



# Long-term effect of resistant starch on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial

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## Summary

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**Background** Observational studies report that higher intake of dietary fibre (a heterogeneous mix including non-starch polysaccharides and resistant starches) is associated with reduced risk of colorectal cancer, but no randomised trials with prevention of colorectal cancer as a primary endpoint have been done. We assessed the effect of resistant starch on the incidence of colorectal cancer.

**Methods** In the CAPP2 study, individuals with Lynch syndrome were randomly assigned in a two-by-two factorial design to receive 600 mg aspirin or aspirin placebo or 30 g resistant starch or starch placebo, for up to 4 years. Randomisation was done with a block size of 16. Post-intervention, patients entered into double-blind follow-up; participants and investigators were masked to treatment allocation. The primary endpoint for this analysis was development of colorectal cancer in participants randomly assigned to resistant starch or resistant-starch placebo with both intention-to-treat and per-protocol analyses. This study is registered, ISRCTN 59521990.

**Findings** 463 patients were randomly assigned to receive resistant starch and 455 to receive resistant-starch placebo. At a median follow-up 52.7 months (IQR 28.9–78.4), 53 participants developed 61 primary colorectal cancers (27 of 463 participants randomly assigned to resistant starch, 26 of 455 participants assigned to resistant-starch placebo). Intention-to-treat analysis of time to first colorectal cancer showed a hazard ratio (HR) of 1.40 (95% CI 0.78–2.56;  $p=0.26$ ) and Poisson regression accounting for multiple primary events gave an incidence rate ratio (IRR) of 1.15 (95% CI 0.66–2.00;  $p=0.61$ ). For those completing 2 years of intervention, per-protocol analysis yielded a HR of 1.09 (0.55–2.19,  $p=0.80$ ) and an IRR of 0.98 (0.51–1.88,  $p=0.95$ ). No information on adverse events was gathered during post-intervention follow-up.

**Interpretation** Resistant starch had no detectable effect on cancer development in carriers of hereditary colorectal cancer. Dietary supplementation with resistant starch does not emulate the apparently protective effect of diets rich in dietary fibre against colorectal cancer.

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## Introduction

The incidence of colorectal cancer rises steeply with age and risk is affected strongly by environmental factors including adiposity, physical activity, and habitual diet.<sup>1</sup> A systematic review of the epidemiological literature shows convincing evidence that higher intakes of red meat, processed meat, alcoholic drinks (men only), and increases in body fat increase the risk of colorectal cancer, whereas greater physical activity reduces risk. Additionally, the evidence was assessed as probable that alcoholic drinks (women only) increase risk whereas foods containing dietary fibre and garlic, milk, and calcium reduce risk of colorectal cancer.<sup>1</sup> A recent meta-analysis of 21 prospective studies showed a significant, dose-dependent protective effect of dietary fibre intake

against colorectal cancer (relative risk [RR] per 10 g a day increase in dietary fibre intake 0.90, 95% CI 0.86–0.94).<sup>2</sup>

Dietary fibre is a food-based measure that attempts to estimate the heterogeneous mix of carbohydrates (non-starch polysaccharides, starches, and oligosaccharides) that escape digestion in the small bowel and flow to the large bowel where they exert a wide range of physiological effects due, in part, to the bacterial fermentation of these carbohydrates to yield biologically active short-chain fatty acids.<sup>3</sup> An inverse association exists between starch intake and risk of colorectal cancer,<sup>4</sup> which could be due to resistant starch (ie, the dietary starch and starch degradation products that escape digestion in the small intestine of healthy individuals).<sup>5</sup> Resistant starch reduced colonic neoplasia in several carcinogen-treated

rat studies<sup>6,7</sup> but high intakes of this starch increased intestinal tumorigenesis in the genetically driven *Apc1638N* mouse model.<sup>8</sup> The antineoplastic effect of resistant starch is believed to result largely from the fermentation endproducts short-chain fatty acids and, in particular, butyrate.<sup>9,10</sup> In addition to inhibition of tumour-cell proliferation, butyrate might reduce risk of colorectal cancer by enhancing the apoptotic response to DNA damage.<sup>7,11–13</sup> Preliminary evidence shows that butyrate might have more potent antineoplastic effects on colon cancer cells with dysfunction of the DNA mismatch repair gene *MLH1*.<sup>14</sup>

Few studies of the effects of resistant starch on colorectal carcinogenesis in human beings have been done and most have used putative biomarkers of colorectal-cancer risk as endpoints. Early studies showed that resistant-starch feeding for short periods (typically 4 weeks) reduced faecal excretion of cytotoxic secondary bile acids<sup>15,16</sup> and in some, but not all, studies reduced mucosal-cell proliferation.<sup>16</sup> Short-term (2–4 weeks) supplementation with resistant starch in 65 patients with colorectal cancer significantly reduced ( $p=0.028$ ) the proportion of mitotic cells in the top half of the colonic crypt and produced differential effects on expression of key cell-cycle regulatory genes (*CDK4* and *GADD45A*) in tumour tissue.<sup>17</sup> The duration of resistant-starch feeding required to provoke changes in biomarkers of colorectal-cancer risk is not known but is probably greater than 1 week.<sup>18</sup> In the Colorectal Adenoma/carcinoma Prevention Programme (CAPP) 1 study in young people with familial adenomatous polyposis, supplementation with resistant starch (1:1 blend of raw potato starch and high amylose maize starch [Hylon V11]) for a median intervention period of 17 months reduced crypt length and cell proliferation but no effect was detected on polyp count in the rectum and sigmoid colon (RR 1.05, 95% CI 0.73–1.49).<sup>19</sup>

Lynch syndrome (also known as hereditary non-polyposis colon cancer) is the most common monogenic predisposition to colorectal cancer with most patients carrying pathological DNA mismatch repair gene variants. In the CAPP2 study done over 6 years, 937 people with Lynch syndrome from 43 international centres commenced intervention with aspirin, resistant starch, or both in a two-by-two factorial design.<sup>20,21</sup> After intervention (mean 29 months [SD 13.7]) there was no evidence that either agent influenced development of colonic neoplasia with most lesions being adenomas.<sup>20</sup> However, the original design of the CAPP2 study included double-blind post-intervention follow-up for at least 10 years and a recent analysis (mean 55.5 months [SD 31.1]), showed that 600 mg aspirin a day for a mean of 25 months [13.4] halved cancer incidence in carriers of hereditary colorectal cancer.<sup>21</sup> We assessed the effect of resistant starch on the incidence of colorectal cancer, the primary CAPP2 outcome, and on other Lynch syndrome cancers as

secondary outcomes. The baseline population differs from our first report, which was confined to those with an exit colonoscopy.<sup>20</sup>

## Methods

### Trial design and participants

Details of the design and conduct of the CAPP2 study have been previously published.<sup>20,21</sup> Recruitment was from January, 1999, to March, 2005. Participants were required to have a proven germline mutation in a mismatch repair gene or a personal and family medical history commensurate with a diagnosis of Lynch syndrome. 83% of all participants had a proven germline mutation.

Ethics committee approval was obtained from all centres from which participants were recruited.

### Randomisation and masking

In this two-by-two factorial trial, randomisation was undertaken centrally by DTB with the SAS (version 6) uniform random number generator to randomise each participant separately for aspirin and for starch.<sup>20,21</sup> We used block randomisation by geographical region so that after 16 randomisations four patients were in each of the four treatment combinations. Masking to treatment allocation was done with coded packaging, which did not reveal the nature of the contents (intervention or placebo).

### Procedures

Patients who were randomly assigned to receive resistant starch were given Novelose 240 and Novelose 330 (National Starch and Chemical Company, Bridgewater, NJ, USA) in one-to-one blend daily with recommended administration in two separate doses, while those assigned to receive resistant-starch placebo were given Amioca waxy starch daily with recommended administration as per resistant starch to maintain masking, for up to 4 years. Novelose 240 and Novelose 330 are fermented in the large bowel to increase concentrations of butyrate and other short-chain fatty acids.<sup>22</sup> The additional digestible starch in the placebo (30 g a day) is nutritionally unimportant compared with typical dietary intakes of 150–350 g a day.<sup>23</sup>

The period of intervention lasted a mean of 29 months (median 25.3 months [IQR 23.7–33.5]) at which point we reported effects of the interventions (aspirin and resistant starch) on colorectal neoplasia (most lesions being adenomas).<sup>20</sup> The original design of the CAPP2 study included double-blind post-intervention follow-up for at least 10 years to investigate effects on cancer risk. All CAPP2 participants were under regular colonic surveillance organised through their local clinical genetics service. Predominantly follow-up was via the routine annual surveillance. A few centres followed up every 2 years. The genetic centres were asked to return information on cancer history to the CAPP2 office after these routine examinations. Follow-up continued as long

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as possible; this analysis reflects the most recent follow-up data available from all participants.

The current analysis focuses on the follow-up of those participants randomly assigned to resistant starch or resistant-starch placebo who started the CAPP2 study from their date of entry into CAPP2 until the last known date for which the local clinical centre had information about their status regarding cancer diagnosis. However, in most cases,

this timepoint corresponded with the date of last attendance at the clinic responsible for their surveillance.

In this analysis, we included (1) patients with Lynch syndrome cancers, which were recorded in the earlier report;<sup>20</sup> (2) all cancers that occurred in patients for whom an exit colonoscopy was not recorded in the initial report, thus excluding them from the statistical analysis in our first report;<sup>20</sup> and (3) cancers that occurred subsequent to exit from the intervention phase. No information on adverse events was gathered during post-intervention follow-up. Details of adverse events reported during the intervention phase of the study are provided as an appendix to a study published by Burn and colleagues.<sup>20</sup>

### Statistical analysis

The analysis was designed to test the hypothesis that resistant starch would reduce the development of colorectal cancer (the primary outcome) and Lynch syndrome cancers (as a secondary outcome). The primary endpoint of this analysis was the development of colorectal cancer in participants, comparing the incidence in those randomly assigned to resistant starch with the incidence in those assigned to resistant-starch placebo.

The analysis was based on time to first occurrence of colorectal cancer with life-table methods and Cox proportional hazards. The life-table analysis used the end of follow-up for each participant as (1) the time of first colorectal cancer diagnosis, if affected, or (2) for those unaffected, the last recorded contact date at which the clinical status of the participant was known. Analyses also included Cox proportional hazards models to estimate sex adjusted hazard ratios (HRs) and 95% CI and Kaplan-Meier curves to non-parametrically assess the outcome differences between the resistant starch and resistant-starch placebo interventions.

We used Poisson regression modelling to estimate incidence rate ratios (IRR) for the effect of resistant starch on the number of primary colorectal cancers diagnosed after randomisation, with the exposure time starting from randomisation until date of last known clinical status. All estimates were adjusted for duration of aspirin taken and sex. Analyses were done on an intention-to-treat basis (intervention assigned at randomisation) and on a per-protocol basis restricting analysis to those taking resistant starch for 2 years or more.

Since patients with Lynch syndrome are susceptible to primary cancers at multiple anatomical sites, a separate analysis addressed the effect of resistant starch on risk of all Lynch syndrome cancers that included all new cancers that occurred as a result of Lynch syndrome (ie, colorectal cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and cancer of the brain, small bowel, gall bladder, ureter, stomach, and kidney).<sup>24</sup> We also compared the incidence of Lynch syndrome excluding cancers of the colorectum as a measure of the potential extra colonic effects of resistant starch.

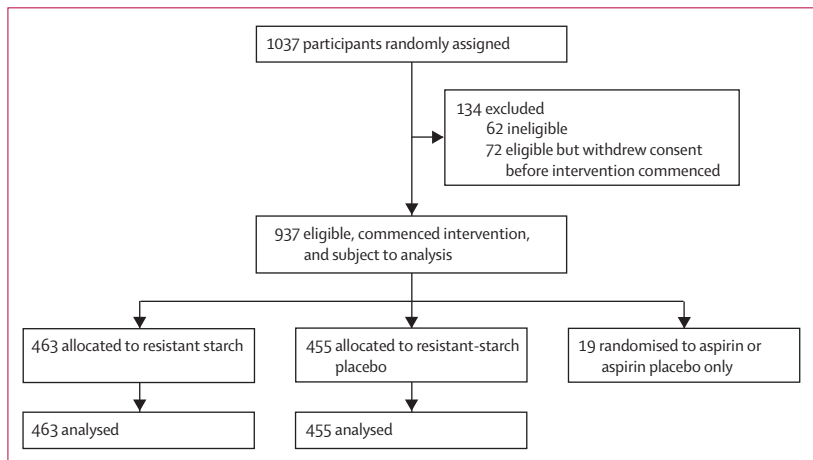


Figure 1: Study profile

	Resistant starch	Resistant-starch placebo
Number of participants	463	455
Sex		
Male	208 (44.9%)	193 (42.4%)
Female	255 (55.1%)	262 (57.6%)
Age, years	44.2 (36.0–52.9)	45.3 (36.7–53.4)
Age group, years		
21–36	124 (26.8%)	109 (24.0%)
37–45	116 (25.1%)	113 (24.8%)
46–53	114 (24.6%)	118 (25.9%)
54–78	109 (23.5%)	115 (25.3%)
Geographical regions		
Northern Europe	212 (45.8%)	198 (43.5%)
UK	133 (28.7%)	118 (25.9%)
Other regions	118 (25.5%)	139 (30.6%)
Long-term follow-up data status		
Total		
Participants with long follow-up	359 (77.5%)	355 (78.0%)
Participants without long follow-up	104 (22.5%)	100 (22.0%)
With exit colonoscopy*		
Participants with long follow-up	301 (84.1%)	318 (86.2%)
Participants without long follow-up	57 (15.9%)	51 (13.8%)
No exit colonoscopy*		
Participants with long follow-up	58 (55.2%)	37 (43.0%)
Participants without long follow-up	47 (44.8%)	49 (57.0%)

Data are number, number (%), or median (IQR). \*Percentages reflect the proportion of all participants with or without long term follow-up as a percentage of those with exit colonoscopy.

Table 1: Characteristics of study participants

All estimated effects of resistant starch were adjusted for sex and duration of aspirin taken, all p values were two-sided, and all analyses were done with Stata (version 10).

This study is registered, ISRCTN 59521990.

### Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The contracts associated with the donations from manufacturers required that they had access to the results before submission with up to 90 days for assessment. JCM, MM, DTB, and JB had access to the raw data. JCM, DTB, and JB took responsibility for the decision to submit for publication.

### Results

Of the 937 eligible participants with Lynch syndrome who started the study, 463 were randomly assigned to receive resistant starch and 455 to receive resistant-starch placebo. The remaining 19 participants were randomly assigned to the aspirin or aspirin placebo intervention only and were excluded from this analysis (figure 1; appendix). There was no evidence of any interaction between the effects of aspirin and starch (Mantel-Haenszel  $\chi^2$  [1 degree of freedom] 0.02;  $p=0.9$ ), however, for completeness, we report the effects of resistant starch adjusted for aspirin usage.

More than half of participants were women (table 1). Long-term follow-up data were not available for 204 (22%) participants. Thus, for 714 participants, we report both on-trial information and longer follow-up information, whereas for 204 we report on-trial information only. Demographic data show that no differences occurred between those traced and not traced after the trial in this follow-up with respect to sex, randomisation category, or geographical location (data not shown). At the time of this analysis, eight (1%) participants were 10 years or longer from randomisation.

Median follow-up was 52.7 months (IQR 28.9–78.4; appendix). Since randomisation, 53 individuals—27 of those given resistant starch and 26 given resistant-starch placebo—developed 61 primary colorectal cancers (table 2, appendix). 45 of these patients had colorectal cancer detected during long-term follow-up (23 of those allocated resistant starch and 22 of those allocated resistant-starch placebo;  $\chi^2$  0.59;  $p=0.7$ ). The remaining eight participants diagnosed with colorectal cancer had information from the intervention phase only (five in those allocated to resistant starch and three in those allocated to resistant-starch placebo [ $\chi^2$  0.44;  $p=0.5$ ]). Of 746 patients with on-trial data, there were 25 patients with colorectal cancers who received resistant-starch placebo and 22 who received resistant starch ( $\chi^2$  0.62,  $p=0.7$ ).

For the period after randomisation, the HR for colorectal cancer in those randomly assigned to resistant starch was 1.40 (95% CI 0.78–2.56;  $p=0.26$ ) showing no

evidence for a protective effect of resistant starch (table 3, figure 2). The HR for colorectal cancer without adjusting for aspirin duration was similar (1.33, 0.73–2.41). The intention-to-treat analysis by the Poisson regression model that took into account the eight multiple primary participants with colorectal cancer (seven in the resistant-starch placebo group and one in the resistant-starch group) also showed no protective effect of resistant starch (table 3). There was no significant modification effect of aspirin taken on the estimated HR for resistant starch ( $p=0.89$ ) and the mean duration of aspirin use was similar for both resistant starch (25.0 months [SD 12.9])

For the study protocol see <http://www.capp3.org>

See Online for appendix

	Resistant starch	Resistant-starch placebo
Number of participants	463	455
Months on CAPP2 intervention study	24.4 (13.3–28.7)	24.6 (17.3–29.2)
Months since study entry	53.2 (29.4–83.2)	52.4 (28.7–74.6)
Number of participants with first colorectal cancer		
Since randomisation	27	26
Within 2 years of randomisation	10	10
More than 2 years from randomisation	17	16
Number of participants with other Lynch syndrome cancers*		
Since randomisation	17	26
Within 2 years of randomisation	6	9
More than 2 years from randomisation	11	17
Number of participants with one or more Lynch syndrome cancers (including colorectal cancer)		
Since randomisation	43	51
Within 2 years of randomisation	16	19
More than 2 years from randomisation	27	32
Number of participants with non-Lynch syndrome cancers	22	22

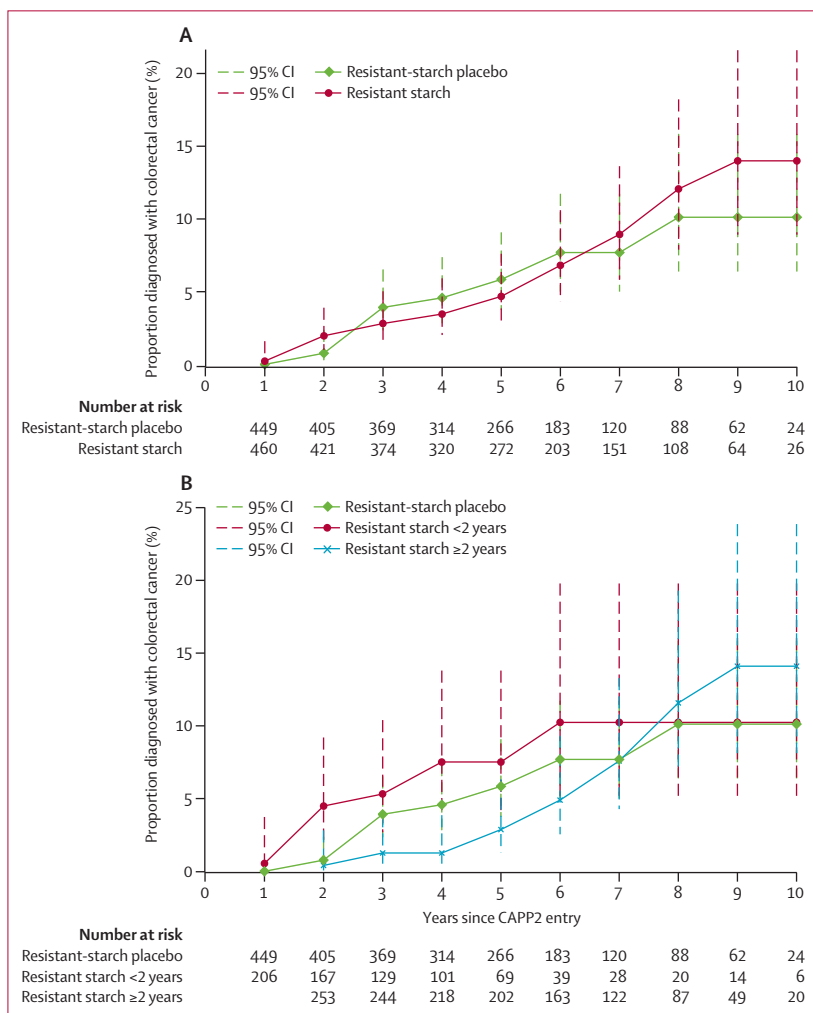
Data are number or median (IQR). \*Two participants (one in resistant-starch placebo group and one in resistant starch group) had colorectal cancer and another had a Lynch syndrome cancer. These two participants are counted in the rows relating to both colorectal cancer and other Lynch syndrome cancers but in the row relating to all Lynch syndrome cancers these participants are counted only once.

**Table 2: Duration of study and cancer burden according to intervention group**

	Hazard ratio*		Incidence rate ratio†	
	HR (95% CI)	p value	IRR (95% CI)	p value
Intention-to-treat analysis				
Resistant starch vs resistant-starch placebo	1.40 (0.78–2.56)	0.26	1.15 (0.66–2.00)	0.61
Per-protocol analysis				
Resistant-starch placebo	1.00	..	1.00	..
<2 years of resistant starch‡	2.38 (0.98–5.77)	0.05	1.59 (0.69–3.63)	0.27
≥2 years of resistant starch‡	1.09 (0.55–2.19)	0.80	0.98 (0.51–1.88)	0.95
Cumulative starch dose (units of 100 resistant starch)	1.01 (0.98–1.04)	0.56	1.00 (0.98–1.03)	0.72

\*Cox proportional hazards analysis based on 53 participants with colorectal cancer involving a total of 61 cancer diagnoses. †Incidence rate ratio from Poisson regression. ‡The threshold for 2 years intervention was consumption of more than 1400 starch packs; rounded down from a 2 year total of 1461 packs to allow for early scheduling of the exit colonoscopy, occasional missed dosage, or both.

**Table 3: Cox proportional hazards analysis and Poisson regression for colorectal cancer (adjusted for sex and duration of aspirin taken) based only on participants randomly assigned to resistant starch or resistant-starch placebo**



**Figure 2: Time to first colorectal cancer in participants randomly assigned to resistant starch versus those assigned to resistant-starch placebo**

Kaplan-Meier analysis, adjusted for sex (A). Kaplan-Meier analysis restricted to participants who had taken the intervention for 2 years or more, adjusted for sex (B). Each point on the plot shows the estimated cumulative incidence by years of follow-up together with the corresponding 95% CI. CAPP=Colorectal Adenoma/carcinoma Prevention Programme.

and resistant-starch placebo groups (25.0 months [SD 12.5]). Additionally, a simple comparison of effect of resistant starch in participants randomly assigned to aspirin showed no significant difference (HR 1.38, 95% CI 0.76–2.51).

We re-estimated the potential protective effect of resistant starch with a per-protocol analysis and obtained similar results. For this analysis, we defined 2 years intervention as consumption of 1400 packs (2x15 g a day); consumption was rounded down from a 2-year total (1461 packs) to allow for early scheduling of the exit colonoscopy, occasional missed dosage, or both. The HR for participants taking resistant starch for less than 2 years was 2.38 (95% CI 0.98–5.77; p=0.05), which suggested a possible adverse effect of shorter-term resistant starch treatment on incidence of colorectal

cancer (table 3, figure 2). By contrast, the HR for participants taking resistant starch for 2 years or more was 1.09 (0.55–2.19; p=0.80) and the IRR was 0.98 (0.51–1.88; p=0.95; table 3, figure 2).

A secondary analysis assessed other Lynch syndrome cancers (ie, all Lynch syndrome cancers except colorectal cancer). Of the participants who developed cancer at a Lynch syndrome site other than the colorectum, 17 were randomly assigned to resistant starch and 26 to placebo (table 2; appendix). The HR for participants randomly assigned to resistant starch was 0.72 (95% CI 0.38–1.35; p=0.30; table 4, appendix) compared with the resistant-starch placebo group. Endometrial cancer was the most common non-colorectal cancer; 21 participants had endometrial cancer of whom ten were randomly assigned to resistant starch and 11 to resistant-starch placebo (appendix). Of note, no participants assigned to resistant starch had pancreatic or small-bowel cancer compared with five cases of pancreatic cancer and three cases of small-bowel cancer in those randomly assigned to resistant-starch placebo. In view of the small numbers, this potential protective effect could be a chance observation. The per-protocol analysis showed that the HR for those allocated to resistant starch who took treatment for less than 2 years was 0.87 (95% CI 0.34–2.22; p=0.77) whereas for those taking resistant starch for 2 years or more the HR was 0.63 (0.28–1.40; p=0.26) with an IRR of 0.56 (0.26–1.23; p=0.15; table 4).

In analyses of all Lynch syndrome cancers including colorectal cancer, there was no evidence of a protective effect for resistant starch in either the per-protocol or intention-to-treat populations, nor when analysed by duration of treatment (table 5, figure 3). Cox proportional hazards models analysis by cumulative resistant starch consumption showed no evidence of a significant dose-response effect for colorectal cancer (p=0.56), non-colorectal Lynch syndrome cancers (p=0.21), or Lynch syndrome cancers overall (p=0.56; tables 3–5).

We have published a detailed analysis of the adenomas that were reported during the intervention phase of the CAPP2 study.<sup>20</sup> Where possible, details of adenoma development were also gathered by masked investigators in the post-intervention period. While incomplete, these data on 1068 colonoscopy reports showed no apparent effect of resistant starch on numbers of participants who developed adenomas subsequent to the intervention phase (ie, 114 reports of adenomas in each of the resistant starch and resistant-starch placebo groups from 558 and 488 colonoscopies, respectively [p=0.25]). No difference was seen in the number of colonoscopies in participants randomly assigned to resistant starch and to the corresponding placebo group (p=0.24; data not shown). Additionally, there was no evidence of an effect of resistant starch treatment on adenomas when the analysis was restricted to those on starch treatment for 2 years or more (p=0.25).

In view of the suggestion that the end product of resistant starch fermentation, butyrate, could have more potent antineoplastic effects on colon-cancer cells with dysfunction of the DNA mismatch repair gene *MLH1*,<sup>14</sup> the data were analysed according to the underlying mismatch repair gene defect and no effect was seen (appendix).

20 (32·8%) of the 61 colorectal cancers diagnosed in resistant starch or placebo groups were Dukes stage A, 25 (41·0%) were Dukes stage B, 12 (19·7%) were Dukes stage C and D, and four (6·6%) were unknown (appendix). 33 (54·1%) tumours were located in the ascending colon, transverse colon, and splenic flexure, six (9·8%) in the descending colon, 13 (21·3%) in the sigmoid and rectum, and nine (14·8%) were unknown (appendix). No significant differences in tumour staging ( $\chi^2$  [3 degrees of freedom] 6·73;  $p=0\cdot08$ ) and tumour location ( $\chi^2$  [3 degrees of freedom] 0·54;  $p=0\cdot91$ ) were seen between resistant-starch and resistant-starch placebo groups.

## Discussion

To the best of our knowledge, our report is the first randomised trial to assess the effectiveness of dietary-fibre treatment (provided as a resistant-starch supplement) on carcinoma in human beings (panel). A recent meta-analysis of 21 prospective observational studies showed a significant protective effect of dietary-fibre intake against colorectal cancer (RR per 10 g a day increase 0·90, 95% CI 0·86–0·94).<sup>2</sup> An earlier pooled analysis of prospective cohort studies<sup>25</sup> showed no effect of dietary fibre on risk of colorectal cancer after adjusting for other dietary factors but that analysis included fewer studies and fewer cases of colorectal cancer and had a narrower geographical reach compared with the recent systematic review and meta-analysis by Aune and colleagues.<sup>2</sup> Previous randomised trials with occurrence of further adenoma as an outcome have not detected any benefit of increased intake of dietary fibre. These included studies with supplements of ispaghula husk<sup>26</sup> and cereal fibre<sup>27</sup> and studies in which participants were counselled to increase intake of fibre-rich foods.<sup>28,29</sup> The lack of benefit associated with increased intake of dietary fibre in these studies led to questions about the usefulness of adenoma recurrence as the primary surrogate endpoint in colorectal cancer chemoprevention research.<sup>30,31</sup> The CAPP2 study has provided experimental support for this scepticism since we reported no effect of aspirin treatment on neoplasia (principally adenomas) during the intervention phase of the study<sup>20</sup> but significant protection against carcinoma in longer-term follow-up.<sup>21</sup>

A limitation of the present study is that lack of resources has restricted longer-term follow-up of all CAPP2 participants. This loss to follow-up was concentrated in centres that had insufficient staff resources to allow long-term follow-up of all the study participants. Since randomisation to treatment was stratified within geographical location, it is unlikely that

	Hazard ratio*		Incidence rate ratio†	
	HR (95% CI)	p value	IRR (95% CI)	p value
Intention-to-treat analysis				
Resistant starch vs resistant-starch placebo	0·72 (0·38–1·35)	0·30	0·71 (0·38–1·32)	0·28
Per-protocol analysis				
Resistant-starch placebo	1·00	..	1·00	..
<2 years of resistant starch‡	0·87 (0·34–2·22)	0·77	1·02 (0·42–2·51)	0·96
≥2 years of resistant starch‡	0·63 (0·28–1·40)	0·26	0·56 (0·26–1·23)	0·15
Cumulative starch dose (units of 100 resistant starch)	0·98 (0·94–1·01)	0·21	0·98 (0·94–1·01)	0·17

\*Cox proportional hazards analysis based on 43 participants with non-colorectal Lynch syndrome cancers involving a total of 46 cancer diagnoses. †Incidence rate ratio from Poisson regression. ‡The threshold for 2 years intervention was consumption of more than 1400 starch packs; rounded down from a 2-year total of 1461 packs to allow for early scheduling of the exit colonoscopy, occasional missed dosage, or both.

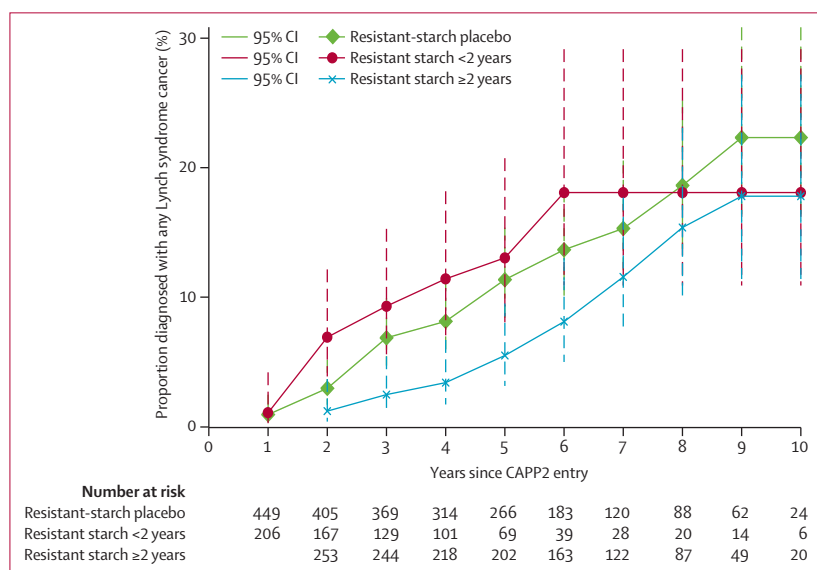
**Table 4: Cox proportional hazards analysis and Poisson regression for non-colorectal Lynch syndrome cancers (adjusted for sex and duration of aspirin taken) based only on participants randomly assigned to resistant starch or resistant-starch placebo**

	Hazard ratio*		Incidence rate ratio†	
	HR (95% CI)	p value	IRR (95% CI)	p value
Intention-to-treat analysis				
Resistant starch vs resistant-starch placebo	1·02 (0·66–1·57)	0·94	0·93 (0·62–1·39)	0·72
Per-protocol analysis				
Resistant-starch placebo	1·00	..	1·00	..
<2 years of resistant starch‡	1·45 (0·77–2·73)	0·26	1·29 (0·70–2·36)	0·41
≥2 years of resistant starch‡	0·83 (0·49–1·40)	0·48	0·77 (0·47–1·26)	0·30
Cumulative starch dose (units of 100 resistant starch)	0·99 (0·97–1·02)	0·56	0·99 (0·97–1·01)	0·52

\*Cox proportional hazards analysis based on 94 participants with Lynch syndrome cancers involving a total of 107 cancer diagnoses. †Incidence rate ratio from Poisson regression. ‡The threshold for 2 years intervention was consumption of more than 1400 starch packs; rounded down from a 2-year total of 1461 packs to allow for early scheduling of the exit colonoscopy, occasional missed dosage, or both.

**Table 5: Cox proportional hazards analysis and Poisson regression for all Lynch syndrome cancers (adjusted for sex and duration of aspirin taken) based only on those randomly assigned to resistant starch or resistant-starch placebo**

any systematic bias exists in loss to follow-up. We examined the numbers of colorectal cancer that occurred during the intervention phase of the study and the follow-up phase, separately, and found no evidence to suggest that loss of cancer data due to failure to follow-up patients was different between those randomly assigned to resistant starch or to placebo; there was also no effect of duration of taking resistant starch. Thus we conclude that there was no evidence for a protective effect of resistant starch even in those participants who were most compliant. We do not have data for intake of dietary fibre for our study participants. However, geographical location is a crude surrogate for dietary and other lifestyle exposures. We randomised participants to treatment within geographical regions. We found that adjusting our analysis for region as well as for sex and aspirin duration gave a hazard ratio of 1·44 (95% CI 0·79–2·62),



**Figure 3: Time to first Lynch syndrome cancer in participants randomly assigned to resistant starch versus those assigned to resistant-starch placebo**

Kaplan-Meier analysis was restricted to participants who had taken the intervention for 2 years or more and the analysis was adjusted for sex. Each point on the plot shows the estimated cumulative incidence by years of follow-up together with the corresponding 95% CI. CAPP=Colorectal Adenoma/carcinoma Prevention Programme.

syndrome cancers. Per-protocol analysis suggested higher risk of colorectal cancer in those taking resistant starch for less than 2 years, but this effect is probably due to chance observation because no effect was seen in participants taking resistant starch for 2 years or more (table 3). We cannot exclude the possibility that resistant starch could have a small positive effect that we did not have the power to detect. A recent meta-analysis of the protective effects of dietary fibre against colorectal cancer suggests an estimated 10% reduction in colorectal-cancer risk.<sup>2</sup> The 30 g a day source of resistant starch used in the CAPP2 study provides 13.2 g resistant starch, which reaches the large bowel and is classed as dietary fibre.<sup>20</sup> On this basis, the resistant starch might have reduced colorectal risk by 8–18%, which is within the 95% CI of our intention-to-treat analysis (table 2). This lack of detectable effect of resistant starch on risk of colorectal cancer contrasts with the weight of observational studies showing a protective effect of higher intakes of dietary fibre but is consistent with the findings from randomised trials<sup>26–29</sup> of increased intake of dietary fibre with occurrence of new colorectal adenoma as surrogate outcome. The effects of resistant starch in carriers of hereditary colorectal cancer could be different from those in the general population and this remains to be tested. Additionally, observational studies might be affected by confounding or the apparent protection afforded by higher intakes of dietary fibre could reflect the health benefit of the dietary patterns (or whole lifestyles) adopted by such consumers rather than the specific antineoplastic effects of the carbohydrates measured as dietary fibre. Evidence shows that the individual carbohydrates (and associated food components) quantified as dietary fibre have highly characteristic physicochemical properties and very different effects on both fermentation in the large bowel and on function of the bowel mucosa.<sup>3</sup> As a consequence, emulation of the effects of naturally occurring dietary fibre in plant-rich diets by a single type of polysaccharide, such as resistant starch, is unlikely.<sup>1,32</sup> We are undertaking several secondary analyses, including investigation of effects of smoking behaviour and of adiposity on risk of colorectal cancer in patients with Lynch syndrome in the CAPP2 study, which will be reported elsewhere.

In conclusion, we found no evidence that supplementation with 30 g a day of resistant starch affected development of colorectal cancer in carriers of hereditary colorectal cancer, although effects in the general population remain to be tested. Our study shows that supplementation with resistant starch does not emulate the apparently protective effect against colorectal cancer of diets rich in dietary fibre, which has been shown in many, but not all, observational studies. From a public health perspective, eating more of a variety of food rich in dietary fibre including wholegrains, vegetables, fruits, and pulses is a preferable strategy for reducing cancer risk.

## Panel: Research in context

### Systematic review

We searched PubMed for articles on use of dietary fibre or resistant starch as a bowel cancer, hereditary colorectal cancer, and Lynch syndrome chemopreventive agent published up to Feb 10, 2012. Our search terms were “colorectal cancer” OR “bowel cancer” AND “prevention” AND “fibre” with the search restricted to randomised trials. Additionally, we replaced “fibre” with “fiber” or with “starch”. Systematic reviews by other investigators had revealed compelling evidence for the protective effect of dietary fibre against sporadic bowel cancer in observational studies. Resistant starch, a dietary starch fraction that is not digested in the small bowel, is a specific form of dietary fibre. Our search of published works showed that no previous randomised trials have tested the efficacy of resistant starch in patients with Lynch syndrome with cancer as the primary endpoint.

### Interpretation

We found no evidence that dietary supplementation with resistant starch affected risk of colorectal cancer in carriers of hereditary colorectal cancer. The lack of effect of resistant starch shows that this supplement does not emulate the apparently protective effect of diets rich in dietary fibre against colorectal cancer, at least in patients with Lynch syndrome. The effect of resistant starch on risk of bowel cancer in the general population remains to be tested.

which suggests that lifestyle factors do not play a major role in modifying the response to resistant starch.

A strength of the present study was that we used patients with Lynch syndrome due to a genetic defect in DNA mismatch repair as a sensitive model, which can show the effectiveness of chemoprevention agents (aspirin) on colorectal cancer and carcinoma at other sites.<sup>21</sup> The intention-to-treat analysis showed no effect of resistant starch on colorectal cancer or on other Lynch

### Contributors

JB, DTB, and JCM designed the study, acquired study funding, managed the study, archived, analysed, and interpreted the data, and wrote the report. MM analysed the data, and prepared the tables and figures. FE analysed the data. GB was the study administrator. RF did participant genotyping. HL was chair of International Advisory Committee. FM, J-PM, GM, SO, DE, GE, ERM, LB, M-LB, MD, JWCH, SH, AL, JL, PJM, VM, RR, LS, RJS, HJWT, HV, A-MG, GC, KP, and JW recruited participants and gathered data.

### Conflicts of interest

We declare that we have no conflicts of interest.

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