



Title	Methylation of E-caderin gene in gastric cancer and in normal gastric mucosa from patients with and without Helicobacter pylori infection
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Methylation of E-cadherin Gene in Gastric Cancer and in Normal Gastric Mucosa from Patients With and Without *Helicobacter pylori* Infection

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Introduction: E(epithelial)-cadherin is an important homotypic adhesion molecule which plays important role in tumor invasion/metastasis. Silencing of E-cadherin by CpG island methylation has been identified to be an important mechanism in both familial and sporadic gastric cancer.

Aim: We investigated methylation of E-cadherin in normal gastric mucosa from normal subjects, and intestinal metaplasia, adenocarcinoma, and metastatic lymph nodes from patients with gastric cancer.

Methods: Methylation at E-cadherin was studied by methylation-specific polymerase chain reaction (MSP) and expression of E-cadherin by immunohistochemical staining. All statistical studies were two-sided.

Results: CpG island methylation was identified in 30% of normal gastric mucosa. Significant association between methylation and *Helicobacter pylori* was observed: 90% of methylated mucosa were *H. pylori* +ve, versus 65% of unmethylated mucosa were *H. pylori* -ve ($p = 0.002$). Methylation in mucosa increases with age ($p = 0.04$). Methylation was observed in 59% of intestinal metaplasia, 58% of tumorous tissues, and 60% of metastatic lymph nodes. Concordancy rate of methylation status between different stages in the same patient was 83%. Methylation at E-cadherin correlated with lymph node metastasis ($P=0.046$), and was observed more frequently in mucinous and signet ring cell tumors ($P=0.0058$).

Conclusion: A possible link exists among E-cadherin methylation, *Helicobacter pylori* and aging. This may provide clue for the initiating mechanism of methylation.

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High Frequency of Promoter CpG Methylation in the *p16* and *Retinoic Acid Receptor 3* Gene in Lung Cancer: Potential Application in the Sensitive Detection of Tumour Cells in Diagnostic Samples

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Introduction: Aberrant promoter CpG island methylation leading to epigenetic silencing of gene expression is an alternative mechanism in inactivating putative tumour suppressor genes. CpG island methylation can be detected by the methylation specific polymerase chain reaction (MSP), with a sensitivity of 10^{-3} . We examined the frequency of promoter methylation of the *p16* and the *retinoic acid receptor 3* (*RAR3*) genes in lung cancer, and tested whether this could be used for the sensitive detection of tumour cells in diagnostic samples.

Materials and Methods: Seventy five surgically resected lung cancer specimens were examined. DNA from fresh or paraffin-embedded specimens was bisulphite treated, followed by MSP for the *p16* and *RAR3* genes with primers specific for the methylated and unmethylated alleles. MSP products were sequenced for confirmation of specificity. Sputum and bronchoalveolar lavage samples from patients with suspected lung cancer were similarly examined.

Results: In 44 cases of adenocarcinoma (M:F = 33:11), the frequencies of *p16* and *RAR3* methylation were 39 and 61%. In 31 cases of squamous cell carcinoma (M:F = 29:2), the frequencies of *p16* and *RAR3* methylation were 58% and 77%. Thirty three of forty four (75%) adenocarcinomas and 26/31(84%) of squamous cell carcinomas were positive for either *p16* or *RAR3* gene methylation. MSP was used as a molecular marker to define the presence of malignant cells in the sputum or bronchoalveolar lavage of patients with suspected/confirmed lung cancer. *p16* methylation was detected in 13/58 samples (22%), and *RAR3* methylation in 31/37 samples (84%).

Conclusion: *p16* and *RAR3* genes are methylated at a frequency of 75-84% in patients with lung cancer. Similar frequencies were observed in sputum and bronchoalveolar lavage. The results show that aberrant gene promoter methylation is an important mechanism in lung carcinogenesis. Furthermore, the detection of promoter methylation can also be used as a sensitive tool for the molecular detection of cancer cells in diagnostic samples.