

THE LANCET

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Burn J, Gerdes A-M, Macrae F, et al, on behalf of the CAPP2 Investigators. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 2011; published online Oct 28. DOI:10.1016/S0140-6736(11)61049-0.

Supplementary Table 1. Study population in detail based on initial randomization to different intervention groups

| | Included in this analysis (n=861 i.e. 427 + 434) | | | | Excluded from this analysis | |
|-------------|--|-----|----------------------|-----|--|----|
| | Aspirin | | Aspirin Placebo (AP) | | Randomised to Resistant Starch (RS) or Resistant Starch Placebo (RSP) only | |
| | Aspirin and RS | 214 | RS and AP | 208 | RS only | 41 |
| | Aspirin and RSP | 204 | RSP and AP | 216 | RSP only | 35 |
| | Aspirin only | 9 | AP only | 10 | | |
| Total (937) | | 427 | | 434 | | 76 |

Supplementary Table 2: The distribution of Serious Adverse Events by randomization group to aspirin intervention on intervention phase

| | Aspirin N (427) | AP N (434) |
|-----------------------------------|--------------------|---------------|
| Probable or possible peptic ulcer | 7 | 8 |
| Cerebrovascular events | 2 | 1 |
| Cardiovascular events | 1 | 5 |
| Deep Venous thrombosis | 2 | 0 |
| Major other | 4 | 9 |
| Minor Other including bleeding | 5 | 1 |
| TOTALS | 21 | 24 |

Supplementary table 2 continued: Detailed breakdown of Serious Adverse Events

| | | |
|--|---|---|
| Abdominal abscess | 0 | 0 |
| Acute cholecystitis | 1 | 1 |
| Anaemia | 1 | 0 |
| Anal epithelioma | 0 | 1 |
| Aspergillosis | 1 | 0 |
| Atrial fibrillation | 0 | 0 |
| Black stools | 1 | 1 |
| Bladder stone | 0 | 1 |
| Bleeding from femoral artery | 1 | 0 |
| Breast cancer | 1 | 2 |
| Caecal spirochaetosis | 0 | 0 |
| Cardiac pain | 0 | 1 |
| Cellulitis in leg | 0 | 0 |
| Cerebral haemorrhage | 0 | 0 |
| Cerebral vasculitis | 0 | 1 |
| Coronary arterial stenosis | 0 | 1 |
| Coronary thrombosis | 1 | 0 |
| Died (before receiving therapy) | 0 | 0 |
| Duodenal ulcers | 3 | 3 |
| Deep venous thrombosis | 2 | 0 |
| Endophlebitis | 0 | 0 |
| Failure of anal stoma repair to heal | 0 | 1 |
| Gastric ulcer | 0 | 1 |
| Gastritis | 0 | 1 |
| Gastrointestinal bleed | 1 | 1 |
| Gum bleeding | 1 | 0 |
| Hernia with gastric reflux | 0 | 0 |
| Hip replacement | 0 | 1 |
| Liver cancer | 1 | 0 |
| Lung sarcoidosis | 0 | 1 |
| Malignant melanoma | 1 | 0 |
| Meningioma brain tumour | 0 | 1 |
| Myocardial infarction | 0 | 2 |
| Numbness on one side of body | 0 | 1 |
| Operation to close abdominal jejunostomy | 0 | 1 |
| Pancreatic cyst | 0 | 1 |
| Hysterectomy | 0 | 1 |
| Pre-tracheal lymphoma | 0 | 1 |
| Prostate cancer | 1 | 0 |
| Pyelonephritis | 0 | 0 |
| Rectal bleed | 1 | 1 |
| Severe nose bleed | 1 | 0 |
| Spinal canal stenosis | 0 | 1 |
| Stroke | 2 | 0 |
| Testicular mass | 0 | 1 |
| Vaginal bleeding | 1 | 0 |
| Ventricular fibrillation | 0 | 1 |

Supplementary Table 3. Demographic details for those with follow-up information showing time on study in months

| | Participants with further long-term follow up data | Participants without long-term follow up data | Total |
|---|---|--|-------------------------|
| Number of participants | 671 | 190 | 861 |
| Time on CAPP2 intervention study mean (sd) (range) | 27.0 (13.0) (1.1, 74.4) | 18.6 (12.9) (0.8, 60.6) | 25.2 (13.4) (0.8,74.4) |
| 0-23 months | 186 (27.7%) | 115 (60.6%) | 301 (35.0%) |
| 24-47 months | 395 (58.9%) | 66 (34.7%) | 461 (53.5%) |
| 48+ months | 90 (13.4%) | 9 (4.7%) | 99 (11.5%) |
| Time since study entry mean (sd) (range) | 66.1 (26.8) (2.5, 128) | 18.6 (12.9) (0.8, 60.6) | 55.7 (31.4) (0.8,128) |
| 0-23 months | 28 (4.2%) | 117 (61.6%) | 145 (16.8%) |
| 24-47 months | 123 (18.3%) | 64 (33.7%) | 187 (21.7%) |
| 48-59 months | 126 (18.8%) | 8 (4.2%) | 134 (15.6%) |
| 60+ months | 394 (58.7%) | 1 (0.5%) | 395 (45.9%) |
| Age at recruitment mean (sd) (range) | 44.7 (10.6) (24.7, 75.5) | 43.0 (10.7) (21.5, 77.9) | 44.3 (10.6) (21.5,77.9) |
| 21-36 years | 159 (23.7%) | 56 (29.5%) | 215 (25%) |
| 37-45 years | 166 (24.8%) | 49 (25.8%) | 215 (25%) |
| 46-53 years | 170 (25.3%) | 45 (23.7%) | 215 (25%) |
| 54- 78 years | 176 (26.2%) | 40 (21.0%) | 216 (25%) |

Supplementary Table 4. Number of years until first colorectal cancer diagnoses by years since randomization for those with a CRC diagnosis

| Years Since randomization | Randomized to aspirin (N=427) | Randomized to AP (N=434) | Randomized to RS or RSP only (N=76)* |
|----------------------------------|--------------------------------------|---------------------------------|---|
| 0-1 | 1 | 0 | 0 |
| 1-2 | 5 | 6 | 0 |
| 2-3 | 5 | 7 | 2 |
| 3-4 | 1 | 1 | 2 |
| 4-5 | 2 | 3 | 1 |
| 5-6 | 1 | 4 | 2 |
| 6-7 | 1 | 2 | 0 |
| 7-8 | 1 | 4 | 0 |
| 8-9 | 1 | 1 | 0 |
| 9-10 | 0 | 0 | 0 |
| 10-11 | 0 | 2 | 0 |
| Total | 18 | 30 | 7 |

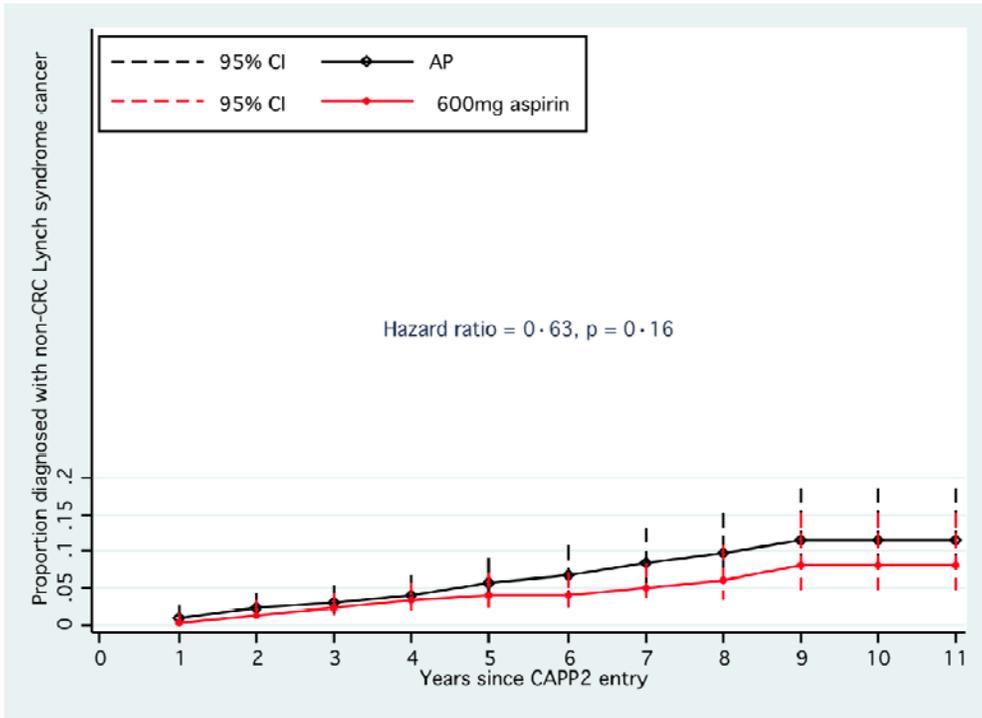
** This group was not included in the analysis for this study.*

Supplementary Table 5. Distribution of Lynch Syndrome related cancers

| | Randomized to aspirin (N=427) | Randomized to AP (N=434) | Randomized to RS or RSP only (N=76)* | Total |
|--|-------------------------------|--------------------------|--------------------------------------|-------|
| Participants with cancer attributed to Lynch Syndrome | | | | |
| Colorectal cancer | 18 | 30 | 7 | 55 |
| Other Lynch Syndrome cancers: | 16 | 22 | 4 | 42 |
| - Endometrial | | | | |
| - Pancreas | 5 | 13 | 3 | 21 |
| - Ureter | 3 | 2 | 0 | 5 |
| - Brain | 2 | 1 | 0 | 3 |
| - Small Bowel | 2 | 0 | 0 | 2 |
| - Gastric | 0 | 2 | 1 | 3 |
| - Cholangiocarcinoma | 0 | 2 | 0 | 2 |
| - Kidney | 1 | 0 | 0 | 1 |
| - Ovarian | 0 | 1 | 0 | 1 |
| | 3 | 1 | 0 | 4 |
| TOTAL | 34 | 52 | 11 | 97 |

* This group was not included in the analysis for this study.

Supplementary figure 1. Kaplan-Meier function of time to first non-CRC Lynch syndrome cancer comparing those randomized to aspirin with those randomized to aspirin placebo (AP) adjusted for gender. Each point on the plot shows the estimated cumulative incidence by years of follow-up together with the corresponding 95% confidence interval.



Supplementary Table 6 CRC by participants' molecular diagnosis

| Gene Status | CRC not detected N(%) | CRC diagnoses* N(%) | Total |
|------------------------------|----------------------------------|--------------------------------|--------------|
| Clinical diagnosis | 156 (96) | 7 (4) | 163 |
| <i>MSH2</i> mutation carrier | 264 (93) | 20 (7) | 284 |
| <i>MLH1</i> mutation carrier | 436 (94) | 28 (6) | 464 |
| <i>MSH6</i> mutation carrier | 26 (100) | 0 (0) | 26 |
| Total | 883 (94) | 55 (6) | 937 |

**Includes 7 cases with CRC randomized to RS or RSP only*