Can an Aspirin a Day Keep the Cancer Away?

Aspirin for Primary Prevention of Colorectal Cancer

Jessica Martinez, Pharm.D.
PGY1 Pharmacy Resident
CHRISTUS Santa Rosa Health System, San Antonio, TX
The University of Texas Health Science Center at San Antonio

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Learning Objectives:
1. Review the epidemiology and pathophysiology of colorectal cancer
2. Describe the mechanism of action of aspirin in colorectal cancer
3. Discuss current evidence for using aspirin for the primary prevention of colorectal cancer
4. Evaluate the risks and benefits of using aspirin for primary colorectal cancer prevention
5. Develop evidence-based recommendations for the use of aspirin for the prevention of colorectal cancer
Colorectal Cancer (CRC)

1. Epidemiology of CRC,2,3,4,5
   a. Lifetime risk of developing CRC is 5%
      i. Surveillance Epidemiology and End Results (SEER) 2008 prevalence rate: 1.1 million people living with CRC
   b. Third most common cancer and third leading cause of cancer death
      i. In 2012, estimated 143,460 new cases and 51,690 deaths in the United States
      ii. In 2012, estimated 9,700 new cases and 2,650 deaths in Texas (third highest after California and Florida)
         1. Total of 210 deaths per year in Bexar county
      iii. SEER average annual death rate: 2005-2009
         1. Centers for Disease Control Healthy People 2010 goal was 13.9 per 100,000
         2. United States is 15.9 per 100,000 people
         3. Texas is 16.2 per 100,000 people
         4. Bexar county is 15.1 per 100,000 people
   c. 5-year survival rates are based on stage at diagnosis
      i. Local (confined to organ of origin): 90%
      ii. Regional (extends to near tissues and/or lymph nodes): 70%
      iii. Distant (metastasis): 12%
   d. Approximately 72% of cases occur in the colon and 28% occur in the rectum
e. CRC incidence and mortality rates are 35-40% higher in men
i. Second leading cause of cancer-related death in men
ii. Third leading cause of cancer-related death in women
f. Incidence and mortality:
   i. African American > Caucasian > Hispanic > Asian American > American Indian/Alaskan Native

Figure 2: Incidence Rates of CRC

Figure 3: Mortality Rates of CRC
g. Proposed causes for decreased incidence and mortality\textsuperscript{6,7}
   i. Promotion of recommendations for prevention and screening
   ii. Advancement in screening methods
   iii. Improvement in treatment modalities

Figure 4: Colorectal Cancer Incidence and Mortality Trends, 1975 – 2010

2. CRC Risk Factors\textsuperscript{1,2,3,5,6,7,8}
   a. Age
      i. 90% of new cases and 94% of deaths occur in patients over 50 years old
      ii. Probability of developing invasive cancer increases with age
         1. Risk is 1 in 85 people if 60 years or older
         2. Risk is 1 in 24 people if 70 years or older
   b. Modifiable
      i. Overweight (BMI 25-29.9)
         1. Men Relative risk (RR)1.5
         2. Women RR 1.3
      ii. Obesity (BMI 30+)
         1. Men RR 2.4
         2. Women RR 1.5
      iii. Diet high in red or processed meat RR 1.2
      iv. Alcohol consumption (>2 drinks/day) RR 1.4
      v. Long-term smoking RR 2.0-3.0
   c. Hereditary or medical
      i. Family history
         1. First-degree relative RR 2.2
         2. More than one relative RR 4.0
         3. Relative diagnosed at age <45 RR 3.9
      ii. Inflammatory bowel disease
         1. Ulcerative colitis RR 2.8
         2. Crohns disease RR 2.6
      iii. Type 2 diabetes mellitus RR 1.2
d. Genetic conditions
   i. Hereditary nonpolyposis colorectal cancer (Lynch syndrome)
      1. 75% of individuals will develop CRC in their lifetime
   ii. Familial adenomatous polyposis (FAP)
      1. 100% of individuals will develop recurring polyps or CRC starting at puberty (age 10-12)

Figure 5: Percentage of CRC Cases by Type

3. Pathophysiology of CRC\textsuperscript{3,9}
   a. The development of CRC occurs slowly, over a period of 10-15 years
   b. Often begins as a noncancerous polyp or adenoma
      i. Only 10% will progress to a carcinoma
   c. Inflammation is a major contributor to the tumor microenvironment
      i. Initiates tumor growth and promotes disease progression
      ii. Cyclooxygenase-2 (COX-2) enzyme levels are increased in premalignant and malignant tumors
         1. Pro-inflammatory cytokines induce expression of COX-2 resulting in an increased prostaglandin endothelin-2 (PGE\textsubscript{2}) expression
            a. Prostaglandin levels in CRC tissue are 3-4 fold higher than in healthy colon tissue
         2. COX-2-derived prostanoid is the most abundant in CRC tissue
            a. Seen in 40-50% of human colorectal adenomas and 80-90% of carcinomas
      iii. Elevated levels of COX-2-derived PGE\textsubscript{2} are associated with:
         1. Resistance to apoptosis
            a. Via upregulation of the anti-apoptotic protein Bcl-2 and induction of nuclear factor-κB
         2. Increased tumor invasiveness
            a. Stimulation of cell proliferation
            b. Stimulation of cell migration
         3. Increased tumor angiogenesis
         4.Immunosuppression
   d. Molecular pathways leading to CRC
      i. Chromosomal instability pathway
         1. Most common, observed in 80% of CRC
         2. Mutations in oncogenes and tumor suppressor genes
            a. Inactivating deletions in the APC gene
               i. APC phosphorylates the B-catenin protein to decrease cell proliferation and increase apoptosis
            b. p53 gene mutations
            c. Activating kras mutations
               i. Kras sends extracellular growth signals to the cell nucleus
      ii. Microsatellite instability pathway
         1. Inactivation of mismatch repair genes
         2. 15% of all CRC
            a. >90% of Lynch syndrome cancers
      iii. Epigenetic pathway
         1. Hypermethylation-induced silencing of tumor suppressor genes
Prevention of CRC

1. Current American Cancer Society (ACS), American College of Gastroenterology (ACG), and United States Preventative Task Force (USPTF) screening recommendations:5,6,7,8,12,13,14,15
   a. Begin screening at age 50 in average risk individuals (grade 2B: see appendix A for levels of evidence)
      i. Consider beginning at age 45 for African Americans (grade 2C)
      ii. Average risk individuals are those who have no identifiable risk factors
         1. Asymptomatic
         2. No personal history of CRC or adenomatous polyps
         3. No family history of colorectal neoplasia
         4. No inflammatory bowel disease or other genetic factors
         5. No unexplained anemia
b. Screening should begin earlier for high-risk individuals
   i. Positive family history
      1. Begin screening at age 40 or 10 years before cancer diagnosis was made in the family member (grade 1B)
   ii. Inflammatory bowel disease
      1. Pancolitis begin screening 7-8 years after diagnosis (grade 2B)
      2. Left-sided colitis begin screening 12-15 years after diagnosis (grade 2B)
   iii. Lynch syndrome
      1. Begin genetic testing at age 21, if results are positive start screening with colonoscopy every 2 years from age 20-40 then annually thereafter (grade 2B)
   iv. Familial adenomatous polyposis
      1. Begin annual colonoscopy and genetic testing at puberty (grade 2B)

   c. Do not continue screening for those age 85 or greater as risks outweigh potential benefits (grade 1B)
   i. Evaluate individuals 75-84 years of age on a case-by-case basis for screening (grade 1B)

2. Options for CRC screening modalities based on ACS, ACG, and USPTF recommendations\(^5,6,7,8,12,13,14,15\)

<table>
<thead>
<tr>
<th>Table 1: Summary of Screening Recommendations for CRC and Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Test</td>
</tr>
</tbody>
</table>
| Colonoscopy | 10 years | Most sensitive test
Screening, diagnosis, and polyp removal | |
| **Alternate Tests** | | | |
| Flexible sigmoidoscopy | 5 years | Only views rectum and distal 1/3 of colon | |
| Double contrast barium enema (DCBE) | 5 years | Less sensitive for small polyps
Low-doses of radiation | |
| CT colonography | 5 years | Less sensitive for small polyps
Low-doses of radiation | |
| Fecal immunochemical test (FIT) | 1 year | For patients that refuse other tests
Less sensitive for precancerous growths | |

a. Colonoscopy recommended every 10 years
   i. Preferred test (grade 1B)
   ii. Most sensitive test
      1. Allows for screening, diagnosis, and removal of a polyp in one visit
      2. Positive results from any other test require a colonoscopy for diagnosis of CRC
   iii. Views the entire colon, but with potential to miss some polyps and cancers
      1. View of the proximal colon depends on physician experience
   iv. Potential to prevent 65% of CRC cases
b. Flexible sigmoidoscopy recommended every 5 years
   i. Alternative to colonoscopy (grade 2B)
   ii. Views only the rectum and distal one-third of the colon
c. Double contrast barium enema (DCBE) recommended every 5 years
   i. Alternative to colonoscopy (grade 1C)
   ii. Less sensitive for viewing small polyps or adenomas
   iii. Exposes patients to low-doses of radiation
d. CT colonography recommended every 5 years
   i. Alternative to colonoscopy (grade 1C)
   ii. Only detects polyps and adenomas 1 cm in size or greater
   iii. Exposes patients to low-doses of radiation
e. Fecal occult blood test annually
   i. Offered to those who decline a colonoscopy or colonoscopy alternative
   ii. Preferred test is the fecal immunochemical test (FIT) (grade 1B)
   iii. Will miss most polyps and precancerous growths

3. CRC screening prevalence for average-risk individuals is between 54-59% in Texas\textsuperscript{1,3,5}
   a. The American Cancer Society’s 2015 goal for screening prevalence is 75%

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{CRC_Screening_Prevalence_Rates_by_State.png}
\caption{CRC Screening Prevalence Rates by State}
\end{figure}

4. Current ACS recommendations for prevention of CRC\textsuperscript{1,2,10}
   a. Regular screening (level I)
      i. Follow screening recommendations recommended by ACS, ACG, and USPTF
   b. Avoid risk factors and increase protective factors for CRC
      i. Maintain a healthy weight throughout life (level III-2)
         1. BMI 18.0-24.9
      ii. Adopt a physically active lifestyle (level III-2)
         1. Moderate to vigorous physical activity for 30-60 minutes per day
      iii. Consume a healthy diet with an emphasis on plant sources (level III-2)
         1. Eat 5 or more servings of a variety of fruits and vegetables each day
         2. Choose whole grains in preference to processed (refined) grains
         3. Limit your consumption of red and processed meats
      iv. If you drink alcoholic beverages, limit your consumption (level III-2)
         1. ≤1 drink per day for women
         2. ≤2 drinks per day for men
      v. Smoking cessation (level III-2)
   c. Currently no recommendations for the use of chemopreventive agents

5. Chemoprevention\textsuperscript{9,14,15,16,17,18,19}
   a. Definition
      i. The use of drugs or other (including natural) agents to inhibit or prevent the development or progression of malignant changes within cells
b. Agents for CRC prevention
   i. Pharmaceuticals
      1. Non-steroidal anti-inflammatory drugs (NSAIDs)
         a. Aspirin
         b. Non-aspirin NSAIDs (non-selective COX inhibitors)
            i. Ibuprofen, ketoprofen, naproxen, sulindac
         c. COX-2 selective inhibitors
            i. Celecoxib
   ii. Nutraceuticals
       1. Folic acid
       2. Omega-3 polunsaturated fatty acid, eicosapentaenoic acid (EPA)
       3. Curcumin
       4. Resveratrol
       5. Green tea extract *Camellia Sinensis*
       6. Vitamin D

**Mechanism of Action of Aspirin**

1. Aspirin$^{16}$
   a. Irreversible inactivation of COX-1 and COX-2 by acetylation of a serine moiety
      i. Aspirin preferentially blocks COX-1 in platelets at low-doses
         1. Prevents the conversion of arachidonic acid to thromboxane
            a. Results in decreased platelet aggregation and a reduction in cloting
      ii. Aspirin modifies COX-2 through the salicylate metabolite
         1. Decreases inflammatory prostanoid production
         2. Increases anti-inflammatory lipoxin formation

Figure 8: Aspirin Mechanism of Action in Platelets and Blood Vessels
Proposed Mechanisms of Aspirin in CRC
(see appendix B for additional mechanisms)

Figure 9: Aspirin Mechanism of Action in CRC

Arachidonic Acid

\[ \text{COX-1} \]
\[ \text{COX-2} \]

\[ \text{PGH}_2 \]

\[ \text{TXA}_2 \]

Prostaglandin Synthases

\[ \text{PGE}_2 \]

\[ \text{EP1 – 4} \]

\[ \text{B-catenin} \]

\[ \text{PI3K/AKT} \]

\[ \text{EGFR} \]

\[ \text{Cyclin D1} \]

\[ \text{Bcl-2} \]

\[ \text{VGFR} \]

\[ \downarrow \text{Immunity} \]

\[ \uparrow \text{Proliferation} \]

\[ \uparrow \text{Migration & Invasion} \]

\[ \downarrow \text{Apoptosis} \]

\[ \uparrow \text{Angiogenesis} \]
1. COX-dependent\(^{17,18,19,20,21,22}\)
   a. COX-1 platelet inhibition
      i. Uncontrolled platelet activation secondary to inflammation can result in cancer growth
      ii. Platelets have a role in the spreading of neoplastic cells to other organs and/or lymph nodes
      iii. Store and release various angiogenesis-regulating factors
         1. Vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF)
      iv. Synthesize and release inflammatory cytokines which contributes to COX-2 induction
      v. Release thromboxane-A\(_2\) which promotes angiogenesis and development of tumor metastasis
   b. Inhibition of COX-2 dependent PGE\(_2\) formation
      i. Antagonism of PGE\(_2\)-mediated immunosuppression
      ii. Decreased tumor invasiveness and angiogenesis

2. COX-independent
   a. Modulation of oncogene-induced expression of transcription factors
      i. Inhibition of NF-\(\kappa\)B, a transcription factor involved in the regulation of anti-apoptotic gene expression
      ii. Inhibition of extracellular signal-regulated kinase (ERK) signaling
         1. Regulates proliferation, survival, differentiation and migration of cells
   b. Inhibition of the Wnt/B-catenin pathway
      i. Inhibition by stimulating phosphorylation and breakdown of B-catenin

### Evidence for the Use of Aspirin in CRC

1. Women's Health Initiative\(^{23}\)
   a. Objective
      i. To examine the effect of aspirin on the risk of cancer among healthy women
   b. Methods
      i. 38,876 US women aged at least 45 years randomly assigned from 1992-2004 to receive aspirin 100 mg or placebo every other day
         1. No previous history of cancer, cardiovascular disease, or other major chronic illness
      ii. Follow-up was an average of 10.1 years
   c. Results
      i. No effect of aspirin on total cancer (n=2865, RR 1.01, CI 0.94-1.08, \(p=0.87\))
      ii. No effect of aspirin on CRC (n=269, RR 0.97, CI 0.77-1.24, \(p=0.83\))
      iii. No reduction in cancer mortality (n=140, RR 0.70, CI 0.50-0.99, \(p=0.04\))
   d. Conclusions
      i. Low-dose aspirin used every other day for an average of 10 years does not lower risk of CRC

2. Physician's Health Study\(^{24}\)
   a. Objective
      i. To examine the effect of aspirin on the risk of CRC using data from the Physicians' Health Study
   b. Methods
      i. 22,071 US male physicians age 40-84 randomized to receive aspirin 325 mg or placebo every other day beginning in 1982
         1. No previous use of aspirin or NSAIDs, no history of myocardial infarction, stroke, cancer, liver or renal disease, gout, peptic ulcer, or contraindications to aspirin
      ii. The aspirin arm was terminated in 1988 after an average follow-up of 5 years
         1. 71% of participants chose to continue aspirin (3 or more days per week) for the remainder of the study
      iii. Intention-to-treat analysis had an average follow-up of 12 years
   c. Results
      i. No effect of aspirin on CRC from random assignment (RR 1.03, CI 0.83-1.28)
      ii. No effect of aspirin on CRC from observational use after 1988 (RR 1.07, CI 0.75-1.53)
   d. Conclusions
      i. Both randomized and observational analysis indicate there is no association between aspirin taken every other day and the incidence of CRC
Table 2:

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>• To examine the influence of aspirin and NSAIDs in prevention of CRC</td>
<td>• To examine long-term data of aspirin on the risk of CRC</td>
</tr>
<tr>
<td>Study Population</td>
<td>• Prospective cohort study of 82,911 women enrolled in the Nurses’ Health Study</td>
<td>• Prospective cohort study of 47,363 men enrolled in the Male Health Professionals’ Follow-Up Study</td>
</tr>
<tr>
<td>Study Population</td>
<td>• Median age (at enrollment) was 47 years, 98% White, 57% former or current smokers, 15% with a positive family history of CRC, average BMI 24.5, average of 2.5 servings of red meat per week</td>
<td>• Median age (at enrollment) was 55 years, 95% White, 54% former or current smokers, 9% with a positive family history of CRC, average BMI 25.6, average of 1.8 servings of red meat per week</td>
</tr>
<tr>
<td>Methods</td>
<td>• The study was established in 1976 when US female nurses aged 30-55 years were mailed a questionnaire</td>
<td>• The study was established in 1986 when US male health professionals aged 40-75 years were mailed a questionnaire</td>
</tr>
<tr>
<td>Methods</td>
<td>• Study follow-up was until 2000 (total 20 years)</td>
<td>• Study follow-up was until 2004 (total 18 years)</td>
</tr>
<tr>
<td>Methods</td>
<td>• In 2004, questionnaires were sent to determine major episodes of GI bleeding</td>
<td>• Follow-up questionnaires were mailed every 2 years with follow-up rate &gt;90%</td>
</tr>
<tr>
<td>Methods</td>
<td>• Follow-up questionnaires were mailed every 2 years with follow-up rate &gt;90%</td>
<td>• For each medication, participants were asked to record the number of tablets or capsules taken each week, the average number per month, and the number of years in use</td>
</tr>
<tr>
<td>Methods</td>
<td>• Cancer diagnosis was confirmed through medical records, pathology reports, and the National Death Index</td>
<td>• Patients were excluded for incomplete information, history of cancer, inflammatory bowel disease, FAP, or Lynch syndrome</td>
</tr>
<tr>
<td>Methods</td>
<td>• Patients were excluded for incomplete information, history of cancer, inflammatory bowel disease, FAP, or Lynch syndrome</td>
<td>• Multivariate Cox proportional hazards model was used to calculate 95% confidence intervals (CIs)</td>
</tr>
<tr>
<td>Statistics</td>
<td>• Relative risks (RRs) were calculated for each disease category</td>
<td>• All multivariate relative risks were adjusted for risk factors previously shown to be associated with CRC risk (age, smoking, BMI, exercise, family history, previous endoscopy, previous polyp, amount of red/processed meat intake, alcohol, multivitamins)</td>
</tr>
<tr>
<td>Statistics</td>
<td>• SAS version 8.2 was used for all analyses</td>
<td>• Relative risks (RRs) were calculated for each disease category</td>
</tr>
<tr>
<td>Statistics</td>
<td>• All p-values were 2-sided with a p&lt;0.05 considered statistically significant</td>
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</tr>
<tr>
<td>Results</td>
<td>• 962 total cases of CRC (607 cases in 53,827 nonusers and 355 cases in 29,084 users)</td>
<td>• 975 total cases of CRC (557 cases in 33,441 nonusers and 418 cases in 13,922 users)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Aspirin Nonusers/Users (RR; 95% CI)</th>
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<tbody>
<tr>
<td>All CRC</td>
<td>All CRC</td>
</tr>
<tr>
<td>607/355</td>
<td>557/418</td>
</tr>
<tr>
<td>(0.77; 0.67-0.87)</td>
<td>(0.79; 0.69-0.90)</td>
</tr>
<tr>
<td>Colon</td>
<td>Colon</td>
</tr>
<tr>
<td>460/252</td>
<td>355/281</td>
</tr>
<tr>
<td>(0.71; 0.61-0.83)</td>
<td>(0.83; 0.72-0.98)</td>
</tr>
<tr>
<td>Proximal</td>
<td>Proximal</td>
</tr>
<tr>
<td>246/148</td>
<td>176/139</td>
</tr>
<tr>
<td>(0.77; 0.63-0.94)</td>
<td>(0.80; 0.65-1.00)</td>
</tr>
<tr>
<td>Distal</td>
<td>Distal</td>
</tr>
<tr>
<td>214/104</td>
<td>167/128</td>
</tr>
<tr>
<td>(0.65; 0.51-0.82)</td>
<td>(0.84; 0.66-1.06)</td>
</tr>
<tr>
<td>Rectal</td>
<td>Rectal</td>
</tr>
<tr>
<td>136/94</td>
<td>126/78</td>
</tr>
<tr>
<td>(0.92; 0.71-1.20)</td>
<td>(0.64; 0.48-0.85)</td>
</tr>
<tr>
<td>Stage 1/2</td>
<td>Stage 1/2</td>
</tr>
<tr>
<td>290/152</td>
<td>253/198</td>
</tr>
<tr>
<td>(0.68; 0.56-0.82)</td>
<td>(0.80; 0.66-0.96)</td>
</tr>
<tr>
<td>Stage 3/4</td>
<td>Stage 3/4</td>
</tr>
<tr>
<td>260/167</td>
<td>201/133</td>
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<tr>
<td>(0.85; 0.70-1.03)</td>
<td>(0.74; 0.59-0.92)</td>
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Table 2 (continued)

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>Results</strong></td>
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</tr>
<tr>
<td><strong>No. of Aspirin 325-mg Tabs/Week</strong></td>
<td><strong>No. of Aspirin 325-mg Tabs/Week</strong></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>All CRC</td>
<td>0.77 (0.62-0.97)</td>
</tr>
<tr>
<td>Colon</td>
<td>0.74 (0.57-0.96)</td>
</tr>
<tr>
<td>Rectal</td>
<td>0.88 (0.55-1.40)</td>
</tr>
<tr>
<td>Stage 1/2</td>
<td>0.62 (0.44-0.88)</td>
</tr>
<tr>
<td>Stage 3/4</td>
<td>0.99 (0.72-1.36)</td>
</tr>
</tbody>
</table>
| • RR of CRC based on duration of aspirin use  
  o 6-10: RR 0.88 (0.73-1.07)  
  o 11-20: RR 0.67 (0.53-0.84)  
  o >20: RR 0.68 (0.54-0.85) | • RR of CRC based on duration of aspirin use  
  o 6-10: RR 0.78 (0.66-0.93)  
  o 11-20: RR 0.73 (0.57-0.93)  
  o >20: RR 0.68 (0.51-0.91) |
| • GI bleeding (events per 1000 person-years)  
  o Nonusers: 0.77  
  o 0.5-1.5 tabs/wk: 1.07  
  o 2-5 tabs/wk: 1.07  
  o 6-14 tabs/wk: 1.40  
  o >14 tabs/wk: 1.57 | • GI bleeding was not reported |
| **Conclusions** | **Conclusions** |
| • Statistically significant benefit was not evident until sustained use of aspirin for at least 10 years.  
  • No benefit was seen for stage 3 or 4 cancer types or for rectal disease. | • Statistically significant benefit was not evident until after 5 years of sustained aspirin use.  
  • Similar risk reduction in all anatomic sites and for cancers of all stages. |
| **Strengths** | **Strengths** |
| • Aspirin data was collected over a long period of time and with a broad range of dosages  
  • Data was obtained prospectively, before a CRC diagnosis was made  
  • Data was collected on potential confounders and a multivariate analysis was used to adjust for these  
  • There was a high rate of follow-up | **Limitations** | **Limitations** |
| • Observational study based on questionnaires  
  • Aspirin use was self-selected  
  • Not all cofounders can be controlled for, there may be unknown causes of CRC |
### Table 3


<table>
<thead>
<tr>
<th>Purpose</th>
<th>To establish the effect of aspirin on cancer incidence and mortality due to colorectal cancer in relation to dose and duration</th>
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</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Follow-up meta-analysis of five randomized trials (total of 14,033 patients) of daily aspirin versus no aspirin in primary and secondary prevention of vascular events</td>
</tr>
</tbody>
</table>
| Methods | Studied trials of aspirin versus control in the UK or Sweden  
- Trials were eligible if they recruited at least 1000 participants and had a median scheduled treatment period of at least 2.5 years  
- Trials included were: Thrombosis Prevention Trial (TPT), British Doctors Aspirin Trial (BDAT), Swedish Aspirin Low Dose Trial (SALT), UK-TIA Aspirin Trial (UK-TIA). Long-term follow-up data on cause of death were also available from the Dutch TIA Trial  
- CRC were identified from death certificate and cancer registration data  
  - Data on death due to CRC were available from all trials  
  - Incidence of CRC was assessed in TPT, BDAT, and UK-TIA  
- Median treatment duration was 6.0 years and median follow-up was 18.3 years |
| Statistics | All analyses were intention to treat, defined as treatment allocation in the original trials  
- Stratified by the dose categories of 75-300 mg versus 500-1200 mg, treatment duration of at least 2.5 years and 5.0 years, and site of cancer  
- Odds ratios (OR) were established for the effect of aspirin on death due to CRC during and after the trials  
- A pooled estimate from the four trials of aspirin versus control was obtained by fixed-effects meta-analysis (Peto method)  
  - The same analysis was used for incidence of colorectal cancer in TPT, BDAT, and UK-TIA  
- Heterogeneity was calculated between trials  
- Kaplan-Meier analysis was used for survival curves and log-rank tests were used to assess significance  
- Cox regression was used to establish hazard ratios for the incidence of colorectal cancer and risk of death |
| Results | 393 total CRC cases (196 cases in 8282 aspirin users, 197 cases in 5741 aspirin non-users) |

#### Incidence of colorectal cancer

<table>
<thead>
<tr>
<th></th>
<th>CRC/Aspirin Users</th>
<th>HR (95% CI)</th>
<th>ARR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>196/8073</td>
<td>0.75 (0.56-0.97)</td>
<td>1.21% (0.19-2.22)</td>
<td>83</td>
</tr>
<tr>
<td>Duration ≥2.5 yrs</td>
<td>185/7383</td>
<td>0.69 (0.51-0.93)</td>
<td>1.33% (0.30-2.36)</td>
<td>75</td>
</tr>
<tr>
<td>Duration ≥5 yrs</td>
<td>135/5077</td>
<td>0.62 (0.43-0.94)</td>
<td>1.55% (0.34-2.76)</td>
<td>65</td>
</tr>
</tbody>
</table>

#### Mortality due to colorectal cancer

<table>
<thead>
<tr>
<th></th>
<th>CRC/Aspirin Users</th>
<th>HR (95% CI)</th>
<th>ARR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>130/8073</td>
<td>0.61 (0.43-0.87)</td>
<td>1.36% (0.44-2.28)</td>
<td>74</td>
</tr>
<tr>
<td>Duration ≥2.5 yrs</td>
<td>119/7383</td>
<td>0.54 (0.36-0.80)</td>
<td>1.49% (0.55-2.43)</td>
<td>67</td>
</tr>
<tr>
<td>Duration ≥5 yrs</td>
<td>91/5077</td>
<td>0.48 (0.30-0.77)</td>
<td>1.76% (0.61-2.91)</td>
<td>57</td>
</tr>
</tbody>
</table>
### Results

- Effect of aspirin (75-1200 mg) versus control stratified by cancer site
  - **Proximal colon**
    - All patients: HR 0.45, CI 0.28-0.74, p=0.01
    - Duration ≥5 yrs: HR 0.35, CI 0.20-0.63, p<0.001
  - **Distal colon**
    - All patients: HR 1.10, CI 0.73-1.64, p=0.66
    - Duration ≥5 yrs: HR 1.14, CI 0.69-1.86, p=0.61
  - **Rectum**
    - All patients: HR 0.90, CI 0.63-1.30, p=0.58
    - Duration ≥5 yrs: HR 0.58, CI 0.36-0.92, p=0.02
  - **Fatal cancers**
    - All patients: HR 0.66, CI 0.52-0.86, p=0.002
    - Duration ≥5 yrs: HR 0.57, CI 0.42-0.78, p<0.0001

### Conclusions

- The 20-year incidence of CRC was reduced by 30% by treatment with aspirin 75-300 mg daily for 5 years
- Reductions in incidence and death due to CRC were greater for proximal colon cancers
- There was no evidence of earlier diagnosis of CRC in patients receiving aspirin

### Strengths

- Long-term follow-up
- Evaluates use of aspirin through randomized controlled trials
- Looked specifically at low-dose aspirin
- Used intention-to-treat study population and calculated heterogeneity between trials

### Limitations

- Trials were originally performed for primary and secondary cardiovascular prevention
- Trials were not designed to study CRC
- No comment on the quality of studies include
- Publication bias is possible
Risks with Chronic Aspirin Use

1. Systematic review of adverse events of low-dose aspirin \(^\text{25}\)
   a. Objective
      i. Define the relative and absolute risk of clinically relevant adverse events with aspirin
   b. Methods
      i. Relative risk and absolute risk increase was determined from 22 randomized controlled trials of low-dose (75-325 mg/day) aspirin versus placebo
   c. Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Subjects: ASA/placebo</th>
<th>RR (95% CI)</th>
<th>Absolute Increase per Year (95% CI)</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any major bleeding</td>
<td>26,673/26,712</td>
<td>1.71 (1.41-2.08)</td>
<td>0.13% (0.08-0.20%)</td>
<td>NNH 769 (500-1250)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>28,686/28,719</td>
<td>2.07 (1.61-2.66)</td>
<td>0.12% (0.07-0.19%)</td>
<td>NNH 833 (526-1429)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>27,671/27,712</td>
<td>1.65 (1.12-2.44)</td>
<td>0.03% (0.01-0.08%)</td>
<td>NNH 3333 (1250-10,000)</td>
</tr>
</tbody>
</table>

Summary

1. Trials of low-dose aspirin taken every other day have not shown any benefit in reducing risk of CRC
2. Observational trials have shown that taking aspirin daily may have a role in primary prevention of CRC
   a. No consensus on dose
   b. Effects are not seen until at least 10 years of aspirin use
3. Risks of GI bleeding may outweigh benefits seen with aspirin for primary prevention on CRC

Unanswered Questions and Future Research

Unanswered Research Questions

1. What is the lowest effective dose for aspirin chemoprevention in CRC?
2. Which populations will most benefit from aspirin chemoprevention?
3. At what age should aspirin chemoprevention be initiated?
4. How long should aspirin be continued for chemoprevention?
5. Is aspirin beneficial in other types of cancer?

Future Research

- Aspirin in Preventing Colorectal Cancer in Patients at Increased Risk of Colorectal Cancer
  - Active, not recruiting
  - Estimated study completion April 2014
- Nitric Oxide-Releasing Acetylsalicylic Acid in Preventing Colorectal Cancer in Patients at High Risk of Colorectal Cancer
  - Completed
  - Results are not published
- Acetylsalicylic Acid and Eflornithine in Treating Patients at High Risk for Colorectal Cancer
  - Recruiting
  - Estimated study completion December 2014
Overall Recommendations

1. There is no clear evidence that benefits outweigh the risks of daily aspirin use for primary prevention in an average risk population
   a. Data is based on observational trials and sub-analyses
   b. No consensus on appropriate dose
   c. No clear information on when to initiate or discontinue aspirin
   d. Exact mechanism of aspirin in CRC is still unknown
   e. Effects seen with aspirin on specific CRC locations are differing

2. Consider initiating aspirin in patients who are considered high risk who do not have increased bleeding risk
   a. Positive family history
   b. Patients with inflammatory bowel disease should not receive aspirin for primary prevention
      i. Increased bleeding risk
References


## Appendix A

### LEVELS OF EVIDENCE:
American College of Gastroenterology Screening Guidelines for CRC 2008

<table>
<thead>
<tr>
<th>Grade of recommendation/description</th>
<th>Benefit vs. risk and burden</th>
<th>Methodological quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1A/Strong recommendation, high-quality evidence</strong></td>
<td>Benefits clearly outweigh risk and burden, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td><strong>1B/Strong recommendation, moderate-quality evidence</strong></td>
<td>Benefits clearly outweigh risk and burden, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td><strong>1C/Strong recommendation, low-quality or very low-quality evidence</strong></td>
<td>Benefits clearly outweigh risk and burden, or vice versa</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but may change when higher quality evidence becomes available</td>
</tr>
<tr>
<td><strong>2A/Weak recommendation, high-quality evidence</strong></td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td><strong>2B/Weak recommendation, moderate-quality evidence</strong></td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td><strong>2C/Weak recommendation, low-quality or very low-quality evidence</strong></td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>

### LEVELS OF EVIDENCE:
American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention 2012

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level I</strong></td>
<td>Evidence obtained from a systematic review of all relevant randomized controlled trials</td>
</tr>
<tr>
<td><strong>Level II</strong></td>
<td>Evidence obtained from at least one properly designed randomized controlled trial</td>
</tr>
<tr>
<td><strong>Level III-1</strong></td>
<td>Evidence obtained from well-designed pseudo randomized controlled trials (alternate allocation or some other method)</td>
</tr>
<tr>
<td><strong>Level III-2</strong></td>
<td>Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case-control studies, or interrupted time series with a control group</td>
</tr>
<tr>
<td><strong>Level III-3</strong></td>
<td>Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group</td>
</tr>
<tr>
<td><strong>Level IV</strong></td>
<td>Evidence obtained from case series, either post-test or pre-test/post-test</td>
</tr>
</tbody>
</table>
Appendix B

Additional proposed mechanisms of aspirin in CRC

1. COX-dependent mechanisms
   a. Inhibition COX-2/peroxidase-mediated activation of carcinogens
      ii. COX-2 promotes carcinogenesis via peroxidase activity
          1. Peroxidase induces the generation of free radicals which bind to DNA and change gene transcription
   b. Generation of aspirin-triggered lipoxin (ATL)
      iii. Acetylation of COX-2 by aspirin switches COX-2 from synthesizing PGE₂ to antitumorigenic lipoxin molecules
           1. Anti-inflammatory
           2. Inhibits proliferation of carcinoma cells
   c. Inhibition of sphingosine-kinase-1
      iv. Sphingosines are present in up to 89% of CRC and mediates angiogenesis, metastasis, and resistance of tumor cells to drug-induced apoptosis
      v. 50% of sphingosine-kinase-1 in blood is stored in circulating platelets and released in a thromboxane-dependent manner
           1. Aspirin inhibits thromboxane-dependent sphingosine release

3. COX-independent mechanisms
   a. Interaction with DNA mismatch-repair genes
      i. Aspirin promotes DNA stability in CRC-cells deficient for mismatch repair genes
         1. Stabilized DNA by prevention of oxidative DNA-strand breaks
   b. Sensitizes tumor cells to apoptotic stimuli
      i. Sensitizes tumor cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)
         1. May have a synergistic effect with inhibition of COX-2 prostaglandin formation
   c. Induction of proapoptotic NSAID activated gene-1 (NAG-1)
      i. NAG-1 is involved in apoptosis and reduced tumorigenesis
         1. In CRC cells, expression is positively correlated with apoptosis and inversely with COX-2 expression
      ii. NAG-1 is upregulated by aspirin
   d. Induction of apoptosis by caspase activation
      i. Aspirin induce apoptosis through cytochrome c release and activation of caspase-9
### Characteristics of trials studied and details of post-trial follow-up

<table>
<thead>
<tr>
<th></th>
<th>TPT</th>
<th>SALT</th>
<th>Dutch TIA</th>
<th>UK-TIA</th>
<th>BDAT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin comparison</strong></td>
<td>75 mg vs. placebo</td>
<td>75 mg vs. placebo</td>
<td>282 mg vs. 30 mg</td>
<td>300 mg vs. 1200 mg vs. placebo</td>
<td>500 mg vs. placebo</td>
</tr>
<tr>
<td><strong>Patients (active/control)</strong></td>
<td>2545/2540</td>
<td>676/684</td>
<td>1231/1224</td>
<td>811/821/817</td>
<td>3429/1710</td>
</tr>
<tr>
<td><strong>Placebo-controlled &amp; double-blind</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Year Completed</strong></td>
<td>1997</td>
<td>1990</td>
<td>1990</td>
<td>1986</td>
<td>1984</td>
</tr>
<tr>
<td><strong>Median (range) duration of treatment (years)</strong></td>
<td>6.9 (4.3-8.6)</td>
<td>2.7 (1.0-5.3)</td>
<td>2.6 (1.0-4.3)</td>
<td>4.4 (1.0-7.1)</td>
<td>6.0 (5.0-6.0)</td>
</tr>
<tr>
<td><strong>Patients with duration of treatment ≥2.5 yrs (active/control)</strong></td>
<td>2545/2540</td>
<td>444/468</td>
<td>648/639</td>
<td>684/653/702</td>
<td>3429/1710</td>
</tr>
<tr>
<td><strong>Patients with duration of treatment ≥5 yrs (active/control)</strong></td>
<td>2207/2219</td>
<td>10/9</td>
<td>0/0</td>
<td>321/312/316</td>
<td>3429/1710</td>
</tr>
<tr>
<td><strong>Patients informed of treatment allocation</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Open throughout</td>
</tr>
<tr>
<td><strong>Methods of post-trial follow-up</strong></td>
<td>Death certificate, cancer registration</td>
<td>Death certificate</td>
<td>Death certificate, record review, patient contact</td>
<td>Death certificate, cancer registration</td>
<td>Death certificate, cancer registration</td>
</tr>
<tr>
<td><strong>Year post-trial follow-up extended to</strong></td>
<td>2009</td>
<td>2007</td>
<td>2003</td>
<td>2006</td>
<td>2002</td>
</tr>
<tr>
<td><strong>Mean (SD) age at randomization (years)</strong></td>
<td>57.5 (6.7)</td>
<td>66.9 (7.1)</td>
<td>65.3 (10.1)</td>
<td>60.3 (9.0)</td>
<td>61.6 (7.0)</td>
</tr>
<tr>
<td><strong>Proportion male</strong></td>
<td>100 %</td>
<td>65.8 %</td>
<td>65 %</td>
<td>73 %</td>
<td>100 %</td>
</tr>
<tr>
<td><strong>Proportion smokers</strong></td>
<td>41.2 %</td>
<td>27 %</td>
<td>45.5 %</td>
<td>53 %</td>
<td>31 %</td>
</tr>
</tbody>
</table>