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COLORECTAL CANCER

Male hormones increase the incidence of colonic adenomas

The observed increased incidence of adenomas and colorectal carcinomas in men compared with women has been linked to male sex hormones, according to a new study.

The authors sought to address whether the lower incidence and delayed onset in women is owing to protection by female hormones or lack of tumour-promotion by male hormones.

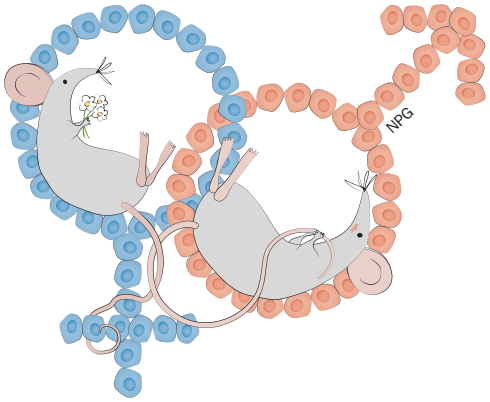
Initially, two animal models of enhanced intestinal adenoma formation were used, the *Apc*$^{Min/+}$ mouse and the *Apc*$^{Pirc/+}$ rat. Both models have mutations in the critical tumour suppressor gene *Apc*, encoding adenomatous polyposis coli protein, frequently mutated in human colorectal cancer.

Apc$^{Min/+}$ mice develop adenomas predominantly in the small intestine and in order to get meaningful data relating to colonic adenomas, the authors analysed a large group of mice. "Systematic analysis of over a decade of *Apc*$^{Min/+}$ mice data ... proved that there was a bias in the colon in [male] mice like that seen in men," says author James Amos-Landgraf.

The *Apc*$^{Pirc/+}$ rat model was used in subsequent studies as there is a higher occurrence of colonic adenomas. Female rats underwent ovariectomy or sham operation followed by placebo or hormone replacement. At the end of the study, no difference was found in adenoma number between groups indicating that female hormones do not modify adenoma development. Male mice had an orchidectomy or sham operation followed by placebo or dihydrotestosterone replacement. Rats in the orchidectomy group receiving placebo had substantially fewer adenomas than rats given hormones.

The pattern of sexual dimorphism in adenoma development was recapitulated in a complementary model, in which mice were injected with the carcinogen azoxymethane.

Low expression of the androgen receptor in mouse and rat intestinal epithelium, compared with tissue from other organs, led the group to believe that the effect of male hormones on adenoma development is indirect.



Future work will aim to differentiate whether hormones are acting on the initiation or progression of adenomas. The group will also explore the interaction of hormones and environmental factors on the adenoma–carcinoma pathway.

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Original article Amos-Landgraf, J. M. *et al.* Sex disparity in colonic adenomagenesis involves promotion by male hormones, not protection by female hormones. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1323064111