Pergamon

European Journal of Cancer Vol. 31A, Nos. 7/8, pp. 1385–1386, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00185-9

The Protocol for a European Double-blind Trial of Aspirin and Resistant Starch in Familial Adenomatous Polyposis: the CAPP Study

J. Burn, P.D. Chapman, J. Mathers, L. Bertario, D.T. Bishop, S. Bülow, J. Cummings, R. Phillips and H. Vasen

INTRODUCTION

FAMILIAL ADENOMATOUS polyposis (FAP) is an important cause of colorectal cancer morbidity. Although the birth frequency is only approximately 1 in 8000, the early progression to malignancy and the presence of polyposis as a predictive biomarker has encouraged the widespread development of regional and national registers [1–3]. The underlying defect involves loss of function of the *APC* gene on chromosome 5, the same gene now shown to be mutated as the usual first step towards sporadic colorectal cancer [4]. Carriers of FAP have thus become a highly motivated group in which to evaluate potential dietary and chemoprevention strategies for the general population. In 1993, the Concerted Action Polyposis Prevention (CAPP) Study was established to provide a research network capable of conducting randomised controlled trials across Europe. To date, 35 centres in 15 countries have agreed to participate.

The first protocol involves the evaluation, using a factorial 2×2 design, of aspirin and resistant starch.

ASPIRIN

A series of epidemiological studies, summarised in Figure 1, have demonstrated an association between regular ingestion of non-steroidal anti-inflammatories, such as aspirin, and a reduced incidence of colorectal cancer [5–13]. Small controlled studies of the closely related compound sulindac [14, 15], which is metabolised to a more active form in the bowel, support the hypothesis that aspirin may reduce the risk of colon cancer.

RESISTANT STARCH

Early studies of the association between fibre intake and colon cancer risk failed to distinguish non-starch polysaccharide from resistant starch [16]. The latter term includes starch unavailable to digestive enzymes because of, for example, packaging in seeds, and crystalline starch whose molecular structure denies access to alpha amylase. Cooking causes gelatinisation and makes starch available to digestion, with the result that a typical Western diet contains very low levels of resistant starch. Figure 2 contains a review of correlation between cancer incidence and starch [17]. The correlation coefficient of 0.76 is significantly better than the correlation of 0.29 with non-starch polysaccharides or "fibre". In addition to this epidemiological support for a protective role for starch, a metabolic case can also be made for a beneficial effect; starch is fermented by colonic bacteria to short chain fatty acids, of which the most important is likely to be butyrate. Experiments *in vitro* and *in vivo* using animal and human subjects have shown a variety of beneficial effects on the mucosal cells and their local environment [18]. The second hypothesis, therefore, is that resistant starch will reduce polyp formation and malignant transformation, possibly as a result of bacterial fermentation to butyrate.

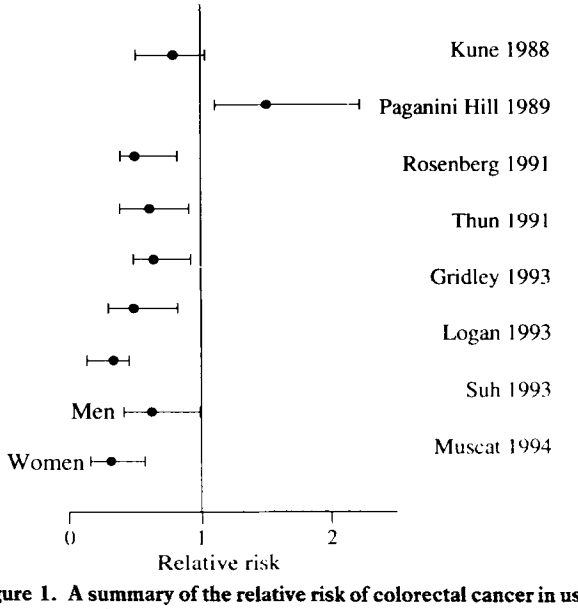

Figure 1. A summary of the relative risk of colorectal cancer in users of anti-inflammatory drugs, such as aspirin.

STUDY DESIGN

Known carriers of FAP, on the basis of phenotypic features or molecular genetic investigation who are over 10 years of age and have an intact colon, are invited to participate. Each participating centre is invited to send a blood sample if diagnostic molecular analysis is required, and this is provided by the resource centre in Newcastle, U.K. Randomisation to one of the four treatment cells (aspirin + resistant starch, aspirin + digestible starch, resistant starch + placebo, digest-

Correspondence to J. Burn.
J. Burn, P.D. Chapman and J. Mathers are at the CAPP Study Coordinating Centre, Dept Human Genetics, 19 Claremont Place, University of Newcastle upon Tyne NE2 4AA, U.K.

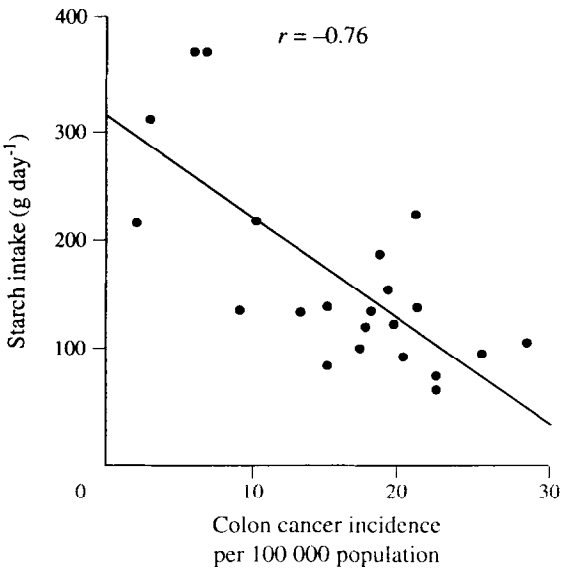

Figure 2. A comparison between colon cancer incidence (cases per 100 000 age-standardised world population per year) and dietary starch (g/day) in different populations. Reproduced with permission from Cassidy A, Bingham SA and Cummings JM. *Br J Cancer* 1994, 69, 937–942 [17].

ible starch + placebo) is carried out by the Imperial Cancer Research Fund genetic epidemiology unit in Leeds, U.K. For those over 40 kg in weight, 600 mg (two tablets) of aspirin are taken once daily together with 30 g of starch powder either as a bolus or in divided doses; the powder may be taken unheated with any food or drink such as yoghurt or milk. Orange- and lemon-flavoured powder to be mixed with a glass of water is also offered. Para amino benzoic acid (PABA) is included as a compliance marker for use in those centres where this is permitted by the ethics committee.

END POINTS

The endoscopist is invited to describe the findings at enrolment and at least annually thereafter. Using video endoscopy, a withdrawal recording of the rectum is sent to the study centre in Newcastle at each examination, together with six mucosal biopsies for crypt cell proliferation rate (CCPR) studies. Two members of the steering group review paired videos to assess whether there has been progression or regression of polyps. These results, together with the findings of CCPR, are made available to the independent data monitoring committee, together with the randomisation code in order that they may terminate the study if and when a statistically significant result emerges.

EXIT CRITERIA

Under the age of 21 years, most surgeons defer surgery, provided there is no significant evidence of disease. Clinicians are asked to treat this issue in the normal way regardless of enrolment in the study. If one or other treatment category is influential on disease progression, this may be reflected in a significant delay in surgery. In those over 21 years, participation is restricted to a maximum of 1 year.

PROGRESS TO DATE

Following commencement in 1993, the protocol was finalised and agreed at the Copenhagen meeting of the Leeds Castle International Polyposis Group. Completion of production of treatment and investigation packs and the management structure allowed the first recruitment in summer 1994. Acquisition of ethical clearance was lengthy, being completed in the Netherlands and Denmark at the end of 1994. To date, there have been 87 recruits of whom 19 have subsequently withdrawn. Original power analysis, based on a reduction of disease penetrance/progression from 80 to 65% indicated a need for a total of 400 enrollees. An application will be submitted in March 1995 for a further 3 years' funding for the concerted action in order that the study can be carried to completion. A parallel aim of the CAPP study is to encourage the establishment of multidisciplinary polyposis registries for the whole of the European population. New centres wishing to develop a registry and/or contribute patients to the trial should contact the resource centre in Newcastle University, U.K.

1. Burn J, Chapman P, Delhanty J, *et al.* The UK northern region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium, and DNA markers in risk calculations. *J Med Genet* 1991, **28**, 289–296.
2. Bulow S, Burn J, Neale K, Northover J, Vasen H. The establishment of a polyposis register. *Int J Colorect Dis* 1993, **8**, 34–38.
3. Burn J, Chapman PD, Eastham EJ. Familial adenomatous polyposis. *Arch Dis Child* 1994, **71**, 103–107.
4. Powell SM, Zilz N, Beazer-Barclay Y, *et al.* APC mutations occur early during colorectal tumorigenesis. *Nature* 1992, **359**, 235–237.
5. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illness, operations, medications: case–control results from the Melbourne Colorectal Cancer Study. *Cancer Res* 1988, **48**, 4399–4404.
6. Paganini-Hill A, Chao A, Ross RK, Henderson BE. Aspirin use and chronic diseases: a cohort study of the elderly. *Br Med J* 1989, **299**, 1247–1249.
7. Rosenberg L, Palmer JR, Zauber AG, *et al.* A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. *J Natl Cancer Inst* 1991, **83**, 355–359.
8. Thun MJ, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 1991, **325**, 1593–1596.
9. Gridley G, McLaughlin JK, Ekbom A, *et al.* Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 1993, **85**, 307–311.
10. Logan RFA, Little J, Hawtin PG, Hardcastle JD. Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: case–control study of subjects participating in the Nottingham faecal occult blood screening programme. *Br Med J* 1993, **307**, 285–289.
11. Suh O, Mettlin C, Petrelli NJ. Aspirin use, cancer and polyps of the large bowel. *Cancer* 1993, **72**, 1171–1177.
12. Muscat JE, Stellman SD, Wynder EL. Nonsteroidal antiinflammatory drugs and colorectal cancer. *Cancer* 1994, **74**, 1847–1854.
13. Hixson LJ, Earnest DL, Fennerty MB, Sampliner RE. NSAID effect on sporadic colon polyps. *Am J Gastroenterol* 1994, **88**, 1652–1656.
14. Labayle D, Fischer D, Vielh P, *et al.* Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology* 1991, **101**, 635–639.
15. Giardiello FM, Hamilton SR, Krush AJ, *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993, **328**, 1313–1316.
16. Bingham SA. Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. *Proc Nutr Soc* 1990, **49**, 153–171.
17. Cassidy A, Bingham SA, Cummings JH. Starch intake and colorectal cancer risk: an international comparison. *Br J Cancer* 1994, **69**, 937–942.
18. van Munster IP, Nagengast FM, Tangerman A. The effect of resistant starch on bile acid metabolism, cytotoxicity of faecal water and colonic mucosal proliferation. *Eur J Cancer Prev* 1993, **2**, 12–13.