

Cancer Genetics Gazette



This gazette is sent to you from the Familial Cancer Unit. It aims to provide specialist clinicians with up-to-date information about developments in cancer genetics.

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The Aspirin, Bran and Calcium of colorectal cancer chemoprevention

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Endoscopic surveillance is currently the best strategy for preventing and managing colorectal cancer in genetically predisposed individuals. More attractive still, however, would be to reduce the incidence of colorectal neoplasia, thus safely avoiding or delaying the need for surgery. This report will outline some of the promising dietary and pharmaceutical agents for the chemoprevention of colorectal neoplasia in people at high genetic risk.

Dietary:

Fibre and Resistant Starch:

Fibre acts to dilute intraluminal contents and hastens colonic transit, both of which reduce epithelial exposure to potential carcinogens. Bacterial fermentation of fibre generates short-chain fatty acids (e.g. butyrate), that reduce intraluminal pH and lead to a reduction in secondary bile acids. This environment promotes colonic epithelial differentiation and enhances apoptosis. These theoretical benefits are supported by observational studies that suggest diets high in fibre are protective against colorectal cancer.¹ Therapeutic trials of fibre supplementation, however, have failed to confirm this benefit.^{2,3} One study even suggested that fibre supplementation actually increased the incidence of adenomas.⁴ The eagerly awaited CAPP 1 study will address the role of resistant starch and aspirin in suppressing adenoma formation in patients with familial adenomatous polyposis (FAP).⁵ In the meantime, patients should maintain a good

fibre intake (30g daily, which should result in at least one large, soft stool per day) as the balance of evidence is in favour of protection.

Calcium:

Calcium has several anti-carcinogenic properties, including sequestration of potentially mutagenic fatty acids and bile salts, as well as directly inhibiting epithelial proliferation through modulation of protein C kinase and K-ras.⁶ In individuals with a history of colorectal polyps the daily administration (over four years) of calcium (1200mg) significantly reduced the incidence of total and advanced adenomas by 19% and 44%, respectively.⁷ One litre of milk contains approximately 1200 mg of calcium, demonstrating the amount of dairy produce required for diet alone to meet the patient's needs.

Other Vitamins and Minerals:

Vitamin A, C, D, E and folate have achieved disappointing results.⁸ In one Finnish study, administration of vitamin E and β -carotene actually increased the risk of colorectal adenomas.⁹ There is, however, some support for supplemental selenium. One trial randomized 1312 individuals with a history of skin cancer to 200 μ g of selenium or placebo for six years. Patients treated with selenium had a significant reduction in colorectal cancer incidence.¹⁰

Other micronutrients:

Other food components such as lycopene, polyphenols, alliums etc. show considerable promise as cancer-preventing agents. Over the next few years we will see a lot more work done addressing these agents. In the meantime, ensure a major component of the diet is plant-based and fresh.

Please take a few minutes to respond to the questionnaire in this newsletter.

Your feedback is much appreciated.

Editorial Responsibility:

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Pharmaceutical:

Non-steroidal anti-inflammatory drugs (aspirin, conventional NSAIDs as well as COX-2 selective inhibitors, i.e. COXIBS):

NSAIDs offer the greatest promise for the secondary prevention of sporadic as well as familial colorectal neoplasia. Cyclo-oxygenase 2 (COX-2) appears to be a critical enzyme throughout all stages of the adenoma-carcinoma sequence.⁸ Aspirin reduces the incidence of polyps following the diagnosis of sporadic colorectal neoplasia,^{11,12} although the optimum dosage is still uncertain. Sulindac and celecoxib both reduce the adenoma burden in patients with FAP,^{13,14} but to what end? It may be reasonable to postulate that suppressing adenoma formation or causing adenoma regression will delay colectomy and that NSAID therapy will provide additional extra-colonic benefits. Unfortunately, colorectal neoplasia can still occur during NSAID therapy.¹⁵ The relative merits of these agents need to be balanced against their potential risks (see Box 1). In FAP NSAIDs are at best a temporizing treatment used in partnership with endoscopic surveillance. The role of NSAID chemoprevention in other familial colorectal cancer syndromes needs further study.

Hormone replacement therapy:

The Women's Health Initiative trial included a combined oestrogen plus progestin hormone-replacement therapy arm, which was associated with a 37% reduction in the incidence of sporadic colorectal cancer. The study was stopped early, however, because of an increased risk of breast cancer.¹⁶

Conclusion

There is burgeoning interest in cancer chemoprevention, but unfortunately for patients with familial colorectal cancer syndromes there has been only moderate success. NSAIDs are the most effective chemoprevention strategy. The benefit of NSAID chemoprevention beyond that afforded by a conventional, endoscopic, polyp-surveillance program alone, however, remains unclear. There are very few completed clinical studies regarding chemoprevention in non-FAP colorectal cancer syndromes, e.g. hereditary non-polyposis colorectal cancer.¹⁷ This makes evidenced-based, global recommendations for chemoprevention difficult. The utility of chemoprevention in protecting against the extra-colonic manifestations of these syndromes remains poorly understood.

In the setting of familial colorectal cancer syndromes an individual should be encouraged to adopt a multi-purpose health regimen, as advocated by the NH&MRC, the National Academy of Sciences of the U.S.A. and the American Cancer Society. Such a

regimen encourages physical activity and a diet that is low in fat, rich in fruit, vegetables, and cereals and often substitutes white for red meat. One should consider calcium supplementation especially when a diet cannot be made naturally-sufficient. In those with FAP, NSAID therapy is a reasonable option, provided the risks of such treatment are carefully discussed with the patient. It is likely that endoscopic surveillance will remain the mainstay of management, at least in the near future.

Are COXIBS safe when used to prevent colorectal neoplasia?

The cardiovascular safety of COX-2-selective inhibitors (COXIBS) was questioned following the VIGOR study, a comparison of rofecoxib with a conventional NSAID, that excluded individuals taking aspirin. The rofecoxib group had a significantly greater risk of myocardial infarction, 0.4% Vs 0.1%. This discrepancy was ascribed to the relative cardiovascular protection of naproxen (with its inhibition of COX-1, and thus platelet aggregation, via thromboxane A2). In contrast, the CLASS trial that compared celecoxib with conventional NSAIDs allowed aspirin use and there was no increase in cardiovascular events. Then late last year data from the APPROVe trial (studying rofecoxib for prevention of colorectal adenomas) became available. Rofecoxib was again associated with an increased risk of thrombotic events (mainly myocardial infarctions and ischaemic stroke) compared to placebo (relative risk 1.92 [95% CI, 1.19 to 3.11; P=0.008]). Rofecoxib was withdrawn from the market because of these results, prompting the review of a similar study into the benefits of celecoxib in sporadic colorectal adenomas (APC study). This time celecoxib was also associated with an increase in cardiovascular events and the treatment arms of this study were stopped.²¹

In patients with FAP, high-dose COXIBS (e.g. celecoxib 400mg bd) are required to reduce adenoma burden,¹⁴ and these doses are likely to be associated with an increased relative risk of cardiovascular events. However, the absolute, COXIB-induced, increase in cardiovascular risk for a young, otherwise healthy person with e.g. FAP is likely to be extremely small (the approximate mean ages for the APC study was 59y,²¹ VIGOR 58y,¹⁸ CLASS 60y,¹⁹ and APPROVe 59y,²⁰ whilst the mean age in the celecoxib in FAP trial was only 37y¹⁴). Nevertheless, when these risks are considered in the context of the relatively subtle benefits of COXIBS, and that there are cheaper alternatives available (conventional NSAIDs, plus/minus proton pump inhibitor therapy for gastroduodenal protection) it is likely that the clinical use of COXIBs in hereditary colorectal cancer will continue to decline, however, they may continue to stimulate medical research.

*References are available upon request.
Contact: Clara Tait on 8291 4153 or by
email:ctait@cancersa.org.au*

Cancer Genetics Gazette

Resource order form

fax to The Cancer Council: 08 8291 4268

1. What topics relating to cancer genetics are of interest to you?
(tick as many boxes as you wish)

- a) Rare cancer syndromes
- b) Reproductive options
- c) New genetic testing methods
- d) New surveillance strategies
- d) Prophylactic surgery
- e) Chemoprevention
- f) Dietary prevention
- g) Prophylactic surgery
- h) None of the above
- i) Other (please specify)

2. Which of the following educational formats would you like? (tick as many boxes as you like)

- a) Cancer Genetics Gazette
- b) CPD workshops
- c) Familial Cancer Service pamphlets
(Please use order form overleaf)
- e) Family history pamphlets
(Please use order form overleaf)
- f) Cancer genetics videos
- g) Web based instruction
- h) None of the above
- i) Other (please specify)

4. Please indicate, by placing a circle around the numbers below, whether you find Cancer Genetics Gazette

- a) **Relevant to your practice**
- | | | | | | |
|-------------------|---|---|---|----------------|---|
| 1 | 2 | 3 | 4 | 5 | 6 |
| Strongly disagree | | | | Strongly agree | |

- b) **Clear and concise**
- | | | | | | |
|-------------------|---|---|---|----------------|---|
| 1 | 2 | 3 | 4 | 5 | 6 |
| Strongly disagree | | | | Strongly agree | |

- c) **Provides up-to-date information**
- | | | | | | |
|-------------------|---|---|---|----------------|---|
| 1 | 2 | 3 | 4 | 5 | 6 |
| Strongly disagree | | | | Strongly agree | |

5. Would you like to receive:

- The Gene Pool**
Cancer Genetics newsletter for GPs
- GeneTrek**
Newsletter for clients of the Familial Cancer Unit

Please use order form overleaf

Familial Cancer Resources

Copy and fax order form to 08 8291 4268

Title	Qty Max 20	Title	Qty Max 20
Introducing the South Australian Familial Cancer Service <i>(pamphlet)</i>		Von Hippel Lindau and Genetic Testing for Families <i>(pamphlet)</i>	
What if I have a family history of cancer? <i>(pamphlet for clients)</i>		Neurofibromatosis Type 2 and Genetic Testing for Clinicians <i>(pamphlet)</i>	
Cancer - The significance of family history <i>(pamphlet for clinicians)</i>		Neurofibromatosis Type 2 and Genetic Testing for Families <i>(pamphlet)</i>	
Guidelines		Newsletters	
Advice about the Familial Aspects of Breast and Ovarian Cancer <i>(chart)</i> <i>National Breast Cancer Centre</i>		Gene Pool Newsletter <i>For General Practitioners</i>	
Current Best Advice about the Familial Aspects of Bowel Cancer <i>(chart)</i> <i>Australian Cancer Network</i>		Gene Trek Newsletter <i>For clients of the Familial Cancer Unit</i>	
Rare cancers		Cancer Genetics Gazette <i>For specialist clinicians</i>	
Retinoblastoma and Genetic Testing for Clinicians <i>(pamphlet)</i>		Miscellaneous	
Retinoblastoma and Genetic Testing for Families <i>(pamphlet)</i>		Familial Aspects of Cancer: A guide to clinical practice <i>NHMRC</i>	
Von Hippel Lindau and Genetic Testing for Clinicians <i>(pamphlet)</i>			

For more information about familial cancer resources you may wish to access the National Cancer Genetics Education Resource Directory on the National Cancer Control Initiative Website:

<http://www.ncci.org.au>

Name: _____

Address: _____

Phone: _____

Email: _____