Aspirin, Ibuprofen and risk of colorectal cancer for carriers of germline mutations in DNA mismatch repair genes

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Abstract code: 311

Disclosure of Interest: None Declared
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Burden of colorectal cancer

International Agency for Research on Cancer
World Health Organization

Male
Female

Australia/New Zealand
Western Europe
Southern Europe
Northern Europe

More developed regions
Central and Eastern Europe
Northern America
Micronesia
Eastern Asia

World
Caribbean
South America
Western Asia
South-Eastern Asia

Less developed regions
Southern Africa
Polynesia
Melanesia
Central America
Northern Africa

Eastern Africa
South-Central Asia
Middle Africa
Western Africa

ASR (W) per 100,000, all ages

GLOBOCAN 2012 (IARC) (8.8.2014)
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Driss Ait Ouakrim | Abstract #311

Lynch Syndrome

- 2% - 4% of all colorectal cancers (Hampel et al. 2008)

- 1 in 370 to 1 in 3,100 in the general population carry a pathogenic mutation in a mismatch repair gene (MLH1, MSH2, MSH6, PMS2) (Dunlop et al. 2000; Hampel et al. 2011)

- MMR mutation carriers are at increased risk of:
  - Colorectal cancer (50% - 80% life-time risk)
  - Other cancers: endometrium, ovary, small intestine, stomach, brain, renal pelvis, ureter and bladder

- Colonoscopy reduces 15-year colorectal cancer risk by 56%, and mortality by 67% (Jarvinen et al. 2000)
**Abstract**

**Background**
Observational studies report reduced colorectal cancer in regular aspirin consumers. Randomised controlled trials have shown reduced risk of adenomas but none have employed prevention of colorectal cancer as a primary endpoint. The CAPP2 trial aimed to investigate the antineoplastic effects of aspirin and a resistant starch in carriers of Lynch syndrome, the major form of hereditary colorectal cancer; we now report long-term follow-up of participants randomly assigned to aspirin or placebo.

**Methods**
861 participants were randomly assigned to aspirin or aspirin placebo. At a mean follow-up of 55.7 months, there was no evidence that either agent affected the development of advanced neoplasia (7.4% and 9.9%, respectively; \( P = 0.35 \); 95% confidence interval [CI], 0.7 to 1.4). There were no significant differences between the two groups with respect to the development of colorectal cancer.

**Findings**
Among 1071 persons in 43 centers, 62 were ineligible to participate in the study, 72 did not enter the study, and 191 withdrew from the study. These three categories were equally distributed across the study groups. Over a mean period of 29 months, there was no evidence that either agent affected the development of advanced neoplasia (7.4% and 9.9%, respectively; \( P = 0.35 \); 95% CI, 0.7 to 1.4). There were no significant differences between the two groups with respect to the development of colorectal cancer.

**Conclusions**
Aspirin has no effect on the incidence of colorectal adenoma or carcinoma among persons with the Lynch syndrome.

**Comment**
Further studies are needed to establish the optimum dose and duration of aspirin use for colorectal cancer prevention in Lynch syndrome carriers.
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The Colon Cancer Family Registry

Fred Hutchinson Cancer Research Center – Seattle
Pl. Polly Newcomb
Recruitment: Puget Sound area

University of Hawaii - Honolulu
Pl. Loic Le Marchand
Recruitment: Hawaii

University of Southern California consortium – Los Angeles
Pl. Robert Haile (Stanford University)
Recruitment: Southern California, Colorado, Arizona, North Carolina, Minnesota, Dartmouth Medical School, Cleveland Clinic

13,500 families
45,000 individuals

Mayo Clinic – Rochester
Pl. Noralane Lindor
Recruitment: Mayo Clinic

Cancer Care Ontario – Toronto
Pl. Steven Gallinger
Recruitment: Ontario

The University of Melbourne
Pl. Mark Jenkins
Recruitment: Melbourne, Sydney, Brisbane, Perth, Adelaide, Auckland
Cohort analysis

- 1,992 MMR gene mutation carriers (1,126 females) from 748 families
- 727 carried a mutation in MLH1, 944 in MSH2, 214 in MSH6 and 107 in PMS2
- Multivariable weighted Cox regression models
  - HRs were calculated by taking into account clustering by family membership to allow for correlation of risk between relatives from the same family using the Huber-White robust variance correction
- Observation time
  - Started at birth
  - Ended at age of cancer diagnosis, polypectomy, death, last contact
- Exposure variables: aspirin, ibuprofen, aspirin or ibuprofen

*Never use*: defined as answering “no” to “Have you ever taken aspirin/ibuprofen at least twice a week for 1 month or longer?”

*Ever use*: defined as answering “yes” to “Have you ever taken aspirin/ibuprofen at least twice a week for 1 month or longer?”

*Duration of intake*: defined as self-reported total number of years of using aspirin/ibuprofen for at least twice a week prior to age at CRC diagnosis or censored age.
Results

• A total of 83,368 person-years

• 775 (39%) developed CRC over the follow up period at a mean age of 43 years (SD=10.6)
## Results

### Aspirin, Ibuprofen and risk of colorectal cancer for carriers of germline mutations carriers in DNA mismatch repair genes

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*Adjusted for year of birth, number of alcohol drinks per day and stratified by sex, country, regular physical activity (at least 30 minutes per week for at least three months) smoking status and multivitamins use.

n, number of colorectal cancer cases; N, total number of carriers; HR, hazard ratio; CI, confidence interval.
### Results

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Discussion

• Summary
  - Regular intake of aspirin associated with 54% to 82% reduction in colorectal cancer risk for MMR genes mutation carriers
  - Regular intake of ibuprofen associated with 61% to 74% reduction in colorectal cancer risk for MMR genes mutation carriers

• Strengths
  - Largest study to date on this issue
  - Weighted cohort approach – to minimise potential selection bias due to oversampling of carriers from high risk families
  - Standardized and uniformly high-quality testing for MMR gene mutations by the Colon-CFR
  - Control for a large number of potential confounders including: medical history, demographic characteristics, reproductive history, physical activity, medication, hormone replacement therapy use, alcohol and tobacco use, and dietary factors

• Limitations
  - Recall bias: affected carriers carriers may recall lifestyle factors differently from unaffected carriers
  - Survival bias: cases with poor survival were less likely to be included in this analysis (as they were unable to provide a blood sample for genetic testing and complete a questionnaire)
Our results suggest that regular long-term use of aspirin and perhaps ibuprofen may be an effective way to reduce colorectal cancer risk for people with Lynch syndrome currently rely on frequent colonoscopies to reduce their risk.
Acknowledgment

• **Funding**
  - Australian National Health and Medical Research Council (NHMRC) - Centre for Research Excellence scheme
  - National Institutes of Health (NIH)

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• **Colon-CFR**
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