toward significance, with strong oviduct-specific glycoprotein staining serving as a predictor of good prognosis ($P = 0.1$). There was a significant positive correlation between oviduct-specific glycoprotein staining and loss of PTEN in the cases of endometrial cancer ($P = 0.004$).

Conclusions: Oviduct-specific glycoprotein may be a useful diagnostic adjunct to more accurately classify premalignant and early malignant change in the endometrium, improving on the current irreproducible histologic classification system.

INTRODUCTION

In mammals, the oviduct secretes a major estrogen-induced glycoprotein known as oviduct-specific glycoprotein. It is a highly glycosylated molecule normally produced by the secretory epithelial cells of the oviduct (1, 2). Its synthesis and secretion is regulated during the menstrual cycle with the highest concentrations of oviduct-specific glycoprotein found during the periovulatory period when estrogen levels are high and it is believed to play a role in fertilization and early embryonic development (3–7).

Oviduct-specific glycoprotein was long considered to be secreted specifically and exclusively by the oviductal epithelium (1, 2, 8). We recently examined the expression of oviduct-specific glycoprotein in ovarian cancer because of the resemblance of ovarian serous adenocarcinomas, the most common type of ovarian cancer, to tubal epithelium. We found that oviduct-specific glycoprotein was expressed in the majority of epithelial inclusion cysts, which are believed to be the preferential sites for the initiation of malignant transformation in ovarian cancer (9). It was also expressed in early, low-grade serous adenocarcinomas, suggesting that oviduct-specific glycoprotein may represent an early indicator of neoplastic transformation (9). In this initial study, we screened different tissues for oviduct-specific glycoprotein with tissue microarrays. Preliminary results showed that 3 of 56 cases of endometrial cancer and 6 of 17 cases of atypical endometrial hyperplasias stained positively for oviduct-specific glycoprotein based on examination of 0.6-mm tissue cores. On the basis of these observations, we hypothesized that oviduct-specific glycoprotein may be a marker of the development and progression of atypical hyperplasias, which are known precursors of endometrial cancer.

Endometrial cancer is the most common malignancy of the

Received 6/29/04; revised 8/12/04; accepted 8/31/04.

Grant support: A grant from the National Cancer Institute of Canada (NCIC) with funds from the Canadian Cancer Society (N. Auersperg M. Woo) and the Michael Smith Foundation for Health Research (M. Woo and P.C.K. Leung) and the Terry Fox Foundation through an award from NCIC.

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female genital tract. In the lifetime of a woman, the probability of developing endometrial cancer is 1 in 38 (10). During carcinogenesis, the endometrium undergoes many phenotypic changes, reflecting the variable cellular differentiation in the Mullerian system (11). Endometrial adenocarcinomas are classified into two predominant histologic groups, endometrioid carcinomas, which account for 80% of endometrial adenocarcinomas, and the nonendometrioid types (12). Nonendometrioid endometrial carcinomas, including uterine papillary serous carcinomas and clear cell carcinomas, are infrequent; however they are high-grade, aggressive tumors with a poor clinical outcome (13–15). Uterine papillary serous carcinomas and clear cell carcinomas are not estrogen-responsive and arise from precancerous lesions that develop in atrophic endometrium (16). In contrast, endometrioid carcinomas are driven by estrogen stimulation and are often preceded by or coexist with endometrial hyperplasia, which is believed to be a precursor lesion (17). Histologically, it is difficult to differentiate nonatypical hyperplasias from atypical hyperplasias and atypical hyperplasias from well-differentiated endometrioid carcinoma. Both atypical hyperplasia and low-grade endometrioid carcinoma show cytological atypia, and they are distinguished primarily by architectural features (18). There is high intra- and interobserver variability in the histologic diagnosis of these lesions (19–21). Accurate classification of these precursor lesions is of great clinical importance because it allows for appropriate preventative measures to be taken. Therefore, in addition to the morphologic classification of endometrial neoplasia, recent reports have identified possible precursor lesions with immunohistochemistry, molecular analysis, comparative genomic hybridization, and DNA microarray technology (20).

In the present study, we tested our hypothesis by examining the expression of oviduct-specific glycoprotein in whole sections of normal, hyperplastic, and malignant endometrium. To determine whether oviduct-specific glycoprotein can predict clinical outcome, immunohistochemistry was also done on a tissue microarray of endometrial cancer cases with follow-up data. Because oviduct-specific glycoprotein is an estrogen-regulated protein and because hyperplasias and endometrioid carcinomas are estrogen driven, we examined the expression of estrogen receptor (ER) in the endometrial tumors. We also examined the expression of PTEN, the loss of which has been proposed as a marker of endometrial neoplasia (22).

MATERIALS AND METHODS

Patients. Paraffin-embedded tissues from 290 hysterectomy specimens were retrieved from the archives of the Vancouver Hospital and Health Science Center's clinical database (Table 1). This study included tissue sections from 15 cases of normal endometria, of which 5 were proliferative, 5 were secretory, and 5 were menstrual phase endometria. There were 43 cases of hyperplasias, 16 nonatypical, and 27 atypical. Of the endometrioid carcinomas ($n = 24$), 15 were low-grade (International Federation of Gynecologists and Obstetricians grade 1), and 9 were high-grade (International Federation of Gynecologists and Obstetricians grade 3). The rest were uterine papillary serous carcinomas ($n = 8$). Two hundred cases were used to construct an endometrial cancer tissue microarray. None of the

Table 1 Summary of cases used in this study

Histological feature	Total no. of cases
Tissue sections	90
Normal	15
Proliferative	5
Secretory	5
Menstrual	5
Hyperplasia	43
Typical	16
Atypical	27
Endometrioid carcinoma	24
Grade 1	15
Grade 3	9
Papillary serous carcinoma	8
Tissue microarray	200
Endometrioid carcinoma	156
Nonendometrioid carcinoma	44

included cases received preoperative radiotherapy or chemotherapy. One hundred fifty-six cases were of the endometrioid type, whereas the rest were nonendometrioid carcinomas. H&E-stained slides and follow-up data were available for all cases. Mid- or late-proliferative oviductal tissues were used as positive controls for oviduct-specific glycoprotein staining.

Construction of Tissue Microarray. The tissue microarrays were constructed as described previously (23). Briefly, using a tissue microarrayer (Beecher Instruments, Silver Spring, MD), the marked area of interest from the donor block was cored twice with a 0.6-mm diameter cylinder and transferred to a recipient paraffin block. The marked area on the donor block was selected based on examining an H&E slide-containing tumor.

Immunohistochemistry. The avidin-biotin method was used for immunostaining and applied to formalin-fixed and paraffin-embedded tissue. Serial sections of the recipient paraffin blocks were cut at 3 μm , deparaffinized with xylene, and rehydrated through a series of graded alcohols. Sections were stained with the antibodies listed in Table 2. Staining for ER and PTEN was done with an automated stainer (Ventana, Tucson, AZ), according to the manufacturer's guidelines. Antigen retrieval was carried out as indicated in Table 2.

For oviduct-specific glycoprotein staining, a polyclonal antibody generated in rabbits was used at a dilution of 1:1000 (1). Sections were incubated in primary antibody overnight at 4°C, followed by incubation in biotinylated secondary antibody (1:200 dilution; Vector Laboratories, Inc., Burlingame, CA) for 1 hour at room temperature, and incubation in avidin-biotin-horseradish peroxidase for 1 hour (Vectastain ABC kit; Vector Laboratories Inc.). The sections were developed with 3,3'-diaminobenzidine tetrahydrochloride (Vector Laboratories Inc.), counterstained lightly with hematoxylin, and dehydrated with graded ethanol concentrations, followed by xylene and mounting (9).

For the tissue sections, scores for the expression of oviduct-specific glycoprotein were assigned semiquantitatively according to the percentage of cells stained (no positive cells, score 0; <5%, score 1; 5 to 50%, score 2; >50%, score 3) and the intensity of staining (no staining, score 0; weak, score 1; mod-

Table 2 Antibodies used for immunohistochemical staining

Antigen	Clone	Supplier	Dilution	Antigen retrieval
ER	6F11	Novocastra	1:50	M
PTEN *	Polyclonal	H.C. Cheng	2.63 μ g/mL	V
OGP	Polyclonal	H.G. Verhage	1 μ g/mL	M

* Antibody generously provided by Dr. Heung-Chin Cheng (University of Melbourne).

Abbreviations: M, microwave; V, as per Ventana protocol Benchmark BMK iView DAB system; OGP, oviduct-specific glycoprotein.

erate, score 2; and strong, score 3). The two scores were then multiplied to get the staining index.

For the tissue microarrays, staining for oviduct-specific glycoprotein was scored by staining intensity as either (a) absent or weak or (b) strong. Sections stained for ER and PTEN were scored by percentage of positive cells with a three-point scale where 0 = 0 to 50% of cells staining, 1 = >50% of cells staining, and 5 = uninterpretable score. Technically unsatisfactory samples (24 for oviduct-specific glycoprotein staining, 42 for the comparison of ER and oviduct-specific glycoprotein, and 49 for the comparison of PTEN and oviduct-specific glycoprotein) were eliminated from additional consideration. As oviduct-specific glycoprotein staining in endometrial tissues is focal, score results for duplicate cores from the same case were consolidated into one score where positive staining always superseded a negative or uninterpretable result.

Statistical Analyses. Statistical analyses were done with SPSS, version 11.0 software (Chicago, IL). Either Mann-Whitney *U* rank sum or Kruskal-Wallis nonparametric tests were

used to evaluate the correlation between oviduct-specific glycoprotein expression and endometrial tissue categories. The Kaplan-Meier method was used to construct a disease-specific survival curve for subgroups of patients based on oviduct-specific glycoprotein expression profile as assessed on the tissue microarray. Comparison of curves was done using log-rank statistic. Time-to-event was defined as disease-specific survival from initial hysterectomy to date of death due to endometrial carcinoma, with all others considered censored. Correlation between oviduct-specific glycoprotein, PTEN and ER expression was compared by either χ^2 or Fisher's exact test. For all analyses, two-sided tests of significance were used with α of 0.05.

RESULTS

Oviduct-Specific Glycoprotein Expression. The glandular epithelium of normal endometrium stained weakly positive in 10 of 15 (67%) of the cases, with a mean staining index of 1.0, whereas the luminal epithelium was oviduct-specific glycoprotein negative in every case. Most of the staining was observed in the basalis layer, where the stem cells reside, and in some adjacent glands in the functionalis layer (Fig. 1). The expression of oviduct-specific glycoprotein was focal, and no difference was observed between stages of the menstrual cycle.

Oviduct-specific glycoprotein was expressed in 41 of 43 (95%) cases of endometrial hyperplasia. The intensity of staining was more pronounced in atypical hyperplasia compared with hyperplasia without atypia ($P = 0.017$; Figs. 1 and Fig. 2A), whereas there was no difference in the percentage of positively stained cells (Fig. 2B). Of 16 cases of hyperplasia without

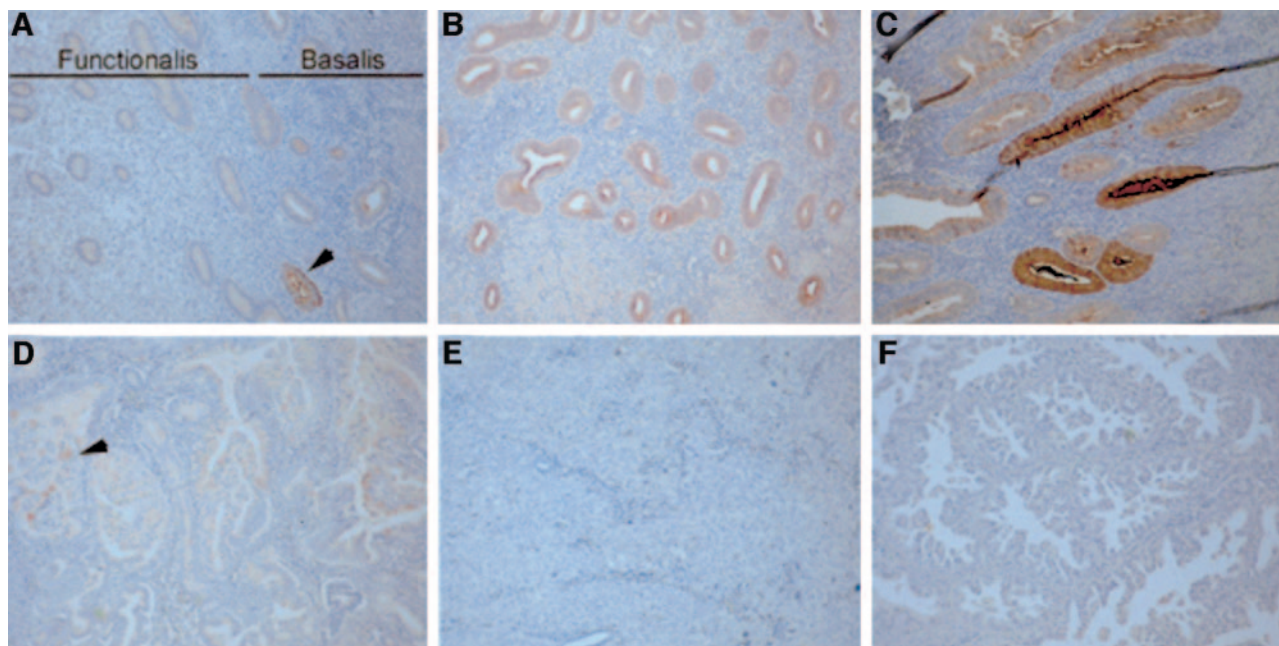


Fig. 1 Oviduct-specific glycoprotein staining in normal, hyperplastic and malignant endometrial tissue. In normal endometrium (A), focal staining (arrowhead) is observed in the basalis layer, where the stem cells reside. On average, nonatypical hyperplastic endometria (B) stained less intensely than atypical hyperplastic endometria (C). Oviduct-specific glycoprotein levels fall with progression to carcinoma, endometrioid carcinoma grade 1 (D), endometrioid carcinoma grade 3 (E), and uterine papillary serous carcinoma (F).

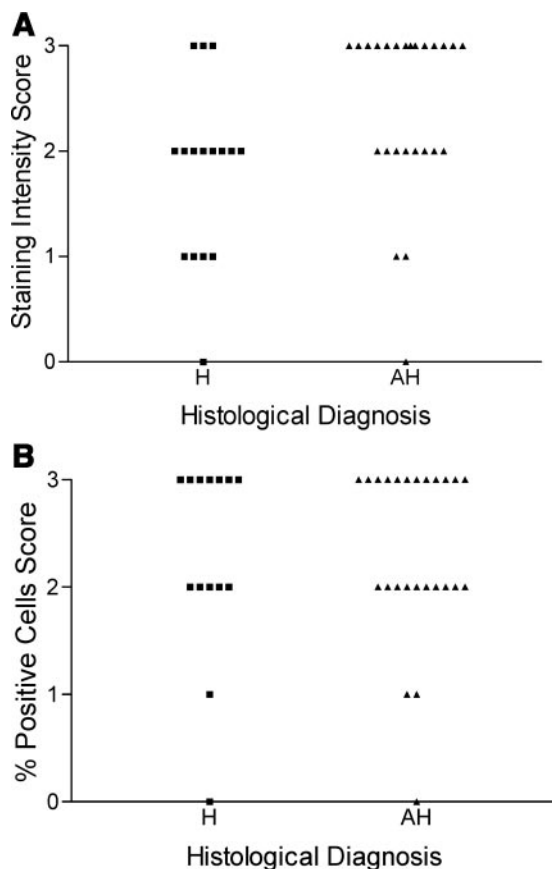


Fig. 2 Comparison of the staining intensity (A) and percentage of positive cells (B) in hyperplasias with and without cytological atypia. Atypical hyperplasias (AHs) stained more intensely than nonatypical hyperplasias (Hs; $P = 0.017$), although the distribution of the percentage of positive cells was not significantly different. Scores for the expression of oviduct-specific glycoprotein were assigned semiquantitatively according to the intensity of staining (no staining, score 0; weak, score 1; moderate, score 2; and strong, score 3) and the percentage of cells stained (no positive cells, score 0; <5%, score 1; 5 to 50%, score 2; and >50%, score 3).

atypia, 15 were positive for oviduct-specific glycoprotein, with a mean staining index of 4.73. Twenty-six of 27 cases of atypical hyperplasia were positive for oviduct-specific glycoprotein with a mean staining index of 5.50. This difference in staining indices is not significant.

Oviduct-specific glycoprotein immunostaining was done on whole sections of 32 endometrial carcinomas (Fig. 1). Fifteen (47%) of the tumors were oviduct-specific glycoprotein positive and 53% ($n = 17$) were oviduct-specific glycoprotein negative. In the oviduct-specific glycoprotein-positive group, 80% ($n = 12$) showed weak (staining index ≤ 4) and 20% showed strong staining (staining index > 4).

Fig. 3 shows the staining index of all ($n = 90$) cases where oviduct-specific glycoprotein staining was done on whole sections. There was a significant increase in oviduct-specific glycoprotein staining in cases of hyperplasia (atypical or nonatypical) compared with normally cycling endometrium ($P < 0.0001$). Progression to carcinoma was associated with a de-

crease in oviduct-specific glycoprotein expression compared with hyperplasia ($P < 0.0001$). A significant difference ($P < 0.001$) was observed between the staining index of atypical hyperplasia and well-differentiated (grade 1) endometrioid carcinoma. There was also a significant correlation between oviduct-specific glycoprotein expression and tumor grade. Percentages of oviduct-specific glycoprotein-positive tumors were as follows: grade 1 endometrioid carcinoma, 80% oviduct-specific glycoprotein positive; grade 3 endometrioid carcinoma, 13% oviduct-specific glycoprotein positive; uterine papillary serous carcinoma, 7% oviduct-specific glycoprotein positive, with oviduct-specific glycoprotein staining index correlating significantly higher in patients with low-grade disease (grade 1 endometrioid carcinoma) compared with those with high-grade tumors (grade 3 endometrioid carcinoma and uterine papillary serous carcinoma; $P < 0.05$).

Oviduct-Specific Glycoprotein Expression Is Related to Better Survival. Analysis of the endometrial cancer tissue microarray showed that the patients with strong oviduct-specific glycoprotein-positive tumors had better survival rates compared with oviduct-specific glycoprotein-weak or -negative tumors, but the difference did not reach statistical significance ($P = 0.1$; Fig. 4). All ($n = 11$) of the strongly oviduct-specific glycoprotein-positive tumors were grade 1 endometrioid carcinomas with 100% survival for at least 11 years. The 20-year survival rate of patients with oviduct-specific glycoprotein-weak or -negative tumors was $\sim 70\%$.

Comparison of ER Expression to Oviduct-Specific Glycoprotein in Malignant Tissue. Because oviduct-specific glycoprotein is regulated by estrogen, ER immunohistochemistry was done on the endometrial cancer tissue microarray (3, 24). There was no significant correlation between ER expression and oviduct-specific glycoprotein staining, although a trend was observed ($P = 0.138$; Table 3).

Comparison of PTEN Expression to Oviduct-Specific Glycoprotein in Malignant Tissue. The appearance of PTEN somatic mutations or deletions is common in low-grade endometrioid carcinomas (25, 26). There was a significant correlation ($P = 0.004$) between the presence of PTEN-null glands and positive oviduct-specific glycoprotein staining in cases on the endometrial cancer tissue microarray (Table 3).

DISCUSSION

Oviduct-specific glycoprotein is a glycoprotein secreted by secretory epithelial cells of the oviduct (3); recently, we showed that it is ectopically expressed in ovarian cancer (9). On the basis of the present study of normal, hyperplastic, and malignant endometrial tissues, it appears that a gain of oviduct-specific glycoprotein begins under conditions of unopposed estrogen exposure, which is a known risk factor for the development of endometrioid carcinoma.

Although oviduct-specific glycoprotein is not normally a secretory product of the normal endometrium, we observed focal staining of the stem cells in the basalis layer with some staining in adjacent glands in the functionalis layer (1). The epithelial cells in the functionalis layer shed each month and regenerate during the next menstrual cycle through proliferation of epithelial cells in the intact basalis layer. It has been proposed

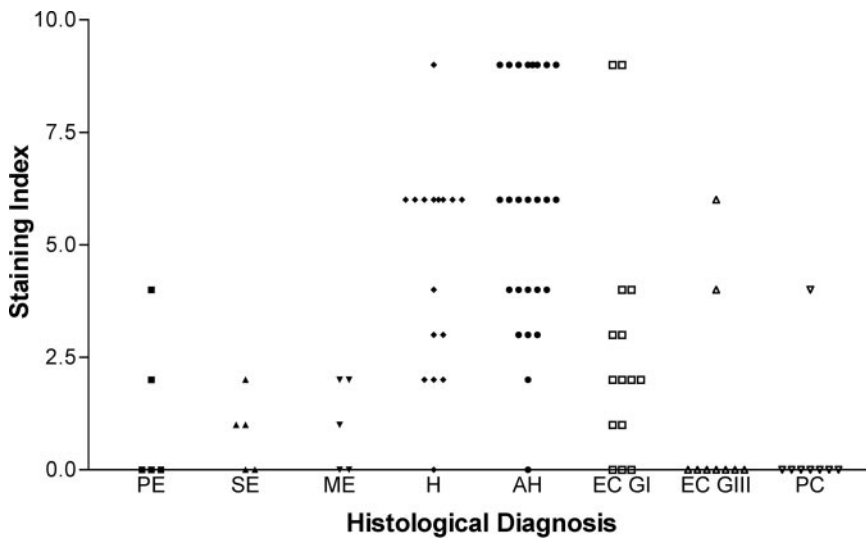


Fig. 3 Staining indices for normal, hyperplastic, and malignant endometria. There were significant differences between all normal cases versus all hyperplasias ($P < 0.0001$), all hyperplasias, and all carcinomas ($P < 0.001$). PE, proliferative endometrium; ME, menstrual endometrium; SE, secretory endometrium; H, nonatypical hyperplasia; AH, atypical hyperplasia; EC GI, endometrioid carcinoma grade 1; EC GIII, endometrioid carcinoma grade 3; PC, papillary serous carcinoma.

that genetic alterations that induce endometrial cancer are acquired sequentially by the nonshedding stem cells (27). Whether the ectopic expression of oviduct-specific glycoprotein observed in the stem cells of the normal endometrium is indicative of early changes in endometrial carcinogenesis is not known, but other studies have shown that overtly normal endometrium can harbor genetic and/or epigenetic alterations of genes such as MLH1 and PTEN, which are common in endometrial cancer (28, 29). In this study, we showed that there was a significant correlation between gain of oviduct-specific glycoprotein and loss of PTEN in endometrioid carcinoma. It would be interesting to determine whether oviduct-specific glycoprotein is expressed in the same glands where PTEN is inactivated, which would

suggest a mechanistic link between loss of PTEN and oviduct-specific glycoprotein expression. Another possible factor for contributing to the ectopic expression of oviduct-specific glycoprotein in the endometrial basalis could be the close embryonic relationship between the endometrial epithelial cells and oviductal epithelial cells (30). Both are derived from Mullerian-duct epithelia, which in turn originate from the coelomic epithelium, and thus, the stem cells of the basalis may be less differentiated and have retained properties similar to the common embryonic precursor.

In the normal oviduct, oviduct-specific glycoprotein secretion is driven by estrogen and changes cyclically during the menstrual cycle (3). In this study, we did not observe any

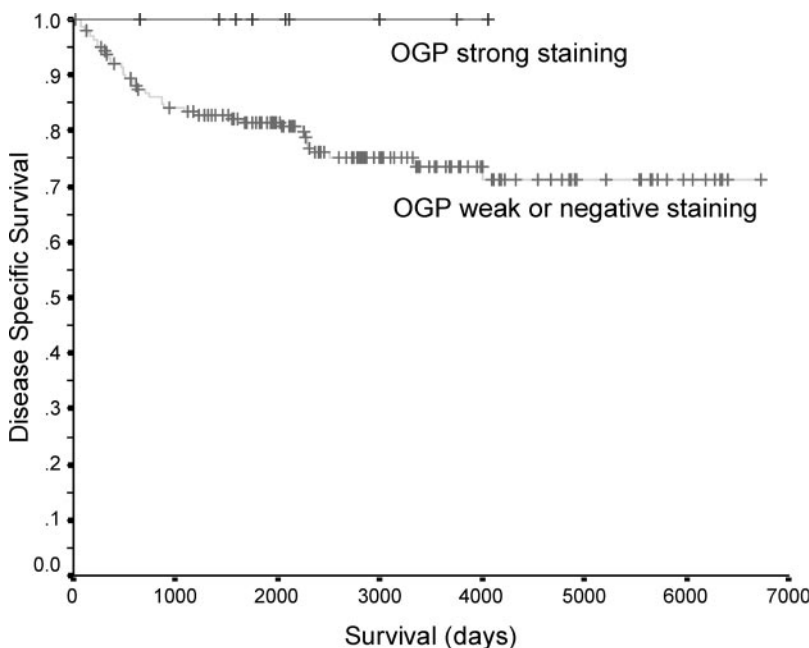


Fig. 4 Kaplan-Meier curve showing survival in days for strong OGP staining versus weak or negative oviduct-specific glycoprotein (OGP) staining. In an endometrial cancer tissue array, 200 cases with known prognoses were examined for OGP expression. Of 139 endometrioid endometrial carcinomas, 11 cases were strongly OGP positive, whereas the other 128 cases were negative or weakly positive. All 37 cases of nonendometrioid carcinomas were negative. Analysis with log-rank statistics showed a trend toward significance for strong OGP staining being a predictor of good prognosis ($P = 0.1$).

Table 3 Comparison of OGP with ER and PTEN staining in endometrial carcinomas

	OGP	
	Negative	Positive
ER		
Negative	27	0
Positive	131	11
PTEN		
Negative	88	11
Positive	63	0

Abbreviation: OGP, oviductal-specific glycoprotein.

significant changes in the levels of oviduct-specific glycoprotein in normal endometrial tissues with the menstrual cycle. However, there was a gain in oviduct-specific glycoprotein under conditions of prolonged estrogen exposure as indicated by the significantly higher staining indices observed in nonatypical and atypical hyperplastic endometrial tissues. Characterization of the human oviduct-specific glycoprotein promoter has revealed eight half-estrogen-responsive elements and an imperfect estrogen-responsive element (31). Despite the presence of estrogen and its receptors in normal endometrium, it may be insufficient for activation of oviduct-specific glycoprotein under normal cycling estrogen levels. This may be due to variations in the relative levels of ER coactivators or corepressors in endometrial epithelium compared with oviductal epithelium (32). However, a recent study showed that the expression of the coactivators, SRC-1 and p300/CBP, decreased in endometrial hyperplasia, whereas the corepressor, NcoR, was elevated (33). Despite the lower levels of coactivators and higher levels of the corepressor, Uchikawa *et al.* (33) showed a topologic correlation between the expression of ER and SRC-1, suggesting that hyperplasias remain responsive to estrogen. On the basis of these findings, we propose that it may be the exposure to prolonged estrogen that is stimulating the ectopic expression of oviduct-specific glycoprotein in hyperplasias. With carcinogenesis, there is a dissociation of ER from its coactivators, as well as methylation of ER rendering it inactive (33, 34). Thus, many endometrial carcinomas no longer respond to estrogen, which may explain the decrease in levels of oviduct-specific glycoprotein expression with progression to carcinoma. Another possibility for the difference in oviduct-specific glycoprotein secretion between normal endometrial and oviductal epithelium may be that coactivator interactions are site-specific (35). Transfection studies have shown a lack of transactivation activity of the oviduct-specific glycoprotein gene in ER-positive breast cells, whereas immortalized oviductal cells showed oviduct-specific glycoprotein promoter activity (31).

With progression to cancer, there was a significant decrease in oviduct-specific glycoprotein expression when compared with hyperplasias, with a significant difference in staining index comparing atypical hyperplasia and well-differentiated endometrioid carcinoma. This raises the possibility of using oviduct-specific glycoprotein immunostaining as a diagnostic adjunct. The differences in staining, although statistically significant, are not absolute, and oviduct-specific glycoprotein would not be of diagnostic use in individual cases as a single

immunomarker. Conceivably it could be part of a panel of immunomarkers that could be used to more accurately classify premalignant and early malignant change in the endometrium, improving on the current irreproducible histologic classification system. Comparison of low-grade and high-grade endometrioid endometrial cancers showed a significant difference in oviduct-specific glycoprotein staining. In cases from the endometrial cancer tissue microarray, all of the strongly positive tumors were grade 1 with 100% of these patients ($n = 11$) surviving for at least 11 years. Use of tissue microarrays does not detect all oviduct-specific glycoprotein positive tumors as the staining is frequently focal, as seen in the higher frequency of oviduct-specific glycoprotein immunostaining in the endometrial cancer cases in which whole sections, rather than 0.6-mm tissue microarray cores, were examined.

In summary, our findings indicate that although oviduct-specific glycoprotein is differentially expressed during the transformation of endometrial hyperplasia and development of endometrioid carcinoma, it appears to be unrelated to uterine papillary serous carcinoma. Additional studies are required to examine whether the ectopic expression of oviduct-specific glycoprotein in the stem cells of histologically normal endometria may indicate early preneoplastic changes.

ACKNOWLEDGMENTS

We thank Brian Shin and Martina Timm-McCann for assistance in immunostaining of tissue sections for PTEN.

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Clin Cancer Res 2004;10:7958-7964.

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