BRAF Mutation in Endometrial Carcinoma and Hyperplasia: Correlation with KRAS and p53 Mutations and Mismatch Repair Protein Expression

Yu-Zhen Feng,1,2 Tanri Shiozawa,1 Tsutomu Miyamoto,1 Hiroyasu Kashima,1 Miyuki Kurai,1 Akihisa Suzuki,1 and Ikuo Konishi1

Abstract

**Purpose:** Although several gene abnormalities have been reported in endometrial carcinoma, the genetic alterations have not fully been elucidated. Recent studies have revealed frequent activating mutations of the gene for BRAF, an effector of Ras protein in the mitogen-activated protein kinase pathway, in several malignancies. However, the prevalence and significance of BRAF mutations in endometrial carcinoma remain unclear.

**Experimental Design:** We examined BRAF mutations in exons 11 and 15 in 97 cases of endometrial carcinoma (endometrioid type, 78; nonendometrioid type, 19), 9 cases of atypical endometrial hyperplasia, and 20 cases of normal endometrium by direct sequencing. In addition, mutations of KRAS and p53 and the immunohistochemical expression of hMLH1 and hMSH2 were also examined.

**Results:** Of the 97 carcinomas and 9 hyperplasias, 20 (21%) and 1 (11%) had BRAF mutations, most of them at previously unreported sites. Twenty samples of normal endometrium and 21 samples of normal endometrium obtained from sites adjacent to neoplastic lesions had no BRAF mutations. There was no apparent difference in the prevalence of BRAF mutation among stages, histologic subtypes, or grades. Mutations of KRAS and p53 were found in 18 (19%) and 22 (23%) cases, and 65 (67%) and 92 (95%) cases showed positive immunostaining for hMLH1 and hMSH2, respectively. BRAF mutation was more frequently found in hMLH1-negative cases (12 of 32, 41%) than in hMLH1-positive cases (7 of 65, 11%; \( P = 0.008 \)), suggesting that it is associated with an abnormal mismatch repair function.

**Conclusions:** These findings suggest that mutations of the BRAF gene are partly involved in the malignant transformation of the endometrium.

Endometrial carcinomas are now classified into two histologic subtypes: endometrioid type and nonendometrioid type (1); and the molecular genetic changes involved differ between the two (2–4). In endometrioid-type carcinomas, mutations of PTEN, KRAS, β-catenin, and p53 genes and microsatellite instability have been reported in ~5% to 50% of cases. By contrast, in nonendometrioid-type carcinomas, as exemplified by serous papillary adenocarcinoma, the p53 gene is reportedly mutated in ~90% of cases. However, the genetic changes in endometrial carcinoma have not fully been elucidated.

Raf proteins are cytoplasmic serine-threonine kinases and play central roles in the conserved Ras/Raf/mitogen-activated protein/extracellular signal-regulated kinase/extracellular signal-regulated kinase pathway, acting to relay signals from activated Ras proteins via mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 to p42/p44 mitogen-activated protein kinase or extracellular signal-regulated kinase 1/2, the key effector of the pathway (5, 6). A recent report has shown the presence of an activating mutation in one of three Raf protein subtypes, B-Raf, in human melanomas and colon cancers, and that the mutation of BRAF transforms NIH 3T3 cells independent of KRAS gene mutation (7). In addition, mutual exclusion between KRAS and BRAF mutations has been reported in colon cancer (8). More recently, BRAF gene mutations have been frequently found in sporadic colorectal carcinomas deficient in mismatch repair (9). However, the occurrence of BRAF gene mutations, as well as their correlation with mutations in other genes and molecules, has not been elucidated in endometrial carcinoma. Therefore, in the present study, we examined mutations of the BRAF gene in DNA samples extracted from normal, hyperplastic, and malignant endometrial tissues using a microdissection technique. We also examined mutations of KRAS and p53 genes in

**Authors’ Affiliation:** 1Department of Obstetrics and Gynecology, Shinshu University School of Medicine, Asahi, Matsumoto, Japan and 2Department of Obstetrics and Gynecology, The Third Hospital, HeBei Medical University, Shijiazhuang, China

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**Requests for reprints:** Tanri Shiozawa, Department of Obstetrics and Gynecology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. Phone: 81-263-37-2719; Fax: 81-263-34-0944; E-mail: tanri@hsp.md.shinshu-u.ac.jp.

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the same tissue DNA to evaluate the correlation with mutations of BRAF. In addition, the occurrence of BRAF gene mutations was compared with the expression of hMSH2 and hMLH1 proteins, which are regarded as key factors in DNA mismatch repair (10, 11).

Materials and Methods

Case selection and DNA extraction. Ninety-seven patients with endometrial carcinoma visited Shinshu University Hospital between 1993 and 2003, and underwent hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection or biopsy. The age of the cancer patients ranged from 30 to 76 years. All cases involved Japanese women, and were sporadic without a familial history of endometrial cancer and/or colon cancer. No patients refused participation in the study. According to the Fédération Internationale des Gynaecologes et Obstetristes (FIGO) classification (1988), 52 patients had stage I, 10 had stage II, 28 had stage III, and 7 had stage IV tumors. The histologic diagnosis was made by two pathologists in the Department of Laboratory Medicine of the hospital. Histologically, 78 had endometrioid adenocarcinoma and 19 had nonendometrioid carcinoma. Of the 78 endometrioid carcinomas, 36 were grade I, 19 were grade 2, and 23 were grade 3. Of the 19 nonendometrioid carcinomas, 12 were serous papillary adenocarcinomas, 6 were clear cell carcinomas, and 1 was a squamous cell carcinoma. Twenty cases of normal endometrium (proliferative phase, 10 cases; secretory phase, 10 cases) and 9 cases of atypical endometrial hyperplasia were selected from the pathology files of Shinshu University. Formalin-fixed, paraffin-embedded tissues were used with the approval of the Ethics Committee of Shinshu University after obtaining written consent from the patients.

DNA was extracted as previously described (12). In brief, four or five 8-μm-thick sections of endometrial tissue were prepared from the paraffin-embedded blocks. In the normal endometrium, endometrial glands were scraped with a razor blade using a microdissection technique. The hyperplastic and malignant tissues were also scraped with a razor from consecutive tissue sections avoiding areas of normal cells. A digestion buffer (2 mg/mL proteinase K and 0.5% Tween 20) was added and the tissue was digested for 16 to 24 hours at 55°C.

Mutational analysis. Because BRAF gene mutations in human cancers have been frequently found in exons 11 and 15 (13), we focused on these two exons. The oligonucleotide primers for sequencing BRAF, designed based on a published sequence, were as follows (14): BRAF exon 11, 5′-TCTGTGTGGCCTGACGCTGACTIT 3′ and 5′-CATGCCATTGGGGCTGTAGAC 3′; BRAF exon 15, 5′-AAATCTTTCAATATGGTCTGGTCTG 3′ and 5′-GGCCAAAATTAATCACTGGAGA 3′.

The primer sets to detect mutations in exon 1 of KRAS and exons 5 and 8 of p53 were designed according to previous reports. KRAS exon 1, 5′-GCTGGACGTATTTGATAGTGTA 3′ and 5′-GGCAAAAATTTAATCAGTGGA 3′; p53 exon 6, 5′-GGAATTCCGAGTGGTCACTGAC 3′ and 5′-GGATATCGAGTGAGCTGAGCTG 3′; p53 exon 7, 5′-GGAATTCCGAGTGGTCACTGAC 3′ and 5′-GGATATCGAGTGAGCTGAGCTG 3′; and p53 exon 8, 5′-GGAATTCCGAGTGGTCACTGAC 3′ and 5′-GGATATTCCCCATCTCTGTATGGTGATC 3′.

Each exon was amplified by PCR using 0.5 μg of template DNA, sense and antisense primers, and an AmpliTaq Gold PCR kit (Applied Biosystems, Foster City, CA). A total of 50 μL of reaction mixture was made up according to the instructions of the manufacturer and PCR was commenced at 94°C for 3 minutes, followed by 35 cycles of 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 1 minute, with a final extension for 5 minutes. The PCR products were purified using an UltraClean PCR Clean-up kit (MO BIO Laboratories, Solana Beach, CA) and subjected to direct sequencing. The direct sequencing was done using purified products and the same sets of primers in a capillary automatic sequencer (ABI PRISM 3100 Genetic Analyzer, Applied Biosystems) at Shinshu University.

Sequence data were analyzed using the Basic Local Alignment Search Tool (BLAST) software located at the National Center for Biotechnology Information web site (http://www.ncbi.nlm.nih.gov).

Immunohistochemistry. Immunostaining was done using specific monoclonal antibodies against hMSH2 (Oncogene Research Products, San Diego, CA) and hMLH1 (BD Biosciences, San Jose, CA). Indirect immunohistochemical staining was done with the avidin-biotin-peroxidase complex method using a Histofine SAB-PO detector kit (Nichirei, Tokyo, Japan) with microwave pretreatment and proteinase K digestion as previously described.

The specific staining of each antibody was identified in the nucleus, and immunoreactivity was evaluated based on the nuclear positive cells. The results were semiquantitatively estimated based on the percentage of positive cells as follows: negative, nuclear-positive cells were absent; weakly positive (+), ≤10% of cells were positive; moderately positive (++), >10% to <50% of cells were positive; and strongly positive (+++), ≥50% of cells were positive.

Results of direct sequencing of BRAF in exon 11 (A) and exon 15 (B and C). Top, wild-type sequence; bottom, mutated sequence. In exon 11, nucleotide 1412A was changed to C, and subsequently the amino acid tyrosine (Y) 471 was altered to serine (S, underlined). In exon 15, 1796T was changed to G (B) and 1850T was changed to G (underlined; C). The amino acid changes were valine (V) 599 to glycine (G) and leucine (L) 617 to tryptophan (W), respectively.

Fig. 1. Results of direct sequencing of BRAF in exon 11 (A) and exon 15 (B and C). Top, wild-type sequence; bottom, mutated sequence. In exon 11, nucleotide 1412A was changed to C, and subsequently the amino acid tyrosine (Y) 471 was altered to serine (S, underlined). In exon 15, 1796T was changed to G (B) and 1850T was changed to G (underlined; C). The amino acid changes were valine (V) 599 to glycine (G) and leucine (L) 617 to tryptophan (W), respectively.
(+), 10% to 50%; strongly positive (+++), >50%, according to previous studies (17, 18).

**Statistical analysis.** All statistical analyses to evaluate the difference in the frequency of \( \text{BRAF} \) gene mutations between positive and negative mismatch repair proteins as well as other factors were made with Fisher’s exact probability test. A tied \( P \) value of <0.05 was considered significant.

**Results**

**Frequency of \( \text{BRAF} \) mutation.** Of the 97 endometrial carcinomas, 20 (21%) contained a total of 21 \( \text{BRAF} \) gene mutations at five sites (Fig. 1; Tables 1 and 2). The number of cases mutated in exon 11 and 15 was 5 and 15, respectively (Fig. 1; Table 2). The 21 mutations consisted of 17 missense and 4 nonsense mutations. All five mutations in exon 11 were related to the amino acid substitution Y471S. Amino acid changes caused by 16 mutations in exon 15 consisted of K590R (one case), V599G (seven cases), R602stop (four cases), and L617W (four cases). Five silent mutations were also noted (data not shown) but were not included in the present analysis.

According to the FIGO classification, the 20 cases with \( \text{BRAF} \) gene mutations consisted of 12 stage I, 6 stage III, and 2 stage IV tumors. With regard to histologic subtype, 18 endometrioid (18 of 78, 23%) and 2 nonendometrioid (2 of 19, 11%) carcinomas had \( \text{BRAF} \) gene mutations. Of the 18 endometrioid carcinomas with a mutation, 8 were grade 1, 5 were grade 2, and 5 were grade 3. The percentage of \( \text{BRAF} \) gene mutations in grade 1, 2, and 3 tumors was 22% (8 of 36), 26% (5 of 19), and 22% (5 of 23), respectively. There was no significant correlation of \( \text{BRAF} \) gene mutation with FIGO stage, histologic subtype, or histologic grade. Of nine atypical endometrial hyperplasias, one (11%) had a mutation in exon 15. None of the 20 cases of normal endometrium showed a \( \text{BRAF} \) gene mutation. In addition, the DNA obtained from a total of 21 normal tissue samples taken adjacent to the neoplastic areas of 20 endometrial carcinomas and one endometrial hyperplasia, all of which harbored a \( \text{BRAF} \) gene mutation, showed no \( \text{BRAF} \) mutation. These results indicate that all mutations are somatic.

**Correlation of \( \text{BRAF} \) mutation with \( \text{KRAS} \) and \( \text{p53} \) mutations and mismatch repair proteins.** Of 97 endometrial carcinomas, 18 (19%) had \( \text{KRAS} \) gene mutations (Table 1) in codons 12, 13, 14, and 23 of exon 1. Of 18 \( \text{KRAS} \) gene mutations, 17 (22%) were observed in endometrioid carcinomas and 1 (5%) in nonendometrioid carcinoma. Of the 18 cases, no case had a mutation in the \( \text{BRAF} \) gene (Table 3), suggesting mutual exclusion between \( \text{KRAS} \) and \( \text{BRAF} \) gene mutations (\( P = 0.009 \)). An analysis of the \( \text{p53} \) gene showed that 22 (23%) cases contained a total of 22 sites where mutations occurred (exon 6, 7; exon 7, 9; exon 8, 6). Of the 22 \( \text{p53} \) gene mutations, 9 were found in endometrioid carcinomas (9 of 78, 12%) and 13 in nonendometrioid carcinomas (13 of 19, 68%). Of the 22 cases, 6 were also positive for \( \text{BRAF} \) gene mutations (Table 3). There

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**Table 1. Number of cases with \( \text{BRAF}, \text{KRAS}, \) and \( \text{p53} \) gene mutations in normal, hyperplastic, and malignant endometrial tissues**

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>( \text{BRAF} )</th>
<th>( \text{KRAS} )</th>
<th>( \text{p53} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial carcinoma:</td>
<td>20 (21%)</td>
<td>18 (19%)</td>
<td>22 (23%)</td>
</tr>
<tr>
<td>Total cases</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I (52)</td>
<td>12 (23%)</td>
<td>11 (21%)</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>Stage II (10)</td>
<td>0</td>
<td>3 (30%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Stage III (28)</td>
<td>6 (21%)</td>
<td>2 (7%)</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>Stage IV (7)</td>
<td>2 (29%)</td>
<td>2 (29%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Endometrioid carcinoma (78)</td>
<td>18 (23%)</td>
<td>17 (22%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Grade 1 (36)</td>
<td>8 (22%)</td>
<td>10 (28%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Grade 2 (19)</td>
<td>5 (26%)</td>
<td>5 (26%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Grade 3 (23)</td>
<td>5 (22%)</td>
<td>2 (9%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>Nonendometrioid carcinoma (19)</td>
<td>2 (11%)</td>
<td>1 (5%)</td>
<td>13 (68%)</td>
</tr>
<tr>
<td>Endometrial hyperplasia:</td>
<td>1 (11%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total cases</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal endometrium:</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total cases</td>
<td>41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** The number of normal endometrium includes that obtained from sites adjacent to neoplastic lesions.

**Table 2. Sites and amino acid changes of \( \text{BRAF} \) gene mutations in endometrial hyperplasia and carcinoma**

<table>
<thead>
<tr>
<th>Nucleotide</th>
<th>Amino acid</th>
<th>Carcinoma</th>
<th>Hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage: grade</td>
<td>I + II</td>
<td>III + IV</td>
</tr>
<tr>
<td>Exon 11</td>
<td>A1412C</td>
<td>Y471S</td>
<td>4</td>
</tr>
<tr>
<td>Exon 15</td>
<td>A1769G</td>
<td>K590R</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T1769G</td>
<td>V599G</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>C1804T</td>
<td>R602stop</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>T1850G</td>
<td>L617W</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

**NOTE:** E type, endometrioid carcinoma; non – E type, nonendometrioid carcinoma.
was no significant correlation between the p53 and BRAF gene mutations.

Results of immunostaining showed that in the normal endometrium, positive staining for hMLH1 and hMSH2 was observed in the glandular cells of the proliferative phase (Fig. 2A and D) and reduced in the secretory phase. In 97 endometrial carcinoma, 65 (67%) were positive for hMLH1 (Fig. 2B and C) with a mean positive percentage of 14.4 (Tables 3 and 4). Of the 65 hMLH1-positive cases, 51 involved endometrioid carcinomas (51 of 78, 65%; grade 1, 24; grade 2, 11; grade 3, 16) and 13 (13 of 19, 68%) involved non-endometrioid carcinomas. BRAF mutation was more frequently found in hMLH1-negative cases (13 of 32, 41%) than in hMLH1-positive cases (7 of 65, 11%) with a significant difference (P = 0.008; Tables 3 and 4). The hMSH2-positive staining (Fig. 2E and F) was observed in 92 (95%) cases with a mean positive percentage of 37.4 (Tables 3 and 4). Of the 92 hMSH2-positive cases, 75 involved endometrioid carcinomas (75 of 78, 96%; grade 1, 35; grade 2, 18; grade 3, 22) and 17 (17 of 19, 89%) involved nonendometrioid carcinomas. There was no significant correlation between BRAF gene mutation and hMSH2 expression.

**Table 3. Correlation between BRAF gene mutations and p53/KRAS gene mutations and mismatch repair protein expressions**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th><strong>BRAF</strong> mutation (+)</th>
<th><strong>P</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS</strong> mutation</td>
<td>(+) 18 of 97 (19%)</td>
<td>0 of 18 (0%)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>(−) 79 of 97 (81%)</td>
<td>20 of 79 (25%)</td>
<td></td>
</tr>
<tr>
<td><strong>p53</strong> mutation</td>
<td>(+) 22 of 97 (23%)</td>
<td>6 of 22 (27%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>(−) 75 of 97 (77%)</td>
<td>14 of 75 (19%)</td>
<td></td>
</tr>
<tr>
<td><strong>hMLH1</strong> protein</td>
<td>(+) 65 of 97 (67%)</td>
<td>7 of 65 (11%)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>(−) 32 of 97 (33%)</td>
<td>13 of 32 (41%)</td>
<td></td>
</tr>
<tr>
<td><strong>hMSH2</strong> protein</td>
<td>(+) 92 of 97 (95%)</td>
<td>19 of 92 (21%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>(−) 5 of 97 (5%)</td>
<td>1 of 5 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

The present study showed that the BRAF gene was mutated in 20 cases (21%) of endometrial carcinoma and 1 case (11%) of endometrial hyperplasia. BRAF gene mutations have been identified in a wide range of human tumors with various frequencies. The incidence of BRAF gene mutations is highest in melanoma (63-66%) and thyroid carcinoma (36-53%; refs. 7, 14, 19, 20), followed by colorectal (5-10%) and pancreatic carcinomas (4-7%; refs. 7–9, 21, 22), and is rare in gastric (0-2.2%) and lung carcinomas (1.6-3%; refs. 19, 23–25). Interestingly, a study reported only one BRAF gene mutation, of unknown functional significance, among 146 endometrial carcinoma cases (26), but the reason for this discrepancy is not clear. An intriguing finding of the present study is the
frequent occurrence of BRAF gene mutations in hMLH1 protein–negative patients. Several studies have reported that the decreased expression of the hMLH1 protein is closely related to the silencing methylation of the hMLH1 gene promoter in colorectal and endometrial carcinomas (10, 11, 27), and the frequency of mutation in mismatch repair genes is low (28). Therefore, the reduced expression of hMLH1 protein in the present study is likely to be caused by promoter methylation. Similarly, BRAF gene mutation was associated with extensive hMLH1 promoter methylation and with microsatellite instability in colorectal carcinoma (9, 29, 30). In endometrial carcinoma, loss of mismatch function is reportedly associated with PTEN gene mutation (3, 4), suggesting that impaired mismatch repair function is an important factor in the early stage of endometrial carcinogenesis. To our knowledge, this is the first report of BRAF gene mutations associated with decreased expression of hMLH1 protein in endometrial carcinomas.

KRA S gene mutations in endometrioid carcinomas and nonendometrioid carcinomas were observed in 22% and 5% of the cases examined in the present study. p53 gene mutations in the two histologic subtypes were observed in 12% and 68% of the cases. These findings are consistent with previous reports (3, 4). In addition, the frequency of BRAF gene mutations tended to be higher in endometrioid carcinomas (23%) than in nonendometrioid carcinomas (11%), supporting a possible difference in pathogenesis between the two subtypes. Interestingly, all 18 KRA S gene mutation–positive cases were BRAF gene mutation negative, indicating mutual exclusion. Mutual exclusion between KRA S and BRAF gene mutations was observed in colorectal tumors as well (8, 9). These findings suggest that either BRAF or KRA S is needed in the pathogenesis of tumors, in which the Ras-Raf pathway is crucial to the tumorigenesis. However, no such inverse relationship was found between BRAF and p53 in the present study. It was reported that there was no association between BRAF and p53 nor APC gene abnormalities in colorectal tumors (29), suggesting that the p53-related pathway is independent of the Ras-related pathway.

The present study revealed the occurrence of a total of 21 BRAF gene mutations at five sites in 97 cases of endometrial carcinoma. Seven mutations involved Val599, a previously identified hotspot in the kinase domain. However, the amino acid switch observed in the present study (V599G) was different from the most common change (V599E). Therefore, the functional involvement of the V599G mutation needs to be clarified. We found three novel missense mutations (i.e., Y471, K590R, and L617W). Y471S locates close to the G-Loop domain, whereas K590R and L617W are close to the activating kinase domain (13). One study suggested that non-V599E mutations in the kinase domain modulate the Ras-Raf-Mek-Erk pathway, and thus are involved in the pathogenesis of the tumor (9). However, another study reported that mutations of the G-Loop site were not related to the increase in kinase activity and transformation activity (31). In addition, the possibility that the R602stop mutation may suppress tumorigenesis cannot be fully excluded.

The present study revealed that only one (11%) atypical endometrial hyperplasia contained a BRAF gene mutation. On the other hand, 23% of endometrioid-type carcinomas in the present study had BRAF mutations with no apparent correlation with tumor stage or histologic grade. These findings suggest that the BRAF gene mutation is important for malignant transformation, rather than the premalignant stages in the tumorigenesis of endometrioid-type carcinomas. This pattern resembles that observed in colorectal carcinoma because the prevalence of BRAF mutations in colorectal adenomas ranged from 1% to 3%, and in carcinomas from 5% to 10% (8, 9). Conversely, in serous borderline tumors of the ovary and nevi, a precursor of malignant melanoma, the prevalence of BRAF gene mutations in premalignant lesions was the same as that in malignant lesions (32, 33), suggesting that the BRAF activating mutation is an early tumorigenic event in these tumors.

In conclusion, the present study indicated that 21% of endometrial carcinomas showed BRAF mutations including several novel sites, and mutation in endometrial carcinoma was associated with a loss of hMLH1 expression. Although the exact molecular mechanisms of these alterations are not yet elucidated, these mutations seem to be involved in the pathogenesis of a subset of endometrial carcinomas.

Table 4. Result of immunostaining for hMLH1 and hMSH2 in endometrial carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>(+)</th>
<th>(++)</th>
<th>(+++)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>hMLH1 (97 cases)</td>
<td>32 (33%)</td>
<td>27 (28%)</td>
<td>30 (31%)</td>
<td>8 (8%)</td>
<td>14.4 ± 18.1</td>
</tr>
<tr>
<td>hMSH2 (97 cases)</td>
<td>5 (5%)</td>
<td>26 (27%)</td>
<td>35 (36%)</td>
<td>31 (32%)</td>
<td>37.4 ± 25.3</td>
</tr>
</tbody>
</table>

References


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