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## Prostanoid Metabolic Enzymes in Endometrial Cancer

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### Abstract Text

*Purpose:* Endometrial cancer (EC) is the commonest gynaecological cancer in the UK. Type I ECs are oestrogen sensitive, develop from premalignant hyperplasia and are low-medium grade. Type II ECs arise de novo, are high grade and have a worse prognosis. Given the role of prostaglandin-endoperoxide synthase (PTGS; cyclooxygenase) products prostaglandin (PG)F<sub>2</sub> alpha and PGE<sub>2</sub> in cancer, this study profiled them and their synthetic/catabolic enzymes in EC carcinogenesis.

*Methods:* PTGS1 and PTGS2 expression profiles were assessed by genome-wide expression microarray of laser capture microdissected endometrial specimens (n=81 normal, 30 hyperplastic, 118 cancerous). Matched tissue samples were analysed by mass spectrometry for PGF<sub>2</sub> alpha, PGE<sub>2</sub> and its inactive metabolite dihydro-15-keto PGE<sub>2</sub> and normalised to protein. Tissue microarrays (n=419 ECs) were immunohistochemically stained for PTGS1, PTGS2 and the PG catabolic enzyme hydroxyprostaglandin dehydrogenase (HPGD).

*Results:* PTGS1 and HPGD were significantly underexpressed in hyperplasia and both cancer types (p<0.05). PTGS2 was significantly underexpressed in hyperplasia and type II cancers only (p<0.05). Immunohistochemistry reveals that, using a cut-off of 2.5, HPGD showed significantly stronger positivity in type I cancers, PTGS1 in type 2 cancers. Only HPGD had prognostic significance, where HPGD<2.5 predicted worse overall (log rank p<0.01) and progression free survival (p<0.05). Although PGE<sub>2</sub> and PGF<sub>2</sub>alpha concentrations were comparable across samples, dihydro 15-keto PGE<sub>2</sub> levels were significantly lower in both cancer types.

*Conclusions:* Surprisingly, given their purported roles in carcinogenesis, levels of PGE<sub>2</sub> and PGF<sub>2</sub>alpha; were not elevated in hyperplastic/neoplastic endometrium, which may reflect their function in endometrial physiology. However, the significantly decreased levels of dihydro 15-keto PGE<sub>2</sub> in EC may reflect the decreased overall HPGD expression and, in turn, prostanoid turnover.