IS-10 MDM2 SNP309 polymorphisms and the risk of gynecological cancer

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[Objective] A functional T to G single nucleotide polymorphism in the promoter region of MDM2 gene (MDM2–SNP309) has been reported to accelerate tumor formation. We investigated germline polymorphism of MDM2–SNP309 and the risk of gynecological cancer. [Methods] Genomic DNA of peripheral blood lymphocytes were collected from 108 normal, 88 cervical, 119 endometrial and 85 ovarian cancer patients under informed consent. MDM2–SNP309 polymorphisms were evaluated using two independent polymerase chain reaction assays for each allele. [Results] When MDM2–SNP309 genotype was classified into two subgroups of TT + TG and GG, the GG genotype was associated with an increased risk for the development of endometrial cancer (OR = 1.91, 95% CI = 1.05 to 3.47) compared with the TT + TG genotype (P = 0.0353). The G allele also increased the risk of endometrial cancer (OR = 1.20, 95% CI = 0.83 to 1.74) compared with the T allele, but no statistical difference was found. The homozygous GG genotype was also associated with postmenopausal status and type I endometrial cancer (P = 0.0306 and 0.0326, respectively). There was no significant difference in the genotype or allele prevalence between control subjects and cervical or ovarian cancer patients. [Conclusion] Homozygous GG genotype of MDM2–SNP309 may be a risk factor for postmenopausal and type I endometrial cancer in a Japanese population.

IS-11 PRIMA-1 Increases CDDP Sensitivity in p53 Mutated Chemoresistant Ovarian Cancer Cells: Dependence on Akt Down-Regulation

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[Objective] We examined the influence of Akt down-regulation on the ability of PRIMA-1 (p53 reactivation and induction of massive apoptosis) to facilitate CDDP-induced apoptosis in chemoresistant ovarian cancer (OVCA) cells carrying p53 mutation. [Methods] Apoptotic response of human chemoresistant OVCA cells (A2780cp) infected with adenoviral dominant-negative Akt (DN-Akt; 40MOI; LacZ as control) and subsequently treated with PRIMA-1 (0–10μM) and/or CDDP (0–10 μM) were assessed by Hoechst nuclear staining. To determine whether p53 is involved in the action of PRIMA-1, cells were transfected with p53-specific or control siRNA (50nM) after the infection with adenoviral DN-Akt. [Results] Apoptosis rate was significantly higher at low PRIMA-1 concentrations plus CDDP group with DN-Akt than LacZ control (p < 0.01). PRIMA-1 significantly induced apoptosis in the DN-Akt groups in a concentration-dependent manner (p < 0.01). Maximal apoptotic response was observed at 0.625μM PRIMA-1 and 10μM CDDP. Apoptosis in cells treated with PRIMA-1 and CDDP was significant suppressed by p53-siRNA. Western analysis showed that PRIMA-1 increased phospho-p53 (Ser-15) content in Akt down-regulated cells treated with CDDP. [Conclusion] These results suggest that PRIMA-1 can sensitize chemoresistant mutant-p53 OVCA cells to CDDP when Akt is down-regulated. The action of PRIMA-1 is associated with p53 activation.

IS-12 Limited benefit of neoadjuvant chemotherapy before surgery in FIGO stage IB–IIA cervical cancer: a case-control study and meta-analysis

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Objective: To evaluate whether neoadjuvant chemotherapy before surgery (NCS) can provide more benefit for improving clinical outcomes than primary surgical treatment (PST) in the International Federation of Gynecology and Obstetrics (FIGO) stage IB-IIA cervical cancer. Methods: We performed a case-control study where 61 patients treated with NCS were matched to 183 treated with PST. Thereafter, we conducted a meta-analysis of 3 randomized controlled trials and 4 observational studies including the current study between 1997 and 2009, where a total of 1,556 patients were enrolled. Results: In the case-control study, NCS was associated with lower rates of intermediate- and high-risk factors (large tumor size ≥ 4 cm, deep stromal invasion ≥ 1/2, lymphovascular space invasion: LVI) and the frequency of adjuvant radiotherapy, whereas there were no differences in the rates of high-risk factors (positive resection margin, parametrial invasion, lymph node metastasis), recurrence rates between NCS and PST. However, NCS showed lower overall survival than PST albeit similar progression-free survival. In the meta-analysis, NCS reduced only LVI among the 5 risk factors except large tumor size, whereas it had no benefit for prolonged survival. Although NCS reduced distant recurrence, it failed to decrease adjuvant radiotherapy, and overall and local recurrences. Conclusions: NCS may not be effective for reducing most of risk factors except large tumor size and LVI, and for decreasing adjuvant radiotherapy, overall and local recurrences in FIGO stage IB-IIA cervical cancer. Furthermore, NCS could provide little benefit for better survival than PST in spite of the reduction of distant recurrence.