The long term impact of aspirin on cancer risk in carriers of hereditary colorectal cancer: the CAPP2 Randomised Controlled Trial

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*A full list of CAPP2 investigators can be found in the Appendix
ABSTRACT

Background Observational studies report reduced colorectal cancer (CRC) among regular aspirin consumers. Randomized controlled trials (RCTs) have demonstrated adenoma reduction but none targeted CRC prevention as primary endpoint.

Methods The CAPPI2 RCT investigated the anti-neoplastic effects of 600mg aspirin and/or 30g of the resistant starch (RS) Novelose for up to 4 years in 937 carriers of Lynch Syndrome (LS), the major form of hereditary colorectal cancer, randomized in blocks of 16 in a 2x2 factorial design with provision for optional single agent randomization and prolonged post intervention double blinded surveillance. At completion of intervention, mean duration 29 months, there was no evidence of effect on adenoma or carcinoma development for either agent among the 746 for whom an exit colonoscopy was recorded. We now report on the primary endpoint of cancer development among those randomized for aspirin in the RCT.

Results Despite surveillance colonoscopy with polypectomy (mean 55.7 months), 48 participants developed 53 primary CRCs (18/427 randomized to aspirin, 30/434 to aspirin placebo). Intention to treat analysis (ITT) of time to first CRC showed a hazard ratio (HR) of 0.63 (95% CI 0.35-1.13, p=0.12). Poisson regression taking account of the multiple primary events gave an Incidence Rate Ratio (IRR) of 0.56 (CI 0.32-0.99, p=0.05). For those completing 2 years intervention, per protocol analysis yielded a HR of 0.41 (CI 0.19-0.86, p=0.02) and an IRR of 0.37 (CI 0.18-0.78, p=0.008). Secondary analysis revealed fewer LS-related cancers in those on aspirin for at least two years (IRR = 0.42 CI 0.25-0.72, p=0.001). There was a negative association of LS cancer incidence with number of aspirin taken (p=0.002).

Interpretation 600mg aspirin/day for a mean of 25 months halved cancer incidence after 55.7 months in carriers of hereditary colorectal cancer. Further studies are needed to establish the optimum dose and duration of aspirin treatment.

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300 words
Introduction

People with monogenic predisposition to cancer offer an ideal focus for chemoprevention trials; the high probability of early tumours provides statistical power and knowledge of genetic basis reduces heterogeneity while providing data relevant to those whose sporadic cancers involve the same molecular pathway. Existing planned surveillance reduces cost and the relevance to family members encourages patient compliance. The Colorectal Adenoma/carcinoma Prevention Programme (CAPP) was launched in 1990. CAPP1 investigated 200 young people with Familial Adenomatous Polyposis. CAPP2, the first large-scale genetically targeted chemoprevention trial, was focused on 1000 people with Lynch syndrome (LS) (also known as hereditary non polyposis colon cancer, HNPCC), the majority carrying pathological DNA mismatch repair (MMR) gene variants plus previously affected persons within families meeting the “Amsterdam criteria”.¹

Both trials used a factorial 2x2 design to assess two agents, aspirin and resistant starch (RS), thought to protect against colorectal cancer (CRC). CAPP1 revealed a weakly significant impact of aspirin on size of largest observed polyp and a significant reduction in crypt length in those given RS². In CAPP2 over 6 years, 937 people from 43 international centers commenced intervention.³ After intervention, mean 29 months, there was no evidence that either agent influenced development of colonic neoplasia, with most lesions being adenomas.³ Given cohort and case-control evidence of a CRC protective effect of aspirin only after prolonged exposure⁴, the original design of the CAPP2 Study included double blind post-intervention follow-up for at least 10 years.
At the end of the intervention period\textsuperscript{3} 128 persons had developed at least one adenoma and 23 had developed CRC. These were pooled for analysis as “neoplasia” since it was considered unlikely that the primary endpoint of CRC would be influenced within 4 years in a population under colonoscopic surveillance. We now report the effect of aspirin on the incidence of CRC, the primary CAPP2 outcome, and other LS cancers as secondary outcomes. The baseline population of 861 persons (randomized to aspirin or aspirin placebo in the RCT) differs from our first report, which was confined to those with an exit colonoscopy.

**Methods**

Between 1999 and 2005, 937 participants started intervention in the CAPP2 Study\textsuperscript{3,5} and 746 were included in the end of intervention analysis (mean 29 months). The study had a preplanned design for 10 years follow-up; at the time of this analysis, the earliest enrolled participants had reached the 10 year threshold. Of the 937 persons, 427 were randomized to aspirin, 434 to aspirin placebo (AP) and the remaining recruits were not randomized for the aspirin intervention having opted not to participate in this study limb (N=76; almost all due to perceived aspirin sensitivity or history of peptic ulceration). All participants in this latter group were randomized to the RS or Resistant Starch Placebo (RSP) intervention only (Figure 1; Consort diagram; Supplementary Table 1).

Analysis focuses on 861 CAPP2 participants randomized to aspirin or AP from entry until the latest date for which the recruiters had information on cancer diagnosis, a time-point usually corresponding to the date of last surveillance attendance. Our analysis includes i) the LS syndrome cancers included in the earlier report\textsuperscript{3} ii) those that occurred
subsequent to exit from the intervention phase and iii) all cancers that occurred in persons without an exit colonoscopy which excluded them from the statistical analysis in our earlier report.³

Due to dispersed international recruitment and because routine surveillance was provided by local healthcare teams, records of adenoma occurrence among CAPP2 participants subsequent to the intervention phase are incomplete. Similarly, no details of adverse events are available post-intervention; during the intervention phase adverse events in the aspirin and placebo groups were similar³ (Supplementary Table 2). There was also no significant difference in compliance (i.e. proportion of scheduled tablets not taken during the intervention phase) between the aspirin and AP groups for those with complete intervention phase data (Chi-squared (1) = 1·27, p=0·20).³

**Statistical analysis**

Analysis was designed to test the primary hypothesis that aspirin would reduce the development of CRC (as primary outcome) and LS cancers (as secondary outcome) in 861 persons randomized to aspirin (427) or AP (434). The original protocol invited participants to continue with the original intervention for a further 2-year cycle following the initial 2 years.

Two approaches were taken: time to first CRC occurrence (our original focus) examined using life-table methods and Cox proportional hazards and second, Poisson regression modeling to investigate primary cancers at multiple anatomical sites, a feature of LS. Poisson regression analysis takes into account the complete cancer history of the
participant since randomization in contrast with the more restricted time to first event analysis.

For life-table analysis, end of follow-up was determined as (i) the time of first CRC diagnosis, if affected, or (ii) the last recorded date at which the clinical status was known. Analyses included Cox proportional hazards models to estimate gender-adjusted Hazard Ratios (HR) and 95% Confidence Intervals and Kaplan-Meier curves to assess non-parametrically the outcome differences between the aspirin and AP interventions. The assumption of proportional hazard was tested to assess compliance.

For the Poisson regression analysis, Incidence Rate Ratios (IRR) for the effect of aspirin adjusted for gender were estimated from log-linear models for the number of primary cancers diagnosed after randomization; exposure time being that from randomization until date of last known clinical status.

All analyses used Stata v10. Analyses were conducted on the basis of “Intention to Treat” (i.e. intervention assigned at randomization) and also “Per Protocol” (restricting consideration to those taking aspirin (or AP) for at least 2 years) as defined in the protocol. A secondary planned analysis addressed the category of “LS cancer incidence” including new cancers considered to result from the underlying genetic defect. Designation of LS cancer spectrum was a clinical assessment, blinded to intervention, and based on a review of the LS phenotype; endometrial, ovarian, pancreatic, small bowel, gall bladder, ureter, stomach and kidney cancers and cancer of the brain were included. A final analysis examined the total burden of LS related cancers in those who had been on intervention for at least 2 years (per protocol).
All p-values are reported 2-sided (in keeping with the original sample size calculation).

Results

Recruitment ran from 1999 to 2005. The mean observation period was 55.7 months (range 1-128 months) and 1% of recruits were ≥ 10 years from randomization by the time of the current analysis (Table 1). Times are measured from the date of randomization.

For 671 persons, we report both “on trial” information and longer follow-up information whereas for 190 we report “on trial” information only (Supplementary Table 3).

Demographic data indicate no differences between those traced and not traced in this follow-up in respect of age, gender, randomization category, or geographical location (data not shown) though it is plausible that the development of a cancer made follow-up reporting more complete. There were no significant regional differences in CRC incidence (data not shown, Chi-squared (2) = 5.03, p=0.08).

Overall, 40 people were diagnosed with CRC among those with post intervention information (13/342 allocated to aspirin and 27/329 allocated to AP). Another 8 CRC occurred among 190 (83 male and 107 female) individuals with intervention phase only information, (5/85 and 3/105 for aspirin and AP arm respectively) (Figure 1).

Evidence has emerged of delayed protection by aspirin against cancer. Despite regular colonoscopy and polyp removal, 48 recruits developed CRC after randomization (Table 1; Supplementary Table 4). Of these, 18 received aspirin and 30 received AP. For the whole post-randomization period, the HR for CRC for aspirin was 0.63 (CI 0.35-1.13, p=0.12) favouring protection in the aspirin group (Table 2a; Figure 2a). Five of the 48 people who developed CRC each had 2 primary colon cancers. Of these, one had
received aspirin and 4 AP. Although the Intention to Treat time-to-event analysis showed a non-significant protective effect of aspirin, the Poisson regression taking into account the five multiple primary CRC participants (53 CRC) indicated a protective effect: IRR 0·56 (CI 0·32-0·99, p=0·05). Because of this protective effect we re-estimated the protective effect with a Per Protocol analysis and obtained similar results.

We examined outcomes in those participants who took aspirin (or AP) for a minimum of 2 years defined as consumption of 1,400 (300mg) tablets; rounded down from a 2 year total (1461 tablets) to allow for early scheduling of the exit colonoscopy and/or occasional missed dosage. Based on this definition, 258 (30%) and 250 (29·1%) participants took aspirin and AP respectively for ≥ 2 years. The HR for those taking aspirin for ≥ 2 years was 0·41 (CI 0·19-0·86 p=0·02, Table 2a; Figure 2b) and the IRR, 0·37 (CI 0·18 – 0·78 p= 0·008). These results are similar to those for Poisson regression in the ITT analysis.

We explored the effect of compliance on outcome (important because noncompliance may be related to factors that also affect CRC risk) using Per Protocol analysis, and found those who took aspirin for ≥ 2 years had an incidence rate of 0·06 per 100 person-years compared with 0·13 per 100 person years among those who took aspirin < 2 years. A similar analysis within the placebo group found no significant difference in CRC incidence between those who took AP for ≥ 2 years (0·14 per 100 person years) compared with those took AP for < 2 years (0·10 per 100 person years)
The planned secondary analysis with other LS cancers as the secondary outcome also showed a trend to protection with aspirin; 18 participants developed endometrial cancer of whom 5 were randomized to aspirin and 13 to AP. In total, 38 participants developed cancer at a site other than the colorectum (additionally 2 participants had CRC and another LS cancer) of whom 16 were randomized to aspirin and 22 to AP (Supplementary Table 5). The HR for those randomized to aspirin was 0·63 (CI 0·34-1·19 p=0·16, Table 2b; Supplementary Figure 1) and IRR was 0·63 (CI 0·34-1·16 p=0·14) compared with AP group. Per Protocol analysis showed that the HR for those who had taken aspirin for \( \geq 2 \) years was 0·47 (CI 0·21-1·06 p=0·07) with IRR =0·49 (CI 0·23-1·05 p=0·07) (Table 2b).

Table 2c gives the combined analysis of all LS cancers including CRC. On intention to treat analysis, the HR was 0·65 (CI 0·42-1·00 p=0·05 and IRR was 0·59 (CI 0·39-0·90 p=0·01) while the Per Protocol analysis HR was 0·45 (CI 0·26-0·79 p=0·005, Figure 3) and IRR was 0·42 (CI 0·25-0·72, p=0·001) supporting the protective effect of aspirin. Cox proportional hazards models analysis by cumulative aspirin consumption suggested a dose-response effect which was significant for non-CRC LS cancers (p=0·03), LS cancers overall (p=0·007) and a trend for CRC (p=0·06, Tables 2a-c). Corresponding outcomes from the Poisson regression analysis were also significant (p=0·03 for non-CRC LS cancers, p=0·002 for LS cancers overall and p=0·03 for CRC).

The CAPP2 study included a group of participants who chose not to be randomized for aspirin and who were randomized for the starch arm only. To see if the apparent protective effect of aspirin might be due to unexpectedly high numbers of cancers in the AP group, we tested the risk of CRC for the non-randomized group (RS or RSP only)
compared with the AP group. The CRC HR in this group was 1·4 times higher compared with AP (not statistically significant (p=0·4)). This gives further support to the protective effect of aspirin.

Where possible, details of adenoma development were collected in the post-intervention period. While incomplete, these data, gathered by blinded contributors’ revealed no apparent effect of aspirin on numbers of participants who developed adenomas subsequent to the intervention phase i.e. 51 and 48 in the aspirin and AP groups respectively.

The data were analyzed according to the underlying MMR gene defect; CRC was reported with equal frequency in those carrying \textit{MLH1} and \textit{MSH2} mutations (6·0% and 7·0% respectively) while none of the \textit{MSH6} mutation carriers developed CRC - in keeping with the anticipated milder phenotype (Supplementary Table 6). The remaining 163 recruits were diagnosed on the basis of Amsterdam Criteria\textsuperscript{1} and had been treated for a LS-related neoplasia. Of these 7 (4·3%) developed CRC. Overall, there was no evidence of difference in CRC incidence by presence of proven germ-line mutation (Chi-squared (2) = 3·1, p=0·38).

Eighteen (34%) of 53 CRC diagnosed in aspirin or AP arms were Dukes stage A, 21 (39·6%) Dukes B, 10 (18·9%) had Dukes C and D, and 4 (7·5%) were unknown. Twenty-seven (51%) tumours were located in the ascending colon, transverse colon and splenic flexure, 6 (11·3) % in the descending colon, 12 (22·6 %) in the sigmoid and rectum, and 8 (15.1%) were unknown. There was no significant difference in staging (Chi-squared (3) = 2·92, p=0·40) and tumour location (Chi-squared (3) = 0.08, p=0·99) between aspirin and AP groups.
Discussion

The CAPP2 Study is the first double blind RCT of aspirin chemoprevention with cancer as primary endpoint. The outcome is consistent with (i) over 2 decades of observational data showing CRC risk is halved in regular aspirin consumers \(^7\) and (ii) recent long term follow-up of aspirin trials for cardiovascular disease (CVD) prevention which found that dosing with \(\geq 75\text{mg aspirin/d}\) for several years resulted in fewer deaths from gastrointestinal cancers, particularly involving the proximal colon.\(^8\, 9\) This concept of delayed cancer chemoprevention was apparent in observational studies, where protection against cancer among regular aspirin users took approximately 10 years to emerge\(^4\, 7\). It was presumed that this effect was dependent on continued aspirin exposure but in the CVD trials trial medication ended at mean 6 years. Analysis of cancer related death in 8 trials\(^10\) revealed significant protection in those allocated aspirin for \(\geq 4\) years but only when followed for a further 5 years. Our observations support this hypothesis of a delayed effect of aspirin on CRC by showing that aspirin reduced CRC incidence with the effect becoming apparent after 3-4 years from beginning aspirin intervention, a difference consistent with faster cancer development in those with LS\(^11\, 12\).

In ITT analysis, Poisson regression analysis, which incorporates more of the follow-up information than the time-to-event analysis (i.e. total number of cancers in follow-up period v. time to first cancer), showed similar estimates of the protective effect but, as anticipated greater significance with the Poisson regression. The Per Protocol analysis showed a similar effect.
In keeping with our observed impact of aspirin on non-colonic LS cancers (endometrial cancer, ovarian cancer, pancreatic cancer, and cancer of the brain, small bowel, gall bladder, ureter, stomach and kidney) (Table 2b), Rothwell et al. 10 reported that aspirin treatment reduced risk of death from several non-colonic solid cancers including oesophageal, pancreatic, brain, lung, stomach and prostate. It is not clear whether LS cancers are more responsive to aspirin therapy. In CAPP2 “non-LS” extra-colonic cancers appeared unaffected by aspirin intervention (Table 1) but this may change with longer follow-up. A weakness of our international study was the inability to collect a comprehensive series of tumor blocks in which to confirm that tumour development was related to the germline MMR mutation.

Our discovery of substantial protection by aspirin against CRC and other LS cancers is in striking contrast with our earlier report3 of no effect of aspirin on large bowel neoplasia. Taken together, these findings may help explain the marked disparity between the 50% cancer reduction reported in observational studies and the outcomes of randomized adenoma prevention trials which have demonstrated, at best, a modest reduction effect; meta-analysis revealed a pooled risk ratio of any adenoma for any dose of aspirin versus placebo of 0·83 (95% CI = 0·72 to 0·96)13. Our recent CAPP1 report2 based on carriers of familial adenomatous polyposis, revealed a small effect of aspirin on adenoma progression but no demonstrable effect on polyp number, albeit using insensitive methods of analysis. In the light of the CAPP2 findings it will be interesting to revisit the CAPP1 participants to see if aspirin has long term effects on their disease progression. Important questions include i) does aspirin target the minority of adenomas with the
greatest malignant potential, ii) do some LS CRCs arise from lesions other than adenomas and iii) why are some tumours aspirin “resistant”?

The mechanism by which aspirin suppresses cancer development long after cessation of exposure to the drug remains unclear. The assumption that the primary action of anti-inflammatories is on COX2 in colonic tumours is unlikely to be the primary mechanism. The rapid progression from adenoma to carcinoma in LS makes it likely that many screen-detected cancers would have begun to develop after aspirin intervention ended. Aspirin may be pro-apoptotic at early stages of CRC development, perhaps preceding adenoma formation. Ruschoff et al reported reduced microsatellite instability and enhanced apoptosis in MMR-deficient cells exposed to aspirin and argued that aspirin may induce genetic selection for microsatellite stability in a subset of MMR-deficient cells. Aspirin may delete those aberrant stem cells most likely to progress rapidly to cancer. Analysis of the conditional MSH2 knockout mouse, reported recently to survive significantly longer when exposed to aspirin, might shed light on the mechanism.

Despite regular colonoscopy, almost 1 in 14 of those not taking aspirin in CAPP2 developed CRC in under 5 years, emphasizing the need for additional prevention strategies. Our results, taken in conjunction with recent literature, provide a basis for recommending aspirin chemoprevention in LS as standard of care. CAPP3 (www.capp3.org) will seek to establish the optimum dose and duration of aspirin treatment.
Funding Disclosure
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The UK Medical Research Council (MRC) approved the trial in 2002 and became the primary funder. MRC steering and data monitoring committees were established. Financial contributions were also made to local sites by the Newcastle Hospitals trustees, Cancer Council of Victoria Australia, THRIPP South Africa, The Finnish Cancer Foundation and SIAK Switzerland. When renewal requests were declined by MRC and CRUK follow up analysis 2009-11 was supported by a donation from Bayer Schering Pharma to Newcastle University.

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**Data Monitoring Committee**: Doug Altman (Chair); Chris Paraskeva; Wendy Atkin; Mark Hull.

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References:


Table 1. Study population: Numbers, time on study, time on follow-up and cancer burden according to aspirin use

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>AP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of participants</strong></td>
<td>427</td>
<td>434</td>
<td>861</td>
</tr>
<tr>
<td><strong>Months on CAPP2 intervention study (mean) (sd, range)</strong></td>
<td>25·0 (12·5) (0·8, 60·6)</td>
<td>25·4 (14·2) (1·1, 74·4)</td>
<td>25·2 (13·4) (0·8, 74·4)</td>
</tr>
<tr>
<td><strong>Months since study entry (mean) (sd, range)</strong></td>
<td>56·6 (30·9) (0·8, 125·4)</td>
<td>54·8 (31·8) (1·6, 128)</td>
<td>55·7 (31·4) (0·8, 128)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Number of participants with first CRC</th>
<th>Since randomization</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>18</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Within 2 yrs of randomization</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>More than 2 yrs from randomization</td>
<td>8</td>
<td>20</td>
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<table>
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<tr>
<th>Number of participants with other LS cancers*</th>
<th>Since randomization</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Within 2 yrs of randomization</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>More than 2 yrs from randomization</td>
<td>11</td>
<td>15</td>
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<table>
<thead>
<tr>
<th>Number of participants with one or more LS cancers (including CRC)</th>
<th>Since randomization</th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>34</td>
<td>52</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Within 2 yrs of randomization</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>More than 2 yrs from randomization</td>
<td>19</td>
<td>33</td>
</tr>
</tbody>
</table>

| Number of participants with non-LS cancers | 19 | 19 | 38 |

*Two participants in placebo group had CRC and another LS cancer. These two participants are counted in the rows relating to both CRC and other LS cancers. In the row reporting to all Lynch syndrome cancers, these participants are counted only once.
Table 2a. Cox proportional hazards analysis and Poisson regression for CRC cancer (adjusted for gender) based only on those randomized to aspirin or aspirin placebo (AP)

<table>
<thead>
<tr>
<th>Estimate of effect of</th>
<th>CRC</th>
<th>p-value</th>
<th>IRR² (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention to treat</strong></td>
<td>Aspirin vs AP</td>
<td>0.63 (0.35-1.13)</td>
<td>0.12</td>
<td>0.56 (0.32-0.99)</td>
</tr>
<tr>
<td>Per protocol analysis</td>
<td>0.62 (0.25-1.52)</td>
<td>0.30</td>
<td>0.72 (0.32-1.59)</td>
<td>0.41</td>
</tr>
<tr>
<td>≥2 years AP**</td>
<td>0.62 (0.25-1.52)</td>
<td>0.30</td>
<td>0.72 (0.32-1.59)</td>
<td>0.41</td>
</tr>
<tr>
<td>&lt;2 years AP**</td>
<td>0.62 (0.25-1.52)</td>
<td>0.30</td>
<td>0.72 (0.32-1.59)</td>
<td>0.41</td>
</tr>
<tr>
<td>&lt;2 years aspirin **</td>
<td>1.07 (0.47-2.41)</td>
<td>0.87</td>
<td>0.90 (0.42-1.91)</td>
<td>0.77</td>
</tr>
<tr>
<td>≥2 years aspirin **</td>
<td>0.41 (0.19-0.86)</td>
<td>0.02</td>
<td>0.37 (0.18-0.78)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

| Cumulative aspirin dose | Units of 100 aspirin¹ | 0.97 (0.94-1.00) | 0.06 | 0.97 (0.94-1.00) | 0.03 |

* Cox proportional Hazards analysis based on 48 participants with CRC involving a total of 33 cancer diagnoses: HR = Hazard Ratio (95% Confidence Interval)
** The threshold for 2 years intervention was consumption of more than 1400 aspirin tablets; rounded down from a 2 year total of 1461 tablets to allow for early scheduling of the exit colonoscopy and/or occasional missed dosage.

² Incidence Rate Ratio (95% Confidence Interval) from Poisson regression

ε Units of 100 aspirin= the total number of aspirin taken divided by 100

Table 2b. Cox proportional hazards analysis and Poisson regression for non-CRC Lynch syndrome cancers (adjusted for gender) based only on those randomized to aspirin or aspirin placebo (AP)

<table>
<thead>
<tr>
<th>Estimate of effect of</th>
<th>Non-CRC Lynch cancer</th>
<th>p-value</th>
<th>Non-CRC LS cancer</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention to treat</strong></td>
<td>Aspirin vs AP</td>
<td>0.63 (0.34-1.19)</td>
<td>0.16</td>
<td>0.63 (0.34-1.16)</td>
</tr>
<tr>
<td>Per protocol analysis</td>
<td>0.96 (0.40-2.34)</td>
<td>0.94</td>
<td>0.82 (0.35-1.96)</td>
<td>0.66</td>
</tr>
<tr>
<td>≥2 years AP**</td>
<td>1.11 (0.46-2.68)</td>
<td>0.82</td>
<td>0.90 (0.38-2.14)</td>
<td>0.81</td>
</tr>
<tr>
<td>&lt;2 years AP**</td>
<td>1.11 (0.46-2.68)</td>
<td>0.82</td>
<td>0.90 (0.38-2.14)</td>
<td>0.81</td>
</tr>
<tr>
<td>&lt;2 years aspirin **</td>
<td>0.47 (0.21-1.06)</td>
<td>0.07</td>
<td>0.49 (0.23-1.05)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥2 years aspirin **</td>
<td>0.96 (0.93-1.00)</td>
<td>0.03</td>
<td>0.96 (0.93-1.00)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Cox proportional Hazards analysis based on 40 case : HR = Hazard Ratio (95% Confidence Interval)
** The threshold for 2 years intervention was consumption of more than 1400 aspirin tablets; rounded down from a 2 year total of 1461 tablets to allow for early scheduling of the exit colonoscopy and/or occasional missed dosage.

ϕ Incidence Rate Ratio (95% Confidence Interval) from Poisson regression

ε Units of 100 aspirin= the total number of aspirin taken divided by 100
Table 2c. Cox proportional hazards analysis and Poisson regression for all Lynch Syndrome (LS) cancers (adjusted for gender) based only on those randomized to aspirin or aspirin placebo (AP)

<table>
<thead>
<tr>
<th>Estimate of effect of</th>
<th>All LS cancers HR (95% CI)</th>
<th>p-value</th>
<th>All LS cancers IRR* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to treat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin vs AP</td>
<td>0.65 (0.42-1.00)</td>
<td>0.05</td>
<td>0.59 (0.39-0.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>Per protocol analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 years AP**</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&lt;2 years AP**</td>
<td>0.79 (0.42-1.49)</td>
<td>0.47</td>
<td>0.76 (0.43-1.37)</td>
<td>0.36</td>
</tr>
<tr>
<td>≥2 years aspirin **</td>
<td>1.13 (0.62-2.06)</td>
<td>0.69</td>
<td>0.90 (0.51-1.59)</td>
<td>0.71</td>
</tr>
<tr>
<td>&lt;2 years aspirin **</td>
<td>0.45 (0.26-0.79)</td>
<td>0.005</td>
<td>0.42 (0.25-0.72)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Cox proportional Hazards analysis based on 86 participants with LS cancers involving a total of 93 cancer diagnoses: HR = Hazard Ratio (95% Confidence Interval)

** The threshold for 2 years intervention was consumption of more than 1400 aspirin tablets; rounded down from a 2 year total of 1461 tablets to allow for early scheduling of the exit colonoscopy and/or occasional missed dosage.

ф Incidence Rate Ratio (95% Confidence Interval) from Poisson regression

£ Units of 100 aspirin = the total number of aspirin taken divided by 100