DECLARATION

I hereby declare that this submission is my own work and that, to the best of my knowledge, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of the MD (Res) degree by the University of London.

Chemoprevention

in a

Validated Rat Model

of

Oesophageal Adenocarcinoma

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for the degree of Doctor of Medicine

ABSTRACT

The UK has experienced an increase in the incidence of oesophageal adenocarcinoma (OAC) in recent years. The prognosis for patients with OAC remains poor with currently available treatments prompting a search for alternative 'chemopreventive' treatments that inhibit oesophageal carcinogenesis. Both non-steroidal anti-inflammatory drugs (NSAIDS) and flavonoids are associated with a significant risk reduction for developing OAC in epidemiological studies. The aim of this study was to validate Levrat's surgical model of OAC in the rat, and assess the chemopreventive effects of the NSAID aspirin, and the flavonoid quercetin on the development of OAC in the validated rat model.

METHODS: Levrat's model was validated in a time course experiment. Morphological and molecular events occurring in the distal oesophagus during disease progression were determined and compared to human disease.

The effect of aspirin and quercetin on disease initiation and progression was determined by commencing treatment either before the onset of reflux, or 4-weeks afterwards. The incidence of Barrett's oesophagus (BO) and OAC within each group was determined, along with methylation levels of the ESR-1, p16 and HPP1 gene promoter regions.

RESULTS: The morphological and molecular changes in the distal oesophagus of the rat model are broadly consistent with those reported in human disease.

The incidence of OAC was significantly lower in aspirin treated rats. A non-significant reduction in incidence of OAC was observed with quercetin treatment. Timing of treatment with regard to onset of reflux had no significant effect on OAC development in either treatment group. Neither treatment significantly effected methylation levels within the gene promoters examined.

CONCLUSION: Use of Levrat's model as a model of human OAC seems justified. Aspirin inhibits development of oesophageal adenocarcinoma induced by reflux in this rat model. No additional reduction in cancer incidence is observed if treatment is commenced prior to inception of reflux disease.

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INDEX

FIGURES AND TABLES