Telomerase Activity in Benign Endometrium and Endometrial Carcinoma

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ABSTRACT

Telomerase, a ribonucleoprotein associated with synthesis of telomeric DNA, is postulated to play a role in cellular senescence and immortalization. Telomerase adds a hexanucleotide telomeric sequence to the chromosomal ends during replication and is preferentially expressed in most malignant and germ-line tissues but is usually undetectable in normal somatic cells. In the current study, 34 human endometrial tissues (20 malignant and 14 benign) were analyzed for telomerase activity by a nonradioactive PCR-based method using the TRAP-eez telomeric repeat amplification detection kit (Oncor). Nineteen of 20 (95%) endometrial carcinomas and 8 of 8 (100%) benign endometrial tissues from premenopausal women exhibited strong telomerase activity, whereas 6 of 6 (100%) benign endometrial tissues from postmenopausal women showed only weak telomerase activity. There was no correlation of telomerase activity with tumor grade, depth of invasion, or DNA content. Benign cycling endometrium, a rapidly proliferating tissue, features positive telomerase activity, whereas 6 of 6 (100%) benign endometrial tissues from postmenopausal women showed only weak telomerase activity. Telomerase activity may be strongly reactivated in patients who develop endometrial cancer.

INTRODUCTION

Telomeres, the distal ends of human chromosomes, seem to function in chromosome stabilization during replication by protecting the chromosomal ends against exonucleases and ligases (1). Consisting of several thousand copies of a repeat nucleotide sequence 5'-TTAGGG-3', telomeres may prevent the activation of DNA-damage checkpoints and counter the loss of terminal DNA segments that occur during DNA replication (1–3). With each cycle of DNA replication, one end of the linear chromosome develops a short 8–12-bp gap generated by the removal of the RNA primer (4). With each cell division, each chromosomal end point will shorten by 50–200 nucleotides, because conventional DNA polymerase cannot completely replicate the base gap generated (5). This progressive shortening of telomeres associated with normal somatic cells provides a means of counting replication events and serves as an internal biological clock that associates telomere length decline with cell aging and senescence (2, 6).

Activation or reexpression of telomerase, a ribonucleoprotein, leads to the synthesis of telomeric DNA that compensates for its loss with each cell division (7–9). Maintenance of a constant telomere length ensures chromosome stability, prevents cell aging, and may confer cellular immortality (7–9). Studies of human tumors and human tumor cell lines indicate that telomerase activity may play a critical role in tumor cell growth by sustaining cellular immortality (9–11). For example, when human HeLa cell line cultures are transfected with an antisense to the RNA component of human telomerase, the loss of telomerase activity leads to growth arrest, senescence, and eventual cell death (12). Viral transformation of human epithelial cell lines and B lymphocytes similarly supports the importance of telomerase and telomere length maintenance in the acquisition of cell immortality (13–14).

Telomerase was first demonstrated in human cancer in a series of ovarian carcinoma tissues (15) and has subsequently been detected in most samples taken from a wide variety of primary human malignancies. In a study of 18 different tissues maintained in cultures, 98 of 100 immortal cell lines expressed telomerase in comparison to 0 of 22 normal somatic cell cultures (9). Telomerase activity has been acquired in a spontaneously immortalized cell culture from a human breast epithelial cell sample taken from a patient with a germ-line p53 mutation (Li-Fraumeni syndrome) that was initially telomerase negative (16). Telomerase activity has been detected in 93% of breast carcinomas (17), 80% of primary lung carcinomas (18), 77–97% of colorectal carcinomas (19–21), 85% of hepatocellular carcinomas (22), 85% of gastric carcinomas (21, 23) 84% of prostate cancer samples (24), 66–94% of brain tumors (25–26), and 67–100% of hematological malignancies (27–28). Although a reduction in telomere length has been reported in endometrial tumors (29), telomerase activity has not been previously studied in endometrial cancer and normal endometrium.

In the present study, we analyzed benign and malignant human endometrial tissues for the presence of telomerase activity and correlated the results in the malignant specimens with tumor grade, depth of myometrial invasion, and tumor DNA content.

MATERIALS AND METHODS

Endometrial Tissue Specimens. Thirty-four endometrial tissues from 32 patients (ages 40–89 years) who underwent hysterectomy for endometrial adenocarcinoma, an ovarian tumor, or a benign condition were obtained from the Tumor Bank of the Albany Medical College. The tissues were originally collected fresh from the hysterectomy specimens in the operating suite, snap-frozen in OCT embedding compound at −65°C, and stored in the Tumor Bank at −85°C. The specimens consisted of tissues from 20 endometrial carcinomas and 14 benign endometriums. The tissues were thawed to −20°C, and frozen sections were performed and stained with H&E for histological confirmation in each case. The benign tissues were evaluated to determine the phase of the menstrual cycle. The tumors were evaluated for the histological type, tumor grade (FIGO), and depth of myometrial invasion.

Extract Preparation. Each individual tissue was washed thoroughly in refrigerated PBS (pH 7.4) to remove the OCT embedding compound. After weighing, each tissue was minced with a sterile surgical blade, placed in 3 ml of 1 X CHAPS lysis extraction buffer, and homogenized on ice using a polytron mechanical tissue homogenizer. The samples were incubated on ice for 30 min and centrifuged at 12,000 × g for 30 min at 4°C, and the supernatants were transferred into fresh tubes. Two hundred μl of the extract were pipetted from each sample to be used for protein concentration determination and subsequent telomerase assay, whereas the remaining extract was immediately stored at −85°C.

Determination of Protein Concentration. Using 1 X CHAPS lysis buffer, serial dilutions of extracts (2–10 μl of extract in 50 μl of buffer) and BSA

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The abbreviations used are: FIGO, Fédération Internationale des Gynécologues et Obstetriciens; CHAPS, 3-[3-cholamidopropyl]dimethylamino]-1-propanesulfonate; TRAP, telomeric repeat amplification protocol.

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(0–500 μg of BSA in 50 μl of buffer) were prepared. Five μl of the sample or standard were added (in duplicate) to the wells of a microtiter plate followed by the addition of 250 μl of Coomassie protein assay reagent (Pierce; catalogue no. 23200) to each well. After mixing and incubating for 5 min at room temperature, A950 nm was read, and the exact protein concentrations were determined from the BSA standard plot of A950 nm versus μg of BSA.

Telomerase Assay. Telomerase activity was determined using the Oncor TRAP-eze telomerase detection kit (Oncor; catalogue no. S7700 kit). The methodology used is based on a modification of the original method described by Kim et al. (9). The TRAP-eze kit is a highly sensitive in vitro assay system using PCR. In the first step, telomerase, if present, adds a number of telomeric repeats (GGT TAG) to the 3' end of a substrate oligonucleotide (TS). In the second step, the extended products are amplified by the PCR using the TS and reverse (RP) primers, generating a ladder of products with 6-base increments starting at 50 nucleotides. The TRAP assay procedure was performed according to the manufacturer's protocol, which briefly is as follows.

A master mix using unlabeled TS primer and all the reagents outlined below except the extract was made for a final volume of 48 μl in each assay. The reagents included 10X TRAP buffer (5 μl), 50X deoxy nucleotide triphosphates mix (1 μl), TS primer (1 μl), TRAP primer mix (1 μl), 5 units/μl Taq polymerase (0.4 μl), and distilled H2O (39.6 μl). Heat-inactivated and test extracts were added to each tube (final volume, 50 μl). Heat inactivation was done by incubating 10 μl of each extract at 85°C for 10 min and adding 2 μl into each of the heat inactivation tubes. Control cell extract containing telomerase (2 μl) was added to the positive control tube. One μl CHAPS lysis buffer (2 μl) was added to the primer-dimer-PCR contamination control tube. All the tubes were placed in a thermocycler block and incubated at 30°C for 10 min. Thirty cycles of PCR were performed, each cycle at 94°C for 30 s and 60°C for 30 s. Gel loading dye (5 μl) containing bromphenol blue and xylene cyanol (0.25% each in 50% glycerol/50 mM EDTA) was added into each reaction tube. Each sample (40 μl) was electrophoresed in a 12.5% nondenaturing polyacrylamide gel in 0.5X Tris-borate EDTA buffer until the bromphenol blue ran off the gel. The gel was stained with 1X SYBR green (Molecular Probes; catalogue no. S7567) for 30 min and visualized under UV light (300 nm) using a UV SYBR green filter (Molecular Probes; catalogue no. S7569).

Data Analyses. The TRAP assay was considered valid when all of the following conditions were fulfilled: (a) Telomerase-positive control lane exhibited the 36-bp internal control band and the ladder of products with 6-base increments starting at 50 nucleotides (i.e. 50, 56, 62, 68, and so forth; Fig. 1, Lane 1); (b) heat-treated sample extract lanes revealed no products except for the presence of the 36-bp internal control band (Fig. 1, Lane 2); and (c) primer-dimer-PCR contamination control lane revealed no product except for the 36-bp internal control band (Fig. 1, Lane 9).

An extract was considered positive for telomerase activity when a 36-bp internal control band and a ladder of PCR products with 6-base increments similar to that of the telomerase-positive control lane were present (Fig. 1, Lanes 3–5 and 7). The internal control band was sometimes light or not visible when the sample contained excessively high telomerase activity due to semicompetitive amplification of the TRAP products and control band (Fig. 1, Lane 3). Extracts that revealed a 36-bp band but no ladder of PCR products were considered negative for telomerase activity (Fig. 1, Lane 6). Extracts showing only the 36-bp band and a faint 50-bp band with no discernable ladder pattern were considered to have a weak residual level of telomerase activity (Fig. 1, Lane 8).

Quantitative DNA Analysis. Formalin-fixed paraffin-embedded 5-μm sections were stained by the Feulgen method and analyzed for DNA content with the CAS 200 image analyzer (Cell Analysis Systems, Lombard, IL). DNA content of the endometrial cancers was measured on a minimum of 100 tumor cells, and the tumor DNA index was determined by comparison with the internal control nonneoplastic diploid cells. All the tumor cell histograms were reviewed without knowledge of the tumor grade and telomerase activity status. A DNA index of 0.77–1.22 was considered to be diploid (30). Hyperdiploid populations and tumors with tetraploid peaks including greater than 15% of the total analyzed cell population were considered nondiploid (aneuploid).

RESULTS

Clinicopathological Data. The mean age of all patients was 61 years (range, 40–89 years). Of the 20 malignant endometrial specimens (mean age, 66 years), 17 were endometrioid adenocarcinomas with 3 FIGO grade 1 tumors, 13 FIGO grade 2 tumors, and 1 FIGO grade 3 tumor. The three remaining malignant specimens consisted of two serous carcinomas and one malignant mixed Mullerian tumor. Of the 20 tumors, 14 (70%) showed a depth of invasion <50%, and 6 tumors (30%) featured a depth of invasion ≥50% of the myometrial thickness. DNA ploidy analysis was available in 15 tumors, of which 9 were diploid, and 6 were nondiploid. Of the 14 benign endometrial tissues, 8 (mean age, 47 years) showed an actively cycling pattern in either the proliferative or secretory phase. The remaining six benign specimens (mean age, 66 years) featured an inactive, noncycling endometrium. The clinical pathological data of the 20 tumors is summarized in Table 1, and those of the 14 benign tissues are summarized in Table 2.

Telomerase Assay. The mean weight of each endometrial tissue sample for all 31 cases was 357 mg (range, 80–780 mg). The mean quantity of protein added per the PCR protocol was 8.9 μg (range, 2.2–17.8 μg). The telomerase detection system that is used in the TRAP-eze kit detected telomerase activity in the tissue extracts and not the mere presence of the RNA or protein constituents of the enzyme. The presence of a primer and a template for amplification in the TRAP-eze kit resulted in the formation of a 36-bp band in every lane (Fig. 1) and served as an internal control to identify false negatives due to the presence of Taq polymerase inhibitors. The heat-inactivated samples (Fig. 1, Lane 2) demonstrated a lack of the ladder pattern due to inactivation of the telomerase. The technique is further controlled for each sample set by testing for both the potential generation of primer-dimer artifacts generated by the input primers alone and PCR products due to carry-over contamination (Fig. 1, Lane 9).

Telomerase Activity in Endometrial Carcinoma. In 19 of 20 (95%) endometrial carcinomas, a ladder of PCR products starting at 50 nucleotides was present, indicating the presence of telomerase activity (Fig. 1, Lanes 3–5). An example of positive telomerase...
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Table I Clinicopathological data in endometrial carcinomas

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yrs)</th>
<th>FIGO grade</th>
<th>Depth of myometrial invasion (%)</th>
<th>DNA ploidy&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Telomerase activity&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>1</td>
<td>&lt;33</td>
<td>ND</td>
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</tr>
<tr>
<td>2</td>
<td>51</td>
<td>1</td>
<td>&lt;50</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>1</td>
<td>20</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>2</td>
<td>&lt;50</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>2</td>
<td>&lt;50</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>2</td>
<td>&lt;33</td>
<td>D</td>
<td>+</td>
</tr>
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<td>7</td>
<td>70</td>
<td>2</td>
<td>50</td>
<td>D</td>
<td>+</td>
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<td>+</td>
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<td>2</td>
<td>33</td>
<td>D</td>
<td>+</td>
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<td>13</td>
<td>68</td>
<td>2</td>
<td>25</td>
<td>D</td>
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<td>62</td>
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<td>D</td>
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<tr>
<td>17</td>
<td>72</td>
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<td>+</td>
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<tr>
<td>18</td>
<td>72</td>
<td>Serous</td>
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<td>+</td>
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<tr>
<td>19</td>
<td>69</td>
<td>Serous</td>
<td>50</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>20</td>
<td>58</td>
<td>MMTM&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;50</td>
<td>ND</td>
<td>+</td>
</tr>
</tbody>
</table>

<sup>a</sup> D, diploid; ND, nondiploid.<br><sup>b</sup>,@, positive; —, negative.<br><sup>c</sup> MMTM, malignant mixed Müllerian tumor.

Activity in an endometrioid adenocarcinoma of each FIGO grade is depicted in Fig. 1 (Lane 3, FIGO 1; Lane 4, FIGO 2; Lane 5, FIGO 3). There was no correlation of positive telomerase assay with FIGO tumor grade, depth of myometrial invasion, or DNA content in the endometrial adenocarcinoma specimens. One grade 2 endometrioid adenocarcinoma with <50% depth of myometrial invasion did not feature telomerase activity (Fig. 1, Lane 6).

**Telomerase Activity in Benign Endometrial Tissue.** All eight (100%) benign tissues from premenopausal women featuring active cycling endometrium in either the proliferative (five cases) or secretory (three cases) phase showed strong telomerase activity (Fig. 1, Lane 7). All six (100%) tissues from postmenopausal women featuring an inactive endometrium showed weak telomerase activity with only a faint 50-bp band present in addition to the internal control band but no discernible ladder (Fig. 1, Lane 8). This pattern was thought to probably represent a low residual level of telomerase activity in postmenopausal women. Though the method used does not allow for exact quantitation of telomerase activity, there was a definite qualitative difference in band intensity between the actively cycling premenopausal and inactive postmenopausal endometrial tissues. However, no qualitative difference in band intensity was observed between the benign actively cycling endometrial tissues and the endometrial adenocarcinomas.

**DISCUSSION**

The balance between the loss of telomeric repeats with each cycle of DNA replication and the synthesis of new telomeres is regulated by telomerase (31, 32). Normal cells in vivo and in culture eventually become senescent, due in part to the progressive shortening of the telomeres caused by absent telomerase activity (2, 8). Most tumor cells and certain cells in culture develop immortality associated with the reactivation of telomerase, leading to telomere elongation and stabilization, enabling unlimited growth capacity. Approximately 66–97% of assayed human tumor samples have shown telomerase activity including cancers of the lung (18), colon (19–21), stomach (21, 23), liver (22), breast (17), prostate (24), and brain (25–26). In the present study, 95% of endometrial cancers revealed telomerase activity, fur-

Table 2 Clinicopathological data in benign endometrial tissues

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yrs)</th>
<th>Reason for hysterectomy</th>
<th>Endometrial pattern</th>
<th>Telomerase activity&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>Leiomyomata</td>
<td>Proliferative</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>Leiomyomata, prolapse</td>
<td>Proliferative</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>Leiomyoma</td>
<td>Proliferative</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>Leiomyoma</td>
<td>Proliferative</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>Leiomyomata, ovarian cysts</td>
<td>Proliferative</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>Leiomyomata</td>
<td>Secretary</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>Leiomyoma</td>
<td>Secretary</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>Leiomyomata</td>
<td>Secretary</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>Ovarian cyst</td>
<td>Inactive</td>
<td>Weak +</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>Carcinoma elsewhere in the endometrium</td>
<td>Inactive</td>
<td>Weak +</td>
</tr>
<tr>
<td>11</td>
<td>64</td>
<td>Carcinoma elsewhere in the endometrium</td>
<td>Inactive</td>
<td>Weak +</td>
</tr>
<tr>
<td>12</td>
<td>67</td>
<td>Ovary tumor of low malignant potential</td>
<td>Inactive</td>
<td>Weak +</td>
</tr>
<tr>
<td>13</td>
<td>64</td>
<td>Metastatic ovarian carcinoma</td>
<td>Inactive</td>
<td>Weak +</td>
</tr>
<tr>
<td>14</td>
<td>60</td>
<td>Papillary serous carcinoma of the ovary</td>
<td>Inactive</td>
<td>Weak +</td>
</tr>
</tbody>
</table>

<sup>a</sup> +, positive; —, negative.
ther supporting the role of telomerase in conferring immortality to tumor cells.

As detected in the current study, telomerase activity was independent of the tumor grade, depth of myometrial invasion, and the total DNA content of the endometrial cancers. Previously reported data with regard to the correlation of telomerase activity with other tumor prognostic markers have yielded variable conclusions. Studies of human breast (17) and gastric carcinomas (23) revealed that tumors expressing telomerase were larger and had more advanced clinical stage with greater frequency of lymph node metastases compared to tumors that did not feature telomerase activity, suggesting that telomerase-positive tumors had greater malignant potential. To the contrary, in gastric adenocarcinomas, both nondiploid and diploid tumors have featured telomerase activity (23). In hepatocellular carcinomas, 71% of well-differentiated tumors less than 2 cm and 91% of moderately differentiated cancers less than 3 cm were positive for telomerase (22), suggesting that telomerase activity was expressed independent of the tumor size or stage. The present study also failed to associate telomerase activity with other established tumor prognostic factors. However, because the assay used in the current study was not quantitative, it is possible that the higher-grade endometrial carcinomas had greater telomerase activity than did the lower-grade tumors, despite no observed qualitative difference in band intensity. It remains to be determined whether there is a certain critical level of telomerase activity that correlates with more aggressive clinical tumor behavior.

Preliminary studies using TRAP assays have indicated that normal somatic cells are telomerase negative and that expression in nonneoplastic tissues is rare (9). Contrary to this and of particular interest in the current study is the presence of strong telomerase activity in the benign endometrial tissues obtained from premenopausal women. Given that the endometrial lining regenerates with each menstrual period in this age group, telomerase may play a role in conferring this proliferative capacity to the cells of the basal endometrial layer that do not slough with each menstrual cycle and are necessary for endometrial regeneration. Other benign tissues in which telomerase activity has been reported include germ cells of the ovary and testis (9), skin (27, 35, 36), and adult human bone marrow (37).

The benign tissues taken from postmenopausal women with an inactive endometrium featured only weak telomerase expression. This residual telomerase activity in postmenopausal atrophic endometrium may reflect the loss of function of the basal endometrial lining that is no longer capable of regenerating. Interestingly, in two women with benign inactive endometrium showing only residual telomerase activity, strong telomerase expression was seen in endometrial carcinomas present elsewhere in the resected uterus. Thus, telomerase activity that is low after menopause may be reexpressed at high levels with the development of cancer.

In summary, the majority of endometrial carcinomas feature positive telomerase activity that is expressed independently of the FIGO tumor grade, depth of myometrial invasion, and total tumoral DNA content. Telomerase activity is present in benign cycling endometrial tissues from premenopausal women but is only weakly expressed in inactive endometrium after menopause. However, telomerase activity may be strongly reactivated in postmenopausal patients who develop endometrial cancer. Additional studies seem to be warranted to investigate the dynamics of telomerase expression, the role of telomerase in the development and progression of endometrial cancer, and for the development of antineoplastic drugs designed to produce telomerase inhibition that may be clinically valuable in the treatment of advanced endometrial cancer.

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